EXHIBIT 58

UNITED STATES DISTRICT COURT
NORTHERN DISTRICT OF CALIFORNIA

IN RE: ROUNDUP PRODUCTS LIABILITY LITIGATION,	)
	) MDL No. 2741
This document relates to:	) Case No.
	) 16-md-02741-VC
ALL ACTIONS	)

VIDEO DEPOSITION OF
BEATE RITZ, MD, PHD
Los Angeles, California
Monday, September 18, 2017

Reported by:
LISA MOSKOWITZ, CSR 10816, RPR, CRR, CLR,
NCRA Realtime Systems Administrator
JOB NO. 128477

September 18, 2017
9:05 a.m.

Video deposition of BEATE RITZ, MD, PHD, held at the offices of Baum, Hedlund, Aristei & Goldman, PC, 12100 Wilshire Boulevard, Suite 950, Los Angeles, California, before Lisa Moskowitz, California CSR 10816, RPR, CRR, CLR, NCRA Realtime Systems Administrator.

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BY: ELYSE SHIMADA, ESQ.

ALSO PRESENT:
SCOTT MCNAIR, Videographer
LEEMON McHENRY

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LOS ANGELES, MONDAY, SEPTEMBER 18, 2017
9:05 A.M.

THE VIDEOGRAPHER: Good morning. This is the start of tape labeled number 1 of the videotaped deposition of Dr. Beate Ritz in the matter of Roundup Products Liability Litigation. This case is before the United States District Court for the Northern District of California bearing MDL Number 2741 and Case Number 16-MD-02741-VC. This deposition is being held at 12100 Wilshire Boulevard in Los Angeles, California. Today's date is September 18, 2017. The time is approximately 9:05 a.m.

My name is Scott McNair from TSG Reporting, Incorporated. I'm the legal video specialist. The court reporter today is Lisa Moskowitz also in association with TSG Reporting.

Will counsel please identify yourselves for the record.

MS. FORGIE: Kathryn Forgie for

the plaintiffs with Andrus Wagstaff.

MR. BAUM: Michael Baum for plaintiffs.

MR. WISNER: Brent Wisner for plaintiffs.

MR. ESFANDIARY: Pedram Esfandiary for plaintiffs.

MR. McHENRY: Leemon McHenry for plaintiffs.

THE VIDEOGRAPHER: On the phone?

MS. FLAHERTY: Yvonne Flaherty, Lockridge, Grindal Nauen for plaintiffs.

THE REPORTER: And the other two counsel for the record on the phone?

MS. FORGIE: Jeff, Mike, you guys? Are you there?

THE REPORTER: Can you please identify yourselves for the video record?

MR. MILLER: Michael Miller and Jeff Travers.

MS. FORGIE: For plaintiffs.

MR. LASKER: Eric Lasker for Monsanto, Hollingsworth, LLP.

MS. SHIMADA: Elyse Shimada for Monsanto, Hollingsworth, LLP.
THE VIDEOGRAPHER: Thank you. Will the court reporter please swear in the witness. 09:06

Beate Ritz, MD, PhD,
called as a witness, having been duly sworn, was examined and testified as follows:

EXAMINATION
BY MR. LASKER:
Q. Good morning, Dr. Ritz.
A. Good morning. 09:07
Q. As you just heard, my name is Eric Lasker. I represent Monsanto. I'll be asking you some questions today.
Have you had your deposition taken before? 09:07
A. Once in, I don't know, 1991 or '2.
Q. I'm sure your attorneys have told you the process, but your deposition is being videotaped, and we have a court reporter. I will try and speak slowly for 09:07

the court reporter's benefit, although I'm not very good at that. I'll warn you. And if we can just wait for the question to be completed before you answer, that makes it easier for the court reporter. Okay? 09:07
A. Yes.
Q. If you have any uncertainties about my question or my question is poorly worded, just let me know. Okay? Great.
Let's start by marking your CV. 09:07
This will be Exhibit 19-1.
(Exhibit Number 19-1 was marked for identification.)
BY MR. LASKER:
Q. So Dr. Ritz, you received your 09:08 medical training in Germany; correct?
A. Correct.
Q. And you received what is identified on your CV as a medical certificate and then a doctoral degree in medical sociology. 09:08
A. Correct.
Q. I'm just trying to understand the terminology here. What is a doctoral degree in medical sociology?
A. It's a PhD equivalent. 09:08

Q. What was your specialty? What was your area --
A. Medical sociology which includes occupational health. So mine was in occupational health. 09:08
Q. Okay. And the medical certificate, is that --
A. That licenses you to be a physician.
Q. Okay. Did you ever -- have you 09:08 ever practiced as a clinical physician?
A. Yes.
Q. Where did you practice?
A. At the University Hospital Hamburg psychiatric department. 09:09
Q. Have you ever provided medical care for patients with -- well, did you ever provide medical care for cancer in patients with cancer?
A. Yes. 09:09
Q. When was that?
A. That was during my final year in medical school at the University of Hamburg pediatrics ward that was filled with children with leukemia and brain tumors. 09:09

Q. And that was somewhere around 1982?
A. '3.
Q. '83.
Other than that, have you provided clinical care for patients with cancer? 09:09
A. No.
Q. You're not an oncologist; correct?
A. No.
Q. You came to UCLA in 1991 to pursue a master's degree and then a PhD in 09:09 epidemiology; correct?
A. No. 1989.
Q. 1989. Thank you.
In 1995, you became an assistant professor of epidemiology at UCLA; correct? 09:09
A. Correct.
Q. One of your responsibilities in that position was advising and mentoring doctoral students; correct?
A. Correct. 09:10
Q. The first doctoral student you mentored was Kurt Straif; correct?
A. Correct.
Q. Had you known Dr. Straif before you became his mentor in 1997? 09:10

A. I knew him as a student. He was a student in the epi department, and he was actually mentored by a different faculty, Dr. Krause, who left UCLA and because of that, Dr. Straif had to be reassigned to another advisor.
Q. Had you known Dr. Straif back in Germany?
A. No.
Q. Did you continue to have a professional relationship with Dr. Straif after he received his PhD?
A. Not a professional relationship but a personal one.
Q. Okay. So you and Dr. Straif are friends?
MS. FORGIE: Objection.
THE WITNESS: I don't know how you would characterize it, but we're collegially affiliated. So he invited me, for example, to spend a visiting year at IARC.
BY MR. LASKER:
Q. Okay. That's where I was going next; so you anticipated that. 09:10 09:10 09:11

A. Yeah.
Q. Beyond -- first of all, just so the record is clear, Dr. Straif is now the head of the IARC Monograph program; correct?
A. As far as I understand, yes.
Q. Was he the head of the Monograph program when he invited you to become a visiting scientist at IARC?
A. No.
Q. What was his position then?
A. He was a senior scientist in the program, as far as I remember. And he was not the official person inviting me. He just recommended to me that I should come to IARC, and it was Dr. Boffetta who invited me officially.
Q. What did you do as a visiting scientist at IARC?
A. Well, my role was to work with -- to mentor and work with junior colleagues who were in the epidemiology program. Actually, one of the senior scientists -- we have a very regular exchange of doctoral students who go for internships to IARC. That is actually under the -- not my own 09:11 09:11 09:11 09:12

students but the students of our cancer research are at UCLA, Dr. Zhang, and one of his former students was actually a member of the epidemiology group at IARC at the time, Mia Hashibe, and she was the one who was helping all the students integrate into the IARC program, and my role as visiting scientist was to actually help her but also mentor a lot of junior scientists there because, at the time, I was considered a senior scientist.
Q. So I didn't understand this. UCLA and IARC have a --
A. A mentorship program.
MS. FORGIE: Wait for him to get the question out before you answer, please.
BY MR. LASKER:
Q. And how long has UCLA had this mentoring program with IARC?
A. I believe it is as long as Dr. Zhang was a faculty member at UCLA because he came -- he had a time where he, in his own professional career, actually spent time at IARC. 09:12 09:12 09:13

Q. So when would that -- a year, what year would that program have started?
A. 1997.
Q. Does that continue to the present?
A. I don't believe so because Dr. Hashibe left IARC, and Dr. Zhang is not very active anymore in terms of research.
Q. Were you paid for your work as a visiting scientist at IARC?
A. I got a stipend that helped me pay for rent. It was not considered pay.
Q. Did you continue to receive pay from UCLA during that period?
A. I was on a sabbatical officially, and yes, during that sabbatical, you're entitled to payment.
Q. How long did you work as a visiting scientist at IARC?
A. I started, I think, in August of 2006, and I left to go back to UCLA in July of the next year, 2007.
Q. I've seen some documents that identify you as also serving during this period as a member of the IARC secretariat; is that right? 09:13 09:13 09:14

A. Not that I recall that that was an official title, however, I was an observer -- a member of the group that was in charge of putting the 100s volume together or the ideas for the 100s volume, and I was an observer at several events that were led by the Monograph group.

They always have observers from visiting professors, junior scientists, but I was not a member of any of the groups. 09:14

Q. And the Volume 100, what is that?

A. That is -- that was a special memorial volume in which they decided which agents to re-review that they had previously reviewed. So the 100 carcinogenic compounds and groups that were previously reviewed in the 100s volume they decided what to re-review. 09:15

Q. Gotcha.

You were working for IARC during the same years that one of the other plaintiffs experts Christopher Portier was also over at IARC, I believe, working on an advisory group to recommend amendments to the preamble. 09:15

Are you familiar with that?

A. No.

Q. Did you have any dealings with Dr. Portier when you were at IARC?

A. None. 09:15

Q. Do you have any professional relationship with Dr. Portier?

A. None.

Q. Do you have any collegial relationship? If that's the word we use -- 09:15

A. I don't.

MS. FORGIE: Careful there.

MR. LASKER: I'm using her word. Trying to find the right word there.

BY MR. LASKER: 09:16

Q. I take it you did not work on any of the amendments to the IARC preamble?

A. No.

Q. Now, I was looking at your CV, and I don't see it. Maybe it's just an oversight, your work for IARC on your CV. 09:16

Is that listed here, and I just missed it?

A. That was a sabbatical. I don't list every sabbatical I take. 09:16

Q. Okay. So I didn't miss it. It's not on your CV?

A. No.

Q. Okay.

A. There may be some talk -- no. I don't know. 09:16

Q. Have you had any discussion with Dr. Straif about IARC's review of glyphosate?

A. None. 09:16

Q. Have you had any discussion with Dr. Straif about any of your work as a plaintiff's expert in this litigation?

A. None.

Q. Your CV mentions that you are a member or originally were a member of the external advisory committee for the Agricultural Health Study and then in 2005, you became the chair of that committee; correct? 09:16 09:17

A. Correct.

Q. And you're currently still serving as the chair of the AHS --

A. Normally but that committee hasn't met since. 09:17

Q. When was the last time that committee met?

A. I think I was the chair once; so it must have been in 2006 or '7.

Q. Okay. How did you first get appointed to the advisory committee? 09:17

A. I was approached, as far as I recall, by Dr. Alavanja at a professional meeting, and he asked me whether I would be interested in this kind of appointment. 09:17

Q. How were you selected in 2005 to become the chair of the committee?

A. Because the chair stepped down, and they thought they needed somebody else to chair. So they asked me, but it was, at the time, already not clear whether this advisory panel would really have much to do in the future. 09:17

That was one reason why I said yes because I knew it wouldn't be much work. 09:17

Q. For the period 2001 to 2005 then, was that a period where there was more work on the advisory committee?

A. Yes.

Q. What was the role of the advisory 09:18

committee during that period of time?
A. That was a very active time for the cohort because they were in the second phase of going out there and interviewing and trying to interact with the farmers. 09:18
And so from year to year, they would present their progress, but at the same time, they were also using the baseline data that they had collected between 1993 and 1997 to do the first analyses and 09:18 produce the first results that came out of this cohort.
So it was a very, very busy time of investigators presenting first results, presenting first ideas on how to do exposure 09:18 assessments and to bang ideas around, and that's what the advisory committee was charged to do, which is to not only follow the fieldwork and make recommendations that was ongoing but also to evaluate those first 09:19 analyses and results coming out of the study.
Q. So this was during the period of time when the De Roos 2005 publication came out which looked at glyphosate; correct? 09:19

A. Correct.
Q. In your role on the advisory committee, would you, then, have received the initial results of that analysis? Have that presented to you for discussion? 09:19
A. Not necessarily. That was actually up to the authors and depended on whether they wanted input from the advisory panel or certain members of the advisory panel, and I can't remember seeing that manuscript. 09:19
Q. Would the advisory committee review the publications that came out of the AHS after they appeared in the --
A. That was not our task. Our task was really to be there for those who wanted 09:20 a pre-review.
Q. Did the advisory committee consult on the methodologies that were being used by the Agricultural Health Study group during that period in preparing their analyses for 09:20 publication?
MS. FORGIE: Objection.
You can answer.
THE WITNESS: There was not one publication that we would ever review. 09:20

Part of what was done at the advisory panel meetings was present to us studies within the Agricultural Health Study that helped us evaluate the exposure assessment methods. 09:20
I remember presentations by Dr. Curwin, by the NIOSH group that went out and did field measurements, and I also remember presentations by Dr. Acquavella from Monsanto. They had 09:20 a relatively close relationship during that time in trying to evaluate exposures in the field.
BY MR. LASKER:
Q. Do you recall then did you review 09:21 Dr. Acquavella's analyses of urinary biomarkers for glyphosate in other pesticides?
A. We did not review it, but we were made aware of it. 09:21
Q. Did you actually have the opportunity to question Dr. Acquavella about his -- and his team about their analyses?
A. Maybe one or two questions. I 09:21

mean, we are in a room with 35, 50 people, and, you know, if you can get your hand up fast enough, you can ask a question.
Q. Do you recall during that meeting whether anybody raised, from the advisory 09:21 committee, raised any concerns about the validity or reliability of the analysis this Dr. Acquavella was conducting?
MS. FORGIE: Objection.
THE WITNESS: I do not. I cannot 09:21 remember.
BY MR. LASKER:
Q. So that -- you mentioned that was from the period before 2005, and you have one meeting that you recall after 2005, 09:22 sometime in 2006 and 2007. Have you had any activity as a member of or as a chair of the external advisory group for AHS since that time?
A. What would happen is from time to 09:22 time we would get a small report of activities that are ongoing in writing. We would have maybe one or two conference calls where we could ask questions about the ongoing activities, and I've been informed 09:22

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that there will be a two-day meeting coming up in February, but I can't attend it because I'm teaching.
Q. Did you have, during that time period, calls addressing the second phase questionnaire to gather more information on exposure information from the cohort? 09:22
MS. FORGIE: Object to form.
THE WITNESS: That was done. There was no more questions about that. 09:23
BY MR. LASKER:
Q. So during the period -- that would have been completed in 2003 or 2004.
A. Yeah, yeah.
Q. Were you advising, or was your committee advising the AHS on the procedures to use during the second phase in gathering additional information from the cohort? 09:23
A. Well, that was already decided prior to them going out in the field; so there was nothing you could change. You don't change methods in the middle of assessments in the field because you get in trouble. 09:23
Q. We'll be talking a little bit later

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about the response rate for the exposure assessment for the AHS and how the AHS group has addressed that in their studies.
Were there any discussions with your group about methods that could be used to address the issue of non-responders in phase 2? 09:23
A. Only insofar as they were trying to come up with field methods to get more people to respond. 09:24
Q. Have you had any discussions with any of the Agricultural Health Study scientists regarding any study data on glyphosate and non-Hodgkin's lymphoma?
A. No. 09:24
Q. Have you had any discussions with anyone at the AHS regarding research into pesticides more generally?
A. Oh, yes.
Q. What discussions -- I know this may be a broad topic. I don't know exactly how to break this down. What discussions have you had with the AHS group about conducting pesticide cancer epidemiology? I assume that's the general category. 09:24

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A. That's --
MS. FORGIE: Wait for the question.
THE WITNESS: That's very broad; so the discussions would have been quite broad. 09:25
BY MR. LASKER:
Q. I realized that as I was asking the question. Have you had conversations with the AHS scientists about how to conduct their dose response analyses of pesticides and non-Hodgkin's lymphoma? 09:25
A. No.
Q. Have you had discussions regarding -- with the AHS scientists about how to deal with issues of selection -- potential selection bias in the -- if there is any in the AHS study? 09:25
MS. FORGIE: Object to form.
THE WITNESS: Selection bias would be a differential bias due to loss to follow-up. Are we talking about cancer, or are we talking any outcome? 09:25
BY MR. LASKER:
Q. Cancer.
A. In terms of cancer we would not

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necessarily expect selection bias. We would expect selection to -- well, we would suspect loss to follow-up only if we cannot find cancer cases in the registries that were being searched for, and that was actually part of the assessments in the -- when I was in the room at those meetings was what search algorithms they were using broadly to find cancer cases, and they included not only the cancer registries in the States but mortality registries and other means including following up with the participants. So in terms of cancer, we would expect them to have been able to find all the cancers. 09:26
Q. Did you have any discussions with AHS scientists about the possibility of misclassification -- exposure misclassification bias in the study? 09:26
A. The study is a very broad term. The study has many, many sub studies including a Parkinson's study I'm very interested in because that's what I do. And yes, there could be selection bias in that Parkinson's study, and it could be very 09:27

severe so I'm sure we've had a lot of discussion around that.
Q. Let me back up because you used selection bias, and I thought we were talking about something different but maybe I misstated. I was talking about exposure and misclassification bias. That's a separate issue than selection bias. 09:27
A. Yes.
MS. FORGIE: Wait for a question. 09:27
BY MR. LASKER:
Q. Have you had conversations with AHS scientists about exposure misclassification bias particularly with respect to pesticides? 09:27
A. That was an ongoing discussion that we had at just about every meeting because in pesticide epidemiology, we are generally aware that that's a big problem. Exposure misclassification is always a problem with when you have time varying exposures, and you have lifelong exposure periods that you have to evaluate. So it's not like, for example, I do a lot of pregnancy studies. You have a nine months period, and that's 09:28

rather easy to recall for the women, or you can even sample urine every month from a pregnant woman. You cannot sample urine over lifetime from the farming population of the size of the AHS. So it's an ongoing debate. 09:28
Q. It would be fair to say that the Agricultural Health Study has made significant efforts through the way it interacts with the cohort and the way that it formulates the questionnaires, including with advice from your committee to minimize the potential for exposure misclassification bias? 09:28
MS. FORGIE: Object to form. 09:28
THE WITNESS: That's a very relative term. Again, when it comes to lifelong exposures, misclassification of exposure gets more and more -- to be more and more problem the older the enrollees are and the longer back they have to recall. It also is a big problem if you're not reassessing exposures every single year. 09:29
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BY MR. LASKER:
Q. Did the advisory committee make recommendations to the AHS scientists on methods to address exposure misclassification or potential for exposure misclassification that the AHS scientists did not accept? 09:29
A. I can't recall.
Q. Dr. Matthew Ross of Mississippi State is also a member of your advisory committee for the AHS group; correct? 09:29
A. As far as I remember, yes.
Q. Have you had any conversation with Dr. Ross about glyphosate?
A. No. 09:29
Q. Have you followed the AHS outside of this litigation -- have you followed the AHS's findings with respect to potential risk factors in the agricultural community for non-Hodgkin's lymphoma? 09:30
MS. FORGIE: Object to form.
THE WITNESS: I have been following the AHS over many years. The focus for me was always my Parkinson's interest. However, since Dr. De Roos was a 09:30

candidate for faculty at UCLA, I have been very interested in her publication; so I'm very aware of her publications.
BY MR. LASKER:
Q. When was Dr. De Roos being considered for a faculty position at UCLA? 09:30
A. A few years ago. Two or three years ago right before she went to Drexel.
Q. And through that process, I take it you then reviewed all of her studies for -- 09:30
A. More or less, yes. Especially the ones I'm familiar with.
Q. What different exposures or risk factors has the AHS through its research associated with non-Hodgkin's lymphoma that you can recall? 09:31
A. It has found diesel, and it has -- there's a small risk increase in certain animal husbandry and solvent exposures, but the one that I recall the most is diesel exposures. 09:31
Q. Your CV also mentions that you are a Fellow at the Collegium Ramazzini. I guess you became that in 2007; correct?
A. Correct. 09:31

Q. What is a Collegium Ramazzini?
A. It's a boys' club. That's one reason why I'm not often there. It is a group of occupational and environmentally interested health professionals who are 09:32
meeting once a year in a small place near Bologna in Italy. Ramazzini was 1700's the first occupational physician credited with finding several occupational disorders or diagnosing them for the first time. So in 09:32
his honor, this is a society. You can only be invited to become a member, and it has a limited number of members. So only when a member expires or leaves can a new one be inducted. 09:32
BY MR. LASKER:
Q. What is the numerical limit?
A. I think it is 189 for some reason.
Q. Do you know who invited you for membership? 09:32
A. Yes. It was Dr. Phillip Grandjean from Denmark.
Q. Where does -- to the extent that you know the Collegium Ramazzini receive funding for its scientific endeavors? 09:32

A. I'm not sure they even have any scientific endeavors, and I wouldn't know where they're getting their funding from, but certainly they are not paying you to go there. 09:33
Q. Are you aware of that the Collegium Ramazzini has announced the intention to conduct research into glyphosate?
MS. FORGIE: Objection.
THE WITNESS: I have no -- I have not followed them for a while. 09:33
BY MR. LASKER:
Q. So the answer is no?
A. No.
MS. FORGIE: Objection. 09:33
BY MR. LASKER:
Q. Dr. Straif is a Fellow of the Collegium Ramazzini; correct?
A. I think he is, but I'm not really certain. I've never met him there. 09:33
Q. Dr. Blair is a Fellow of the Collegium Ramazzini; correct?
A. I think that's true. Again, I don't recall seeing him there.
Q. And Dr. Portier is a fellow of the 09:33

Collegium Ramazzini; correct?
A. I wouldn't know that.
Q. In 2009, you were elected as a counselor for the International Society for Environmental Epidemiology; correct? 09:33
A. Correct.
Q. What is the role of a counselor for the ISEE?
A. Well, that's kind of like a board member, and what you do is you're on a phone 09:34
call once a month with all the other members including the president and the president elect and the treasurer, and you're conducting business of the society.
Q. One of the things that you've done 09:34
-- at least I see from your CV -- is that you have been a member of the ISEE's conference organizing committee.
A. That's correct.
Q. What does that committee do? I 09:34
think it's halfway self-evident but . . .
A. Yes, it is self-evident. So we are the ones who are reviewing the applications that come in from members for conducting the conference every year, and we also are 09:34

trying to help the conference organizers in every way we can. And we have guidelines for conference organizers. So that's pretty much it.
Q. Okay. In your expert report, you 09:34
discuss what you describe as some of the peer review that's conducted in connection with abstracts and presentations at the ISEE conferences; correct?
A. Correct. 09:35
Q. Can you describe that peer review process?
A. Yes. Every year when the conferences are being conducted, we elicit peer reviewers from among the council as 09:35
well as from the membership. So we have a call for the membership out to nominate peer reviewers for the abstracts and then we appoint the -- the council appoints these peer reviewers with the help of the 09:35
conference organizers, and they then are tasked with peer reviewing the abstracts. And there are guidelines for that. There is a point system for that, and it's always at least three reviewers who review, and then 09:35

it's being summarized and discussed in the conference committee or better with the conference organizers.

Q. So the abstract obviously is going to be a fairly short document. Does the peer review process involve reaching out and talking to the investigators about their work? What actually is done as part of that peer review? 09:36

MS. FORGIE: Object to form. 09:36

THE WITNESS: What we're trying to do is match the abstracts with people in the specific areas of knowledge so that we have expertise in terms of the outcomes assessed, the exposures 09:36 assessed, the type of studies conducted. So the peer reviewers are not reaching out, but they are to evaluate whether there is enough information to make this a scientifically solid abstract. 09:36

BY MR. LASKER:

Q. And did you attend the ISEE conference in Brazil in 2015?

A. I did.

Q. Did you sit in on the presentation 09:36

or any of the presentations of the NAPP investigators?

A. Unfortunately not.

Q. Dr. Ritz, let's talk about some of -- let's get your expert report as the 09:37 next document. I don't know that we'll be dealing much with your CV so you can set that aside.

(Exhibit Number 19-2 was marked for identification.) 09:37

BY MR. LASKER:

Q. So this will be Exhibit 19-2. Dr. Ritz, on page -- you address some of the methodological issues with epidemiology and epidemiological studies in your report; 09:38 correct?

A. Yes.

Q. I'd like to take you to page 6 and carrying over to page 7 you're discussing what you identify as the null hypothesis; 09:38 correct?

A. Yes.

Q. The null hypothesis is an essential concept in scientific methodology not only in epidemiology but in all areas of 09:38

scientific endeavor seeking to analyze cause and effect; correct?

MS. FORGIE: Object to form.

THE WITNESS: Yes, we generally formulate something of a null hypothesis 09:38 in science, yes.

BY MR. LASKER:

Q. The scientific method is based upon generating a hypothesis and then testing to see if they can falsify -- if that 09:39 hypothesis can be found to be not true; correct?

MS. FORGIE: Object to form.

THE WITNESS: Actually a null hypothesis is one specific hypothesis. 09:39 It's the hypothesis that there's no difference.

BY MR. LASKER:

Q. Right.

A. And that is actually in scientific 09:39 circles being discussed as probably not the best way to go about science all the time. Sometimes you actually want to specify a hypothesis of a certain type of difference. However, there is a multitude more 09:39

ways of specifying that difference in terms of size or extent so that people can't easily agree to that kind of hypothesis. But one in science could decide to hypothesize something that's not a null 09:39 hypothesis, but the convention is to start with a null hypothesis.

Q. If we are using a null hypothesis, the process of a scientific method is to generate a hypothesis to see if that null 09:40 hypothesis could be shown to be not true; correct?

A. I would not state it that way. We are starting with a null hypothesis, and then we are trying to provide data that 09:40 either confirms or refutes the null hypothesis.

Q. Got it. Better.

In epidemiology and in cancer epidemiology, for example, the null 09:40 hypothesis would be that an exposure being studied is not a cause of cancer; correct?

MS. FORGIE: Object to form.

THE WITNESS: We would, yes. A null hypothesis we would state as no 09:40

difference in risk.
BY MR. LASKER:
Q. Epidemiologists will then design studies to test that null hypothesis; correct? 09:41
A. Well, we are testing the hypothesis whether or not that agent contributes to the disease. The null hypothesis would be that it doesn't.
Q. And when you design an 09:41 epidemiological study, you are designing the study to be able to test that null hypothesis; correct?
A. We can't really -- as I said, we are testing whether an agent adheres or 09:41 whether the exposure to an agent falls under the null hypothesis, or we can generate data that refutes that null hypothesis, yes.
Q. All right. So in designing an epidemiologic study, you are designing the 09:41 study to try and generate data that would at least -- would allow you to test the null hypothesis?
A. That would allow me to test whether there is a difference or not. 09:41

Q. Correct. In epidemiologic studies, the null hypothesis is reflected in an odd ratio or risk ratio of 1.0; correct?
MS. FORGIE: Object to form.
THE WITNESS: Well, that is one 09:42 measure. We are using different measures: odds ratio, risk ratios, rate ratios. And these ratios have point estimates and confidence intervals. The null hypothesis is that, yes, there's no 09:42 difference in the risk among the exposed compared to the risk among the unexposed or the rate in the exposed compared to the rate in the unexposed. And since the ratio measure when there's no 09:42 difference is one, that would be considered no effect.
BY MR. LASKER:
Q. Epidemiologists will then analyze the data to determine whether that null 09:42 hypothesis can be rejected from that data; correct?
MS. FORGIE: Object to the form.
THE WITNESS: Modern epidemiologists would not go out to test 09:43

a null hypothesis or that kind of null hypothesis in the term of statistical testing. What we're trying to do is estimate parameters. So we estimate the parameter of interest which in this case 09:43 is the relative risk, the risk ratio, or the odds ratio.
BY MR. LASKER:
Q. We'll be talking about exactly how to test that. I'm not talking about how 09:43 they would test it, but as a threshold epidemiologists using whatever approach -- and we'll talk about this in a moment. But epidemiologists will analyze the data from their study to determine whether the null 09:43 hypothesis can be rejected; correct?
MS. FORGIE: Objection. Asked and answered.
You can answer it again.
THE WITNESS: Again, I would not 09:43 formulate it in this way. It's an estimation problem. We are trying to estimate a relative risk, a rate ratio, or an odds ratio which are parameters that tell me something about the risk in 09:43

the exposed compared to the risk in the unexposed. Along with that goes statistics, but, in essence, we are estimating parameters.
BY MR. LASKER: 09:44
Q. The process of estimating parameters in epidemiologic study is to determine whether that data would provide evidence against a null hypothesis; correct?
MS. FORGIE: Object to form and 09:44 asked and answered.
THE WITNESS: Again, I would want to estimate this parameter and then also see in statistical terms how informative this parameter is. 09:44
BY MR. LASKER:
Q. Right. And the -- what you're looking for with respect to that parameter is whether or not the data you are analyzing would exclude the null hypothesis, if you're 09:44 going to reach a causation opinion; correct?
MS. FORGIE: Object to form, asked and answered.
THE WITNESS: There's a lot more to that than just a null hypothesis. 09:44

There's a lot more that we're doing in epidemiology to convince ourselves that there is causation.

BY MR. LASKER:

Q. That's fair enough. One step in the process to determine whether or not there is causation through an epidemiologic study is whether or not the data is -- allows one to exclude the null hypothesis; correct? 09:45

MS. FORGIE: Object to form, asked and answered.

You can answer it again.

THE WITNESS: Again, we are trying to estimate parameters. These parameters have point and interval -- point and interval estimates, and a lot more goes into evaluating the validity of that parameter. 09:45

BY MR. LASKER: 09:45

Q. I agree with that, and we'll be talking about that. But the purpose of determining the point estimate and the parameters for the statistical analysis part of that -- and we'll talk about the other 09:45

parts as well -- is to determine whether or not at that step the null hypothesis of 1.0 is at least not due to chance. Is that fair?

MS. FORGIE: Objection. Wait. 09:46

Object to form and asked and answered.

You can do it again.

THE WITNESS: Chance is one -- is just one criterion we are considering as epidemiologists, and I teach bias 09:46 analysis in the basic methods class at UCLA. What I teach my students is that what we have to make sure is that there's no bias and that before everything else we are ever considering. 09:46 So I would not even consider data unless we would go through a rigorous analysis of all the biases.

BY MR. LASKER:

Q. Fair enough. In your analysis of 09:46 the issues of chance, the issues of bias, the issues of confounding, when you're looking at all of those issues together, what you are trying to, as an epidemiologist, is to determine whether or 09:47

not those factors can be at least addressed efficiently so that together that would allow you to determine that the null hypothesis has been rejected in that study. Is that fair? 09:47

MR. LASKER: Object to form.

THE WITNESS: I do not formulate my research ever in that way. I'm estimating parameters, and I'm assessing validity of studies. 09:47

BY MR. LASKER:

Q. What would you need to -- what steps would you need to go through then in an epidemiological study in analyzing the issues of chance and bias and confounding to 09:47 reach a conclusion in your mind that that study demonstrates a positive association between the exposure at interest and the outcome at interest?

MS. FORGIE: Objection to form. 09:48

THE WITNESS: That is a very long lecture. I don't know whether we want to have it here. It takes me ten weeks and four hours a week to do that. So the short form is that you start with 09:48

the study design, that you start with the exposure assessment validity, that you start with the outcome assessment validity, that you then go into a sample size, exposure prevalence, any kind of 09:48 bias you can think of, and once you have wrapped it all together, that's when you're doing a lot of sensitivity analyses in your data to convince yourself that no way -- no matter how 09:48 you look at your data, there is a signal.

BY MR. LASKER:

Q. And I think that you mentioned this -- you may have mentioned it in your 09:48 report. I know you mentioned it in some of your class materials -- that the fundamental question that an epidemiologist must ask before reaching a causation opinion is is there any other way of explaining the set of 09:49 facts before us, is there any other answer that is equally or more likely than cause and effect; correct?

MS. FORGIE: Object to form.

THE WITNESS: We generally like to 09:49

challenge each other. Epidemiologists are extremely critical of their own work and that of their colleagues. So we are asking many, many questions trying to debunk a positive result that we might be seeing in a study. We're coming up with causal models, with -- yeah, bias analyses, sensitivity analyses, and after we've done all of that, there might be a positive association; there might not be a positive association. Whether that's causal, we would usually want more than one study to decide.

BY MR. LASKER:

Q. And the underlying -- the fundamental question that you're trying to answer when you look at an epidemiologic study or a body of epidemiologic literature is whether there is any other way of explaining the facts before you other than cause and effect; correct?

A. That would be any one way because there's always one way or another in any type of study that I can think of that you can find alternative explanations, but what

you are looking for then is just as consistent a pattern that would explain everything else.

Q. And if you are not -- if you find that there is some other explanation that could explain the findings, then you would not be able to reach an opinion of cause and effect. Is that fair?

MS. FORGIE: Object to form.

THE WITNESS: That would depend. So I would want to see that -- there could be an alternative explanation in one study but not in another. So what we would like to see is studies done on different continents, in different counties, by different investigators with different methods. If they all show the same results, then I'm pretty happy because there's probably not one explanation that explains it away.

BY MR. LASKER:

Q. The null hypothesis in this case is that glyphosate is not associated with non-Hodgkin's lymphoma; correct?

A. It's either glyphosate or

glyphosate-related formulations.

Q. For epidemiology, it would actually be glyphosate-based herbicides; correct?

A. Correct.

Q. There are no epidemiology studies that are just pure glyphosate. It's all the formulate herbicide product?

A. Epidemiology is done in the real world. So what is out in the real world is what we're studying.

Q. Okay. And the question, then, on to the scientific method and the question for you, I take it, in this case is whether the epidemiologic studies provide data that would allow you to exclude -- well, strike that.

You have reviewed, as part of your work in this case, IARC's assessment of the glyphosate epidemiology; correct?

A. I have read that monograph, yes.

Q. And in your expert report -- I think it's on page 16 -- it's actually the last sentence on page 16, you state that you "concur with the IARC conclusions after conducting my own independent analysis of

the studies included in the IARC review"; correct?

A. Yes, that's what it says.

Q. Okay. And that's the opinion that you are -- you'll be presenting in this litigation; correct?

A. I will be presenting my own conclusions.

Q. And your own conclusions concur with the IARC's conclusions; correct?

MS. FORGIE: Object to form.

THE WITNESS: It concurs with the overall IARC conclusions.

BY MR. LASKER:

Q. And just to be clear, when you're talking about the IARC's conclusions in your report, you're talking about IARC's conclusions with regard to epidemiology; correct?

MS. FORGIE: Object to form.

THE WITNESS: I am meaning the overall IARC conclusions.

BY MR. LASKER:

Q. Okay. In this section in your report where you state that you concur with

IARC's conclusions after conducting your own independent analysis of the studies, first of all, what studies did you review in connection with your work on this case?
A. What studies did IARC review? 09:53
Q. No, did you review. Because you state, "After conducting my own independent analysis of the studies included in the IARC review," which studies are we talking about there? 09:54
A. That overlap with IARC's? They should be all in IARC plus I looked at several others.
Q. But IARC looked at studies dealing with genotoxicity and dealing with 09:54 toxicology and all the like.
A. Yes.
Q. Did you review the genotoxicology studies that IARC reviewed?
A. I did review several papers on 09:54 genotoxicity as well as animal studies, yes.
Q. And did you conduct an analysis, your own independent analysis of the animal toxicology studies?
A. As far as I'm able to do that, I 09:54

did.
Q. That's not your area of expertise, I take it?
MS. FORGIE: Objection. Object to form. 09:54
THE WITNESS: Well, in effect, I'm a member of the interdisciplinary program in molecular toxicology at UCLA. So I teach toxicologists. So yes, I do know how to read toxicology literature. 09:55
BY MR. LASKER:
Q. With respect to the conclusions that can be reached with respect to the animal toxicology studies, would you defer to the other experts that have been put 09:55 forth by the plaintiff's counsel on those issues?
MS. FORGIE: Object to form.
THE WITNESS: I'm sure that a toxicologist can read these papers in 09:55 different ways, but since I am -- I have been working with toxicologists for 25 years. I'm a member of this teaching program, I would say that I have a certain ability to draw my own 09:55

conclusions. Plus I'm medically trained, and I know animal pathology because it's very close to human pathology.
BY MR. LASKER: 09:55
Q. So if I were to ask you questions about the Sugimoto rodent study, would you be in a position to answer those questions here today?
MS. FORGIE: Object to form. 09:56
THE WITNESS: You would have to show me those papers, and I would tell you.
BY MR. LASKER:
Q. In your expert report up until the 09:56 line -- up until page 16, you do not discuss any studies other than the epidemiologic studies; correct?
A. Correct.
Q. And in your discussion on page 16 09:56 when you're talking about the conclusions that IARC reached, you are talking about IARC's -- the only thing you discussed is IARC's conclusion with regard to the epidemiology; correct? 09:56

MS. FORGIE: Object to form.
THE WITNESS: Well, as a scientist, you read everything, and as a scientist, I did go back to the toxicology and genotoxicity literature, and I did read 09:56 the IARC Monograph on that. So when I come to a conclusion, it's in the totality of everything I have reviewed.
BY MR. LASKER:
Q. I understand that, but your expert 09:57 report in discussing the IARC conclusions that you concur with, the only conclusions that you discussed up to this point in your report are IARC's conclusions with respect to the epidemiology; correct? 09:57
MS. FORGIE: Object to form. Asked and answered.
You can answer it again.
THE WITNESS: Again, I cannot exclude what I know and what I've read 09:57 and what I've evaluated. So even if I just refer in this report to the epidemiology, which, of course, I consider myself most an expert, when I make that comment, I'm referring to the 09:57

whole IARC conclusion which included the toxicology and the genotoxicity.
BY MR. LASKER:
Q. Do you concur with IARC's conclusions with respect to the epidemiology? 09:57
MS. FORGIE: Object to form.
THE WITNESS: Well, IARC's conclusions are IARC's conclusions. They are very categorical. As a scientist, I wish it wasn't as categorical, and I may or may not confer with the way they are drawing these categorical conclusions. I think the epidemiology is quite strong. 09:57 09:58
BY MR. LASKER:
Q. Let me be clear, though. When you state in your expert report on page 16 that you concur with the IARC's conclusions, do you concur with IARC's conclusions with respect to the epidemiology? 09:58
MS. FORGIE: Object to form and asked and answered.
You can answer it again.
THE WITNESS: Well, I'm concurring 09:58

here with the overall IARC conclusion.
BY MR. LASKER:
Q. I understand that, but that's not my question.
MS. FORGIE: Wait, wait. 09:58
BY MR. LASKER:
Q. When you state here that you are concurring with the IARC's conclusions, you state that at page 16 of your expert report, after talking to the epidemiological literature, my question to you is: Do you concur with the IARC's conclusions regarding the glyphosate epidemiology? 09:58
MS. FORGIE: Object to form, asked and answered twice before. 09:58
You can answer it again.
THE WITNESS: IARC drew conclusions based on three criteria. I read the IARC Monograph. I went back to some of the literature on the genotoxicity and on the animal studies, and I concur with IARC's conclusions. 09:59
BY MR. LASKER:
Q. Okay. Again, I want to be clear for the record so that the court understands 09:59

and the answer can be yes or no. That's obviously your answer.
With respect to IARC's conclusions, with respect to the epidemiological literature of glyphosate, and you know that IARC separately analyzed the epidemiology; correct? 09:59
MS. FORGIE: Object to form.
THE WITNESS: IARC has several groups that are evaluating pieces of science. One is an epidemiology group. One is a genotoxicity -- one is a mechanistic group. Genotoxicity is part of it. One is an animal group. Each of them evaluate the literature independently, come up with conclusions, but then they are meeting together and discussing with each other the literature and possible conclusions from it. 09:59 09:59 10:00
So every scientist in the room gets to know what the other group is doing and how they are reaching possible conclusions, and they may disagree. A toxicologist may disagree with an 10:00

epidemiologist or the epidemiologist group and vice versa. But --
BY MR. LASKER:
Q. I understand --
MS. FORGIE: Wait let her finish, please. 10:00
THE WITNESS: In the end, they have to come together with a conclusion, and the conclusions are very categorical, and they are balance of evidence type of conclusions. 10:00
BY MR. LASKER:
Q. I understand that. But my question to you is specific to the epidemiology subgroup in IARC, and they reached a conclusion with respect to the epidemiological literature; correct? 10:00
MS. FORGIE: Objection. Asked and answered.
You can answer it again. 10:00
THE WITNESS: Actually, the epidemiology group alone isn't who comes up with these conclusions. It is everybody in the room at the overall meetings who agrees on these. 10:00

BY MR. LASKER:
Q. Okay. And everybody in the room came to a conclusion with respect to the epidemiologic literature; correct?
MS. FORGIE: Object to form. 10:01
THE WITNESS: They came to a balanced evaluation that then was put into the Monograph and got a category number which is 2A possible carcinogen.
BY MR. LASKER: 10:01
Q. Okay. And that is the overall assessment of glyphosate. I understand that. There is also a separate assessment in the Monograph for the epidemiology, and there's a separate assessment for the animal 10:01 toxicology, and there is a separate assessment for the mechanisms; correct?
A. Yes.
Q. What I am asking you is specific to the conclusion that IARC reached with 10:01 respect to the epidemiology. Okay?
MS. FORGIE: Objection.
THE WITNESS: Again, the epidemiology group made their conclusion. I'm not going to question 10:01

their conclusion. I make my own conclusion, but my conclusion as a scientist is based on reviewing all of the literature. I'm more than an epidemiologist. I have medical 10:02 training, and I have been working with toxicologists and animal experimentalists for 25, 30 years.
BY MR. LASKER:
Q. Right. I understand all of that, 10:02 but my question for you is specific to the epidemiology. The IARC working group came to a conclusion that the glyphosate epidemiology with respect to non-Hodgkin's lymphoma fit into their category of limited. 10:02
You understand that; correct?
MS. FORGIE: Object to form. Asked and answered.
You can answer it again.
THE WITNESS: I understand the 10:02 categories that IARC is using, and they have some unfortunate language including the word "limited" because it's not -- it's a common language word that is very easy to misunderstand. 10:02

BY MR. LASKER:
Q. Okay. Well, let's just be clear on what IARC means by "limited" with respect to epidemiology.
IARC defines limited as: "A 10:02 positive association has been observed between glyphosate" -- "between exposure to glyphosate in this instance and NHL for which a causal interpretation is credible but chance, bias, or confounding cannot be 10:03 ruled out with reasonable confidence."
Correct?
A. Correct.
MS. FORGIE: Object to form.
BY MR. LASKER: 10:03
Q. And IARC determined that the glyphosate epidemiology -- epidemiologic literature fit within that definition; correct?
MS. FORGIE: Object to form, asked 10:03 and answered.
You can answer it again.
THE WITNESS: The working group gave the label 2A which is this kind of definition, yes. 10:03

BY MR. LASKER:
Q. Okay. Let's just be clear about this. 2A is the overall assessment. We're talking about the epidemiologic studies.
A. Uh-huh. 10:03
MS. FORGIE: Wait for a question.
BY MR. LASKER:
Q. With respect to the epidemiologic studies, IARC concluded for glyphosate and non-Hodgkin's lymphoma that a positive 10:03 association has been observed for which a causal interpretation is credible but chance, bias, or confounding cannot be ruled out with reasonable confidence; correct?
MS. FORGIE: Object to form, asked 10:04 and answered.
You can answer it again, but you're getting --
THE WITNESS: That is --
MS. FORGIE: Wait, let me finish. 10:04
You're getting to a point where you're badgering the witness.
THE WITNESS: That's the IARC definition.
///

BY MR. LASKER:
Q. And you state in your expert report -- and I'm just trying to understand what this means -- you state in your expert report that you concur with the IARC conclusions. 10:04

My question to you -- and the answer can be yes or no -- is whether you concur with IARC that for glyphosate and non-Hodgkin's lymphoma and the epidemiological studies, a positive association has been observed for which a causal interpretation is credible but chance, bias, or confounding cannot be ruled out with reasonable confidence? 10:04

MS. FORGIE: Object to form. Asked and answered. Also mischaracterizes the IARC, as you know, the IARC categories.

THE WITNESS: Again, on page 16 of my document what I'm referring to is the overall IARC conclusion. 10:04

BY MR. LASKER:
Q. My question to you is, independent of whatever you mean or you're interpreting the sentence on page 16 in your expert 10:05

report to mean, the question to you is very simple. Do you agree with IARC in its classification of the epidemiological literature for glyphosate and non-Hodgkin's lymphoma that a positive association has been observed for which a causal interpretation is credible but chance, bias, or confounding cannot be ruled out with reasonable confidence? 10:05

MS. FORGIE: Object to the form, asked and answered. Also you're deliberately misreading the IARC categories. 10:05

THE WITNESS: Again, IARC has unfortunate wording in their categories. One of the unfortunate words is "limited." They are expanding on it in a way that to non-epidemiologists is problematic, and I'm not going to argue with IARC about this. 10:05

BY MR. LASKER:
Q. My question is not about use of the word "limited" or whatever word they use. My question is the substance of what IARC concluded, and you may agree or you may 10:06

disagree, but you haven't told me yet which of those things it is. That's all I'm trying to find out. It's a simple question, and if we need to mark this and the judge can answer, that's fine. We'll do that. 10:06 But it's a simple question, yes or no.

Do you agree with IARC in its review of the glyphosate and Roundup epidemiological literature for non-Hodgkin's lymphoma that a positive association has been observed for which a causal interpretation is credible but chance, bias, or confounding could not be ruled out with reasonable confidence? 10:06

MS. FORGIE: Objection. Object to the form. You're mischaracterizing and misreading the categories of IARC, as you know, and it's been asked and answered at least five or six times now.

You may answer it again. 10:06

THE WITNESS: Again, IARC does their evaluation the way they do. I'm a scientist. I did my independent evaluation. I used my words. They used theirs. I may not agree with the kind 10:07

of wording they are using. I think the epidemiology is extremely strong.

BY MR. LASKER:
Q. Do you believe based upon your review of the epidemiological literature for glyphosate and non-Hodgkin's lymphoma that a positive association has been observed for which a causal interpretation is credible but chance, bias, or confounding could not be ruled out with reasonable confidence? 10:07

MS. FORGIE: Object to form. Asked and answered.

You can answer it again.

THE WITNESS: My reading of the literature is that the epidemiology is very strong especially since there was additional literature since IARC conferred in 2015. 10:07

BY MR. LASKER:
Q. Okay. Is your analysis, then, of the epidemiological literature, your conclusions, informed by epidemiological data that has come out subsequent to the IARC working group meeting? 10:07
A. I reviewed the NAPP, yes. 10:08

Q. Okay. And so in reaching your conclusions about the strength of the epidemiology for glyphosate and non-Hodgkin's lymphoma -- strike that.

Let me just circle back. Including your analysis of the glyphosate literature and the NAPP data, do you believe that a positive association has been observed between exposure to Roundup and non-Hodgkin's lymphoma for which a causal interpretation is credible but chance, bias, or confounding could not be ruled out with reasonable confidence? 10:08

MS. FORGIE: Object to form. Asked and answered.

You can answer it again.

THE WITNESS: I believe there's a positive association for which causal association is quite credible.

BY MR. LASKER: 10:08

Q. Do you believe that chance, bias, and confounding can be ruled out with reasonable confidence?

MS. FORGIE: Objection. Asked and answered. 10:09

You can answer it again.

THE WITNESS: Again, I think that a causal association is quite credible, and I, as a scientist who is not just an epidemiologist, put this in context with everything I know, and I agree with IARC that it's a 2A. 10:09

BY MR. LASKER:

Q. My question, though, is with respect to the epidemiologic literature. With respect to the epidemiologic literature for the glyphosate and non-Hodgkin's lymphoma, do you think that chance, bias, or confounding can be ruled out with reasonable confidence? 10:09

MS. FORGIE: Object to form, asked and answered. This is like the tenth time.

You can answer it again.

THE WITNESS: Okay. I think the epidemiology is quite strong. I think that there is enough reason to make causal associations. However, I put this in the context of the animal data and the mechanistic data. As a 10:09

scientist, I cannot split my mind into three different parts, and that's also not what IARC does.

IARC sits in a room and discusses this with everyone and comes to their conclusion overall. However, there's additional data that came out since IARC met, and that strengthens the evidence. 10:10

BY MR. LASKER:

Q. Let's talk about chance. 10:10

MS. FORGIE: If you're at a reasonable breaking point, just let us know.

MR. LASKER: Sure. How long have we been? Over an hour? 10:10

MS. FORGIE: An hour and ten minutes.

MR. LASKER: That'll be fine.

THE VIDEOGRAPHER: We're off the record at 10:10 a.m. 10:10

(Recess taken from 10:10 a.m. to 10:27 a.m.)

THE VIDEOGRAPHER: We are back on the record at 10:27 a.m.

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BY MR. LASKER:

Q. Hello, Dr. Ritz. During the break I was looking through your expert report, and I did not see any mention in your report about any of the animal cancer bioassays regarding glyphosate. Am I correct that there's no mention of those animal cancer bioassays in your expert report? 10:29

MS. FORGIE: Object to the form.

THE WITNESS: Well, they are mentioned, but I am not critiquing them in the way that I would critique an epidemiology study. But I certainly reviewed them. 10:29

BY MR. LASKER: 10:29

Q. Can you point in your expert report where you mentioned any of the animal cancer bioassays?

A. Under biologic plausibility and where I say what I searched. Where is that? 10:29

Q. I think that's your literature review.

A. Literature search, yeah.

Q. Okay. So let's start with the biological plausibility because I read that 10:29

through a number of times. Maybe I missed it. There are some discussions of a handful of genotoxicity studies, and you cite them. But I don't see mentioned anywhere in these two paragraphs of the animal cancer bioassays. Is that correct? 10:30

MS. FORGIE: Object to form.

THE WITNESS: Well, the animal studies I mention on page 25.

BY MR. LASKER: 10:30

Q. Which animal studies?

A. Animal experiments.

Q. With regard to cytotoxic and genotoxic effects. I see that. Where do you mention any animal cancer bioassays? 10:30

A. That says models. Correct. What are you referring to now?

Q. I'm asking if there's any mention anywhere in this section of biological plausibility to an animal cancer bioassay 10:30 because I'm not seeing it.

MS. FORGIE: Object to the form.

THE WITNESS: Well, has been confirmed by laboratory experiments listed above is what I was referring to, 10:31

and the listed above are mentioned in my search algorithm.

BY MR. LASKER:

Q. First of all, the listed above, just so we're clear in the section of 10:31 biological plausibility, is referring to studies of genotoxicity and oxidative stress; correct?

MS. FORGIE: Object to the form.

THE WITNESS: No, that's a compound 10:31 sentence, and what I was referring to here is, one, the oxidative stress and genotoxicity as a mechanism and, two, the lab experiments that also confirmed carcinogenicity. 10:31

BY MR. LASKER:

Q. Can you point anywhere -- first of all, in biological plausibility -- we'll go to your literature search as well, but anywhere in biological plausibility in those 10:32 two paragraphs where you mention an animal cancer bioassay?

A. To me the lab experiments are exactly that. That's what they mean.

Q. You state, "The lab experiments 10:32

listed above," and the lab experiments listed above are dealing with cytotoxic and genotoxic effects.

MS. FORGIE: Wait. Is there a question? 10:32

BY MR. LASKER:

Q. Where is there a reference anywhere in these two paragraphs to an animal cancer bioassay?

A. No, the listed above does not refer 10:32 to the mechanisms. The listed above is in terms of the whole document.

Q. Your whole expert report?

A. Uh-huh.

Q. And you believe that you mentioned 10:32 the animal cancer bioassays in your literature search?

A. Yes.

Q. Let's go to the literature search then. Now, the literature search, just so 10:32 the record is clear is at pages 8 and 9 which is some 16 -- 15 or 16 pages before that sentence in the biological plausibility section; correct?

A. I can't see it right now. Oh, 10:33

here. Yes. Page 8. It starts on page 8.

Q. Where in pages 8 and 9 do you mention animal cancer bioassays?

A. Animal and mechanistic literature. It's on page 9. 550 articles for animal and 10:33 mechanistic literature and 600 citations for cancer. So that includes the oncology of animals.

Q. And the bracket after that says, "Most citations were not immediately 10:33 relevant to the present question due to their focus on topics such as effects in fish resulting from runoff, effects on present pregnancy and child development, or effects on other cancer types." 10:33

Do you see that?

A. Yes.

Q. In your discussion of the literature search, you stated that you were looking to obtain all published studies on 10:33 the relationship between non-Hodgkin's lymphoma and glyphosate; correct?

A. Yes.

Q. And --

A. And ingredients. The active 10:34

ingredient in Roundup. So it included Roundup.

Q. And your statement to then is that this reference to the fact that you conducted a literature search that yielded over 550 articles for animal an mechanistic literature was a disclosure that you had reviewed the animal cancer bioassays and were rendering an opinion on them in this case? 10:34

MS. FORGIE: Object to the form.

THE WITNESS: This disclosure means that yes, everything that's out there in the literature I am willing and able to look at and select from and form my opinion on. That's what I do as a scientist.

Actually as a scientist I often spend Sundays doing exactly this, searching the literature broadly to find animal and other types of studies that then give me an hint in terms of what I'm doing as an epidemiologist, and it's great fun. I like it.

///

BY MR. LASKER:

Q. First of all, is it your understanding that you will be proffering any opinions in this case with respect to animal cancer bioassays? 10:35

MS. FORGIE: Object to the form.

THE WITNESS: Well, my -- what I understand is that I'm here as an expert epidemiologist but also as a scientist. As an expert epidemiologist, I rendered you with my evaluation of the epidemiology. As a scientist I'm curious. I go beyond epidemiology. I look at other types of literature. And I disclosed this here because I was told that I'm supposed to disclose that.

MR. LASKER: Okay. For the record we'll state there is nothing in this expert report that mentions an animal cancer bioassay. There is no disclosure as required under the federal rules of any opinion being proffered on animal cancer bioassays, and unless counsel is here to represent that this witness will not be offering opinions with respect to

animal cancer bioassays, we will petition the court for a second deposition of this witness because we were not prepared to question the witness on those issues because of the expert report she submitted. And we would also move to strike because those opinions have not been properly disclosed.

MS. FORGIE: Well, we're not going to agree to a second deposition, of course. I would say she clearly has stated in there that she has looked at over 550 articles for animal and mechanistic literature. There's another reference in there about the effects in rodents of glyphosate and she's talked about the CARC report and the IARC Monograph all of which, as you well know, do discuss animal literature.

MR. LASKER: Well, to be quite clear, that is not what her expert report is, and the judge will be able to read her expert report; so we don't need to debate that. But my question to

you just so I understand -- we have to have motions practice. Is it plaintiff's intention to proffer Dr. Ritz to offer expert opinions with regard animal cancer bioassays? 10:37

MS. FORGIE: She intends to give her opinion --

MR. WISNER: Objection. Kathryn, you don't have to answer questions in a deposition. Are we off the record? 10:37

MR. LASKER: We are on the record.

MR. WISNER: You can't question attorneys. That's ridiculous. Let's go off the record if you want to ask that question. 10:37

MR. LASKER: I certainly can. If we have to get on record with the court and call the court right now, we can do that as well. I need to know right now because I'd like to move on. If the plaintiffs' counsel are not willing to state on the record that Dr. Ritz will not be offering opinions on animal cancer bioassays, then we'll have an issue with the court including a motion

to strike and a motion for leave to seek additional deposition.
MS. FORGIE: You can bring whatever motions you want. You can bring whatever motions you want. She's made it very, very clear that she has expertise in toxicology. You have a copy of her CV. She's talked about studies and the effects in rodents of glyphosate which for whatever reasons you haven't found. She's talked about the IARC Monograph. She's talked about the CARC report. She's talked about the 550 articles on rodents, and she's talked about the fact that she intends as a scientist in epidemiology to look at the totality of sciences, and that's exactly what's in her report. Make whatever motions you want to make. I'm not going to argue about this with you.
MR. LASKER: Just to be clear, the statements in her report with respect to animals which you want to talk about are specific to genotoxicity and cytotoxicity. They do not mention

cancer bioassays, and the 550 articles that you are referencing are the ones talks she about from her initial search which she excluded.
MS. FORGIE: I'm not going to argue with you.
MR. WISNER: Objection. How are you testifying? What's going on here?
MR. LASKER: We will file a motion with the court as necessary to strike this witness' testimony and also to seek a second deposition.
MS. FORGIE: You do whatever you think is appropriate. She has clearly stated in her expert report that she intends to give full opinions including all kinds of science.
MR. LASKER: We will submit and, in fact, the judge has a full expert report in front of him, and he can look at that himself.
BY MR. LASKER:
Q. Dr. Ritz, in your report you provide a definition of a number of terms that epidemiologists use to try to address

the issue of chance; correct?
A. Uh-huh. There are definitions in there in terms of chance and bias, yes.
Q. We'll get to bias. I want to talk about the terms you identify with respect to chance. You provide definitions of the terms "P-value" I believe on page 11 in your report; correct?
A. It's the -- the title says "Statistical Significance," but the P-value is mentioned.
Q. Okay. And you explain in your expert report -- and we're going to get into some of the issues with this, but epidemiologists at least present P-values in trying to address the issue of whether or not a reported odds ratio or relative risk might be due to chance; correct?
MS. FORGIE: Object to form.
THE WITNESS: Epidemiologists are trained -- modern epidemiologists -- and those are the ones who drive the methods in epidemiology -- are trained to at least rely on one parameter. P-value is one parameter.

BY MR. LASKER:
Q. Okay.
A. So epidemiologists are taught what a P-value is and how to evaluate it, but they're also taught never to use just a P-value to evaluate a study or chance.
Q. And that's what I'm going to be getting to right now in my next questions. You mention in your report at pages 11 to 12 that the -- there is a convention of using a P-value of less than .05, but some studies will use P-values such as less than .01 or P less than negative 10 to 7 which is one in 10 million; right?
MS. FORGIE: Object to the form.
THE WITNESS: So what is the question?
BY MR. LASKER:
Q. It is correct that epidemiologists in various studies will use different P-values including P less than .05 but sometimes P less than .01 or P less than 10 to negative 7; correct?
MS. FORGIE: Object to the form.
THE WITNESS: These type of

P-values have been defined and used in studies, but a P-value has a very different meaning depending on the type of test you are conducting. For example, there are test of pair-wise comparisons. There are tests of trends. There are tests of heterogeneity. There are many, many testing situations in which we use P-values, and they have a very different meaning. 10:42

BY MR. LASKER:

Q. One of the articles that you use in teaching your epidemiology students about P-values is an article by Charles Poole entitled "Low P-values or Narrow Confidence Intervals: Which are More Durable?" Correct? 10:42

A. Yes, I love that article.

Q. Good. I have some questions about that. This will be Exhibit 19-3. 10:42

(Exhibit Number 19-3 was marked for identification.)

BY MR. LASKER:

Q. In this article, Dr. Poole, as you explain in your report, in your expert 10:43

report, talks about the fact that a P-value -- and this is on page 293, but you've been using this article in your teaching for a long time. I think you probably know better than I do. 10:43

Dr. Poole mentions that a P-value cannot be read as a probability of obtaining a particular result if there is no true association between an exposure and disease; correct? 10:43

A. Where is that?

Q. I may be paraphrasing but hold on a second. Well, let me just ask it from your report because you state this as well. I think it's in here somewhere, but I'm not 10:44 going to find it as quickly. You state in your expert report that a P-value should not be interpreted as a probability that glyphosate -- in this instance, glyphosate causes NHL; correct? 10:44

MS. FORGIE: Object to the form.

THE WITNESS: I would never use a P-value to say anything about causation. A P-value is a parameter, one of many types of parameters we are using in 10:44

evaluating data in order to reach causal conclusions, but it's really just one. It is a knee-jerk reaction in the medical field unfortunately, and that's what this article is all about, to just 10:44 look at P-values and not the data overall to draw conclusions on the validity or reliability of data and come to a conclusion.

And at UCLA we are taught not to do 10:45 that, and we are teaching our students not to do that.

BY MR. LASKER:

Q. And you agree that it is not proper scientific methodology to point to a P-value 10:45 alone as providing evidence that data -- of the data being analyzed substantiates a conclusion of causation?

A. Well, a P-value alone is nothing any epidemiologist worth their salt would 10:45 consider for coming to causal conclusions. What we do is we look at the data overall in the context of the study design, the biases, the size of the study, the effect we are trying to estimate, the effect size. 10:46

So a P-value could be highly statistically significant, and that 10 to the minus 7 is one of those genomic studies have P-values of 10 to the minus 10, and still the effect size is an odds ratio of 10:46 1.03. So that gene contributes 3 percent increase to a disease. Is that meaningful clinically? Can we do something with that? Is that even useful? We need to debate that. But the P-value is the P-value. It's 10:46 10 to the minus 10, and it's huge. Does it point to something? We need a lot of other reasoning to make use of that.

Q. I think one of the things that Dr. -- first of all, let me make sure that 10:46 I'm clear. The -- if a test result -- a test statistic results in a P-value of .05, that does not mean that there's only a 5 percent likelihood that the null value is correct; correct? 10:47

MS. FORGIE: Object to the form.

THE WITNESS: A P-value doesn't refer to a likelihood. That's a likelihood ratio test.

///

BY MR. LASKER:
Q. So where the test on a glyphosate and carcinogenicity, a P statistic of .05 does not mean that there is a 95 percent chance that glyphosate caused the observed cancers; correct? 10:47
A. It means that if you repeat a trial a hundred times, 95 percent of the time you may find a result as large or larger than what you're seeing. 10:47
Q. Okay. But my question was a little bit different. A P-value of .05 in a glyphosate cancer study does not mean that it is 95 percent likely that glyphosate caused the observed cancers; correct? 10:47
MS. FORGIE: Object to the form. Asked and answered.
Go ahead.
THE WITNESS: That was a double negative; so I have to restate this. A 10:48
P-value alone will not be used for causal evaluation, and a P-value of .05 means that if a hundred times I repeat this experiment in the same population, 95 percent of the time I would see a 10:48

result as large or larger than what I've seen.
BY MR. LASKER:
Q. But a P-value of .05 does not mean there's a 95 percent likelihood that 10:48
glyphosate caused the observed cancer being analyzed; correct?
MS. FORGIE: Object to the form. Asked and answered.
You can answer it again. 10:48
THE WITNESS: This is not a way I would ever express the meaning of a P-value.
BY MR. LASKER:
Q. And that's because, as I think you 10:48
explained, the P-value does not tell us anything about the study's internal validity in being able to accurately identify a causal association if it exists; correct?
MS. FORGIE: Object to the form. 10:48
THE WITNESS: A P-value is not a measure of validity. A P-value is a measure of randomness or chance.
BY MR. LASKER:
Q. And Dr. Poole explains -- and this 10:49

time I think I do have the quote for you.
MS. FORGIE: What page are you?
MR. LASKER: On page 293.
BY MR. LASKER:
Q. That -- and this is on the left 10:49
column, the second paragraph from the top, that "Statisticians who have examined these questions in detail have found under widely ranging conditions that P-values on the order of .05, .01, and even lower provide 10:49
much less evidence against the null value than they appear to provide at face value." Correct?
A. That's what it states.
Q. And Dr. Poole explains that 10:49
P-values in the vicinity of .05 provide almost no evidence against the null hypothesis at all; correct?
A. It says as a general matter P-values in the vicinity of .05 provide 10:49
almost no evidence against the null hypothesis at all.
Q. And that's what you teach your epidemiology students; correct?
MS. FORGIE: Object to the form. 10:50

THE WITNESS: What I teach my epidemiology students is to take these statements and put them in the context of how we use P-values in epidemiology as one parameter and not the end-all of 10:50
causal reasoning.
BY MR. LASKER:
Q. And you agree with Dr. Poole that a P-value in the vicinity of .05 generally provide almost no evidence against the null 10:50
hypothesis -- well, I put the "generally" in the wrong place. Let me put it exactly how he says it.
You agree with Dr. Poole that as a general matter P-values in the vicinity of 10:50
.05 provide almost no evidence against the null hypothesis at all; correct?
MS. FORGIE: Objection. Asked and answered.
You can answer it again. 10:50
THE WITNESS: Well, this sentence is taken out of context. What I interpret him to be saying here is that a threshold of .05 because he continues by talking about a P of .04, which is, 10:50

you know, the next from .05, that keeping decision-making at a threshold of .05 is a pretty ridiculous experiment -- way of arguing.

What you really want to do is look at the P-value distribution, and that's what this sentence refers to that, you know, thresholds are thresholds. Whatever evidence you think you can draw out of them, why this threshold and not the next? So we should look at distributions and not thresholds. 10:51

BY MR. LASKER:

Q. In fact, the next sentence that you refer to, Dr. Poole states that a P-value of .04, for instance, is typically found to be almost equally probable under the null and alternative hypotheses; correct? 10:51

A. Correct. That's what it states.

Q. And you agree with that; correct? 10:51

A. It refers to the structure of a P-value being a distribution -- coming from a distribution, but we are deciding arbitrarily what threshold to use, yes.

Q. And you agree that P-values of .04 10:52

are typically found to be almost equally probable under the null and alternative hypotheses; correct?

MS. FORGIE: Object to the form.

THE WITNESS: Again, this is taken out of context. This can be misunderstood. Since this sentence is taken out of context, what I think he's referring to is the misuse of thresholds such as .05. And what he's trying to argue here is that there's no real difference between a P-value of .05 and a P-value of .04 or a P-value of .06. It's just that we as a scientific community or the medical community has agreed that P .05 is it. That does not necessarily make sense if you want to look at data in a much more comprehensive way, you should look at a P-value distribution, and the P-value has a continuum. 10:52 10:52 10:53

And insofar as we're trying to have a scientific dialogue, we should use the most data we can and not just the threshold for decision-making. Human 10:53

lives are not light bulbs. P-values of .05 come out of light-bulb testing that statisticians used -- right -- in industrial settings. And why it's a simple matter. We like to think without having to go back to all the data, and that's a bad habit, and we are trying to teach our students not to get into those bad habits. 10:53

THE REPORTER: Counsel, excuse me. I just had a technical difficulty. I need to go off and restart very quickly. 10:53

MR. LASKER: Okay.

THE VIDEOGRAPHER: We're off the record at 10:52 a.m. This marks the end of videotape number 1. 10:53

(Recess taken from 10:52 a.m. to 10:57 a.m.)

THE VIDEOGRAPHER: We are back on the record. The time is 10:57 a.m. This marks the beginning of videotape number 2 in the deposition of Dr. Beate Ritz. 10:57

BY MR. LASKER:

Q. Dr. Ritz, going back to the Poole 10:57

paper that you use in teaching your epidemiologic students, I'd like to return to this sentence that Dr. Poole has in his article that P equals .04 is typically found to be almost equally probable under the null and alternative hypothesis. 10:57

Do you see that?

A. Yes.

Q. And so in our circumstance, in this case, the null hypothesis is that glyphosate does not cause non-Hodgkin's lymphoma, and the alternate hypothesis would be that glyphosate does cause non-Hodgkin's lymphoma; correct? 10:57

MS. FORGIE: Object to the form. 10:57

THE WITNESS: Actually, there's usually more than one alternate hypothesis. So the alternate hypothesis could be it is tenfold more probable to suffer from non-Hodgkin's lymphoma. It's twofold more probable. So these are all parameter estimates of an effect size, meaning the alternative is not just one alternative. The alternative is a continuum. 10:58 10:58

That's what I tried to explain an hour ago when I said why we are usually going with the null hypothesis is because that is one point while alternative hypotheses are many fold. 10:58

BY MR. LASKER:

Q. Understood.

What Dr. Poole is stating then is that a P-value of .04 would be almost equally probable under the null hypothesis 10:58 here that glyphosate doesn't cause non-Hodgkin's lymphoma and the alternative hypotheses of various possible measures in which glyphosate does cause non-Hodgkin's lymphoma; correct? 10:58

MS. FORGIE: Object to the form.

THE WITNESS: Well, what he's trying to say here, as I interpret this, is that he is emphasizing that we should not be using one P-value of .04 or .05 10:59 or .06, but we should be evaluating the data, and that's how I teach it, in terms of what the overall picture in terms of chance, bias, et cetera, is, and if we are just talking P-values, 10:59

what the picture is in terms of a P-value distribution and you can actually find that in Dr. Greenland's book where he discusses on the P-value is the P-value distribution as an 10:59 alternate to this threshold kind of experiment.

BY MR. LASKER:

Q. When you use that distribution, you find that a P-value of .05 generally 10:59 provides almost no evidence against the null hypothesis; correct?

MS. FORGIE: Object to the form.

THE WITNESS: No, that's not the right interpretation. It means it's 11:00 almost equally probable. It doesn't say that I'm rejecting or not rejecting either the null or the alternative hypothesis.

BY MR. LASKER: 11:00

Q. Understood.

Okay. So then if you have a P equals -- and to use Dr. Poole's specific quote here -- if you have a P equals .04 then in a study, you will find it is equally 11:00

probable that here glyphosate, in fact, caused the cancer or that glyphosate did not cause the cancer; correct?

MS. FORGIE: Object to the form. Mischaracterizes, asked and answered. 11:00

THE WITNESS: The P-value here says nothing about glyphosate. What he says here is that a P of .04 is typically found to be almost equally probable under a null alternative hypothesis. He 11:00 speaks about a P-value, not about a null hypothesis that glyphosate is or isn't causing NHL.

BY MR. LASKER:

Q. I understand that. We can take it 11:00 from both steps, but we want to discuss the fact that -- and I think you mentioned this before -- in the context of this case, the null hypothesis that we're looking at is whether or not glyphosate causes 11:01 non-Hodgkin's lymphoma?

A. And what I would be --

MS. FORGIE: Wait, wait. There's no question.

///

BY MR. LASKER:

Q. So the null hypothesis would be the glyphosate does not cause non-Hodgkin's lymphoma here, and the alternative hypothesis might be a variety of other 11:01 things with respect to the nature of glyphosate's association with non-Hodgkin's lymphoma.

What I'd like to understand here, and I think I'm reading this as it's stated 11:01 here, but if that is our understanding of the null hypothesis here, a P-value of .04 would typically be found to be almost equally probable under that null hypothesis or under an alternative causation 11:01 hypothesis; correct?

MS. FORGIE: Object to the form. Asked and answered.

And you can answer it again.

THE WITNESS: This is about the 11:02 P-value. It's about threshold. It's about null hypotheses and alternative hypotheses. It's not about how I assess causation.

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BY MR. LASKER:
Q. I'm not saying it is. I'm just trying to understand P-values, and I think it's consistent with what you said, but a P-value of .04 in the context of a glyphosate study or glyphosate cancer study you could be equally likely to find that P-value if glyphosate actually was a cause of cancer or if glyphosate was not a cause of the cancer; correct? 11:02
MS. FORGIE: Object to the form. Asked and answered.
You can answer it again.
THE WITNESS: No. It means you have to state your null hypothesis or you have to state your alternative hypothesis. Under those hypotheses, you are able to calculate a P-value. If it is .04, then it might be equally probable under both types of hypotheses. That what this means. 11:02
BY MR. LASKER:
Q. Okay. So if you were to do a test, and you were testing the null hypothesis of whether glyphosate causes cancer and you get 11:03

a P-value of .04, what Dr. Poole is stating is that that result would be equally likely if, in fact, the glyphosate had caused those cancers or the glyphosate had not caused those cancers? 11:03
MS. FORGIE: Object to the form. Asked and answered.
You can answer it again.
THE WITNESS: No, that's not how I would interpret this. 11:03
BY MR. LASKER:
Q. If you're doing a test in which the null hypothesis is glyphosate does not cause cancer and the alternative hypothesis is that glyphosate does cause cancer and you get a P-value of .04, that would make the null hypothesis and the alternative hypothesis equally likely; correct? 11:03
MS. FORGIE: Object to the form. Asked and answered. 11:03
You can answer it again.
This is like the fifth time on the same question, Eric.
THE WITNESS: Again, the P-value of .04 that he refers to here is the 11:03

threshold P-value, and he calls this threshold P-value equally probable under the null and alternative hypotheses. We have to state all these hypotheses. We then can calculate P-values. 11:04
We can calculate P-value distributions, and we can see how likely the P-values are, not the associations, not the causation, not everything else.
BY MR. LASKER: 11:04
Q. And the P-value is equally likely under the null and the alternative hypothesis; correct?
MS. FORGIE: Object to the form. Asked and answered. This is like the eighth time. 11:04
You can answer it again.
THE WITNESS: Again, as I understand what Dr. Poole is trying to say here is to avoid thresholds such as P-values of .04 because they are always referring to one type of hypothesis, and we are rarely ever asking the other alternative hypotheses. So we are usually just testing one hypothesis. We 11:04 11:05

could, of course, then decide to also test other hypotheses, and we could get for or against those hypotheses with a similar equal chance of P-value of .04. That's what it says. 11:05
BY MR. LASKER:
Q. Dr. Poole also notes that one upshot of this work has been a statistical research program devoted to calibrating, standardizing, conditioning, and adjusting low P-values to make them higher so that they reflect more realistically the limited statistical evidence they provide against null hypothesis; correct? 11:05
MS. FORGIE: Object to the form. That's misread. 11:05
But you can answer.
THE WITNESS: He's referring to Bayesian methods being developed here, yes. 11:05
BY MR. LASKER:
Q. And you agree that's appropriate; correct?
A. I'm not a Bayesian.
Q. So you don't know one way or the 11:05

other?
MS. FORGIE: Object to the form.
THE WITNESS: No. I'm saying that Bayesian versus frequentist statisticians have a lot of things in common, and I would not want to be on one side or the other. I think they're useful for different purposes.
BY MR. LASKER:
Q. You do agree, though, that statistical methods devoted to calibrating, standardizing, conditioning, and adjusting low P-values to make them higher so that they reflect more realistically the limited statistical evidence they provide against a null hypothesis is a good idea?
MS. FORGIE: Objection. Asked and answered.
You can answer it again.
THE WITNESS: I'm saying I'm not of either statistical camp, frequentist or Bayesian. I believe that they are both useful. They have appropriate purposes and when needed, I use either one of them, and what he says here is that

there are developments in statistics that, you know, we should be looking out for, and this is 2001. So some of these might have happened.
BY MR. LASKER:
Q. You also talk about confidence intervals in your expert report; correct?
A. Correct.
Q. And, again, the standard methodology or the standard measure used by epidemiologists to exclude chance using confidence intervals is the 95 percent confidence interval; correct?
MS. FORGIE: Object to the form.
THE WITNESS: The 95 percent confidence interval is a convention just like the P-value of .05.
BY MR. LASKER:
Q. Under that convention, a confidence interval is considered statistically significant if it excludes the null hypothesis of 1.0; correct?
A. The confidence interval projects similar types of data as the P-value in this case. You are correct that if a P-value of

.05 is what I'm looking for, then a 95 percent confidence interval would exclude the 1.
Q. And, again, you would not state that a statistical significance -- if a test is significant at the 95 percent confidence interval, that would not mean to you that you can have 95 percent confidence that the value that you see in a given study is not due to chance; correct?
MS. FORGIE: Object to the form.
THE WITNESS: That's not how we interpret confidence intervals. Confidence intervals have similar information but also more information than a P-value. So I have to first decide on the confidence limit, which is 95 percent, which is also similar to a P-value of .05.
So if I use a confidence interval in the same bad manner as a P-value, meaning as a threshold, then that's all I get out of it. However, I teach my students that a confidence interval actually tells them a lot more than what

a P-value would. A singular threshold P-value, not a P-value distribution.
BY MR. LASKER:
Q. One thing you teach your students to look at is what's called the confidence limit ratio; correct?
A. Yes, we can look at that as well.
Q. And the confidence limit ratio is the ratio between the upper and the lower end of the confidence interval; correct?
A. Correct.
Q. So if we have a study that reports an odds ratio of 1.5 and, let's say, a confidence interval of 0.8 to 3.2 -- do the; math work well -- the confidence limit ratio would be 4' correct?
MS. FORGIE: Object to the form.
THE WITNESS: What would the ratio be.
BY MR. LASKER:
Q. If it's a 95 percent confidence level of 0.8 to 3.2, then your confidence limit ratio is 3.2 divided by 0.8 or 4; correct?
A. Right.

Q. You can use the CLR -- we'll call it CLR for confidence limit ratio -- you can use the CLR calculation to compare the power after the fact of different studies to exclude chance as the explanation of a potential association; correct?

MS. FORGIE: Object to the form.

THE WITNESS: Well, this is just one way of looking at confidence intervals again. So what actually Dr. Poole does when he shows his Table 1 is that he -- that's what I teach my students is that you should not use any one of these parameters whether it's a relative risk, a 95 percent confidence interval, a P-value, or a 95 percent CLR as just one piece of information to decide anything.

You should use each piece of that puzzle to put it -- and put them together and evaluate the data appropriately within that context. And these are one, two, three, four types of ways of doing that.

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BY MR. LASKER:

Q. Right. I understand that.

But with respect to the CLR, the CLR calculation allows you to compare the power of the different studies to either exclude or not exclude a potential causal association; correct?

MS. FORGIE: Object to the form and asked and answered.

You can answer it again.

THE WITNESS: Actually, it doesn't really because the CLR, as we have just done here. As an example, you are dividing an upper limit above one by a lower limit, the low one. So that ratio alone doesn't tell you anything about whether the P-value actually would be above or below a threshold.

So his example here is when you see the last one, part D, that a relatively narrow confidence limit ratio then reflects a P-value that under conventional statistics would not be considered significant; however, the CLR tells you you have a fairly nice

confidence interval width.

BY MR. LASKER:

Q. Right. I'm just trying to understand what that means. I recognize it's not going to tell you about statistical significance.

My understanding of a CLR was that it would give you some indication of the power of the study to find or not find an effect; is that correct?

MS. FORGIE: Object to the form. Asked and answered.

You can answer it again.

THE WITNESS: Again, it is one way of looking at the confidence interval widths. That's all it is. However, confidence intervals can and cannot include the null value. They can be close to the null value. They can be far away from the null value. They can be very wide but very far from the null value, and anybody would then jump and say that's a study that proves. Okay.

So each part of that equation of parameters cannot be taken out of

context. What I'm trying to teach my students is use everything, every bit of information you can get. Calculate all of these values. Look at them with an informed mind and don't exclude one in favor of the other.

BY MR. LASKER:

Q. Can we go to the 2010 PowerPoint.

MS. FORGIE: Are we putting 19-3 aside?

MR. LASKER: We can just keep it. We might refer back to it.

MS. FORGIE: Okay. Thank you.

(Exhibit Number 19-4 was marked for identification.)

BY MR. LASKER:

Q. Dr. Ritz, I'm not sure if you remember --

MS. FORGIE: Is this 4?

THE REPORTER: 4.

MR. LASKER: 19-4.

BY MR. LASKER:

Q. Dr. Ritz, these are PowerPoint slides of yours we found on the internet. One of the slide decks that you use in your

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lectures, at least this was in 2010; correct?
A. I imagine. If nobody played with it.
MS. FORGIE: I don't know about that. 11:13
BY MR. LASKER:
Q. On pages 123 -- actually, 124 and 125. The one thing we did do is we put numbers on these slides. So it's actually in the bottom right-hand corner. It's the only change we made; so we can actually do this in a somewhat efficient manner. 11:14
MS. FORGIE: What number again on what page? 11:14
MR. LASKER: 124 and 125. This is the same slide actually that appears in Dr. Poole's article.
BY MR. LASKER:
Q. On page 125, you make the point that the estimates with a smaller CLR -- here it's B and D -- mean the width of the confidence intervals is tighter -- are findings that stand the best chance of holding up in the context of existing and 11:14

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future research; correct?
MS. FORGIE: Object to the form.
THE WITNESS: Conditional on their validity.
BY MR. LASKER: 11:14
Q. Correct.
A. Uh-huh.
Q. And those studies with the tighter confidence limit ratio would weigh more heavily into a meta-analysis; correct? 11:15
MS. FORGIE: Object to the form.
THE WITNESS: Not necessarily. It depends on the study size. So we could have -- it depends.
BY MR. LASKER: 11:15
Q. Okay. In your lecture notes to your class, you state that "Estimates B and D would weigh more heavily into meta-analysis and would exert stronger influences on probability distributions in properly conducted Bayesian analyses"; correct? 11:15
A. Yes.
Q. And that is correct; right?
A. Yes, that is correct. 11:15

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Q. And you also state that these estimates with the more narrow CLR are the results that should be put forth for emphasis as the most statistically stable results that this study has to offer; correct? 11:15
MS. FORGIE: Object to the form.
THE WITNESS: What was the question? That I state this?
BY MR. LASKER: 11:15
Q. You state that these estimates B and D with the more narrow CLR are the results that should be put forth for emphasis as the most statistically stable results this study has to offer; correct? 11:16
MS. FORGIE: Object to the form.
THE WITNESS: Actually, it doesn't refer to the CLR. It refers to the whole of the data provided under B and D. 11:16
BY MR. LASKER:
Q. Okay. And the data with a narrower CLR, one of the points you're making here is that even though, for example, your category C is statistically significant to the P, it 11:16

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was .02 level, because it has a wider CLR than, for example, number D or letter D, which is not statistically significant, it is -- has less chance of holding up conditioned on its validity in the context of existing and future research; correct? 11:17
MS. FORGIE: Object to the form.
THE WITNESS: Indeed that is one thing I try to explain to my students to not rely just on the P-value, P less than .05, which in the C row, we see is the case, but we also have a wide CLR, and we have a very strong point estimate and a wide confidence interval. 11:17
So when you're taking all of that into consideration, then the estimate D would be at least, if not more, valid, might prove more valid in the end or more reproducible in the end than the estimate C. However, you know, all this depends on validity, as I said. 11:17
BY MR. LASKER:
Q. Okay. And you state in your expert report -- and it's on page 12 in your expert report -- that -- the last sentence of the 11:18

first full paragraph that starts "Importantly, however."
A. Which page?
Q. Page 12.
A. Yes. 11:18
Q. And you state that "The odds ratios or the risk ratios least likely to be influenced by chance are not those with low P-values, but those with narrow confidence intervals or low CLRs." Correct? 11:18
MS. FORGIE: Object to the form.
THE WITNESS: Where was that?
BY MR. LASKER:
Q. The last sentence of the second paragraph. 11:18
A. "Importantly, estimates least influenced by chance are not those with low P-values but those with narrow confidence intervals."
Q. That's correct; right? 11:18
A. In the context of this, yes.
Q. Okay. And when we talk about narrow confidence intervals, the measurement that you provided for us that I'd like to be able to use is the CLR; correct? 11:19

MS. FORGIE: Object to the form.
BY MR. LASKER:
Q. That's a measurement of the width of the confidence interval?
A. It's a measurement of the width of 11:19
the confidence interval; however, the CLR does not tell you anything about the placement of the confidence interval.
Q. Understood.
MS. FORGIE: Wait. Let her finish. 11:19
THE WITNESS: What I've been trying to say is we should not rely solely on a P-value especially a P-value threshold or a confidence interval or a CLR or a point estimate. 11:19
So don't be fooled by a high point estimate but a confidence interval that goes from .5 to 200 because that data is pretty much uninformative.
BY MR. LASKER: 11:19
Q. Now, on page -- in your expert report on page 15, you provide a table listing of different publications with epidemiological data in glyphosate and non-Hodgkin's lymphoma; correct? 11:20

A. Where is this?
Q. Page 15 in your report.
A. Yes.
Q. And just so it's clear, this table does not tell you or does not provide you 11:20
with a -- the relative -- a sense of the relative power of the listed studies to identify a causal association between glyphosate and non-Hodgkin's lymphoma; correct? 11:20
A. This table shows what it says in the sentence above. "I show the sample size of each human study of glyphosate in NHL." That's exactly it. It shows the sample size. 11:20
Q. Okay. This table did not tell you -- did not tell you which of these studies is the most powerful study in being able to assess an association between glyphosate and non-Hodgkin's lymphoma; 11:20
correct?
MS. FORGIE: Objection. Asked and answered. That's the exact question you just asked.
You can answer it again. 11:21

THE WITNESS: Well, powerful has many meanings. If we're talking about statistically powerful versus powerful in a sense of validity, then, you know, those are different discussions. 11:21
BY MR. LASKER:
Q. This table does not tell us anything about which study is the most statistically powerful in determining whether there is a causal relationship 11:21
between glyphosate and non-Hodgkin's lymphoma; correct?
MS. FORGIE: Objection. Asked and answered. This is the third time.
You can answer it again. 11:21
THE WITNESS: This table was meant to show sample size.
BY MR. LASKER:
Q. It does not tell you anything about the power of the study to determine a causal 11:21
association between glyphosate and non-Hodgkin's lymphoma; correct?
MS. FORGIE: Objection. Asked and answered. This is the fourth time.
THE WITNESS: Wrong. Sample size 11:21

is one element of the power of a study.
BY MR. LASKER:
Q. Okay. The top listed study on your table is the Cocco study 2013; correct?
A. Yes. 11:21
Q. And the Cocco study is the least powerful of all the epidemiologic studies to be able to assess the association between glyphosate and non-Hodgkin's lymphoma; correct? 11:22
MS. FORGIE: Object to the form.
THE WITNESS: This table shows sample size. It has nothing to do with statistical power in the sense that it's a complete evaluation of statistical 11:22 power. However, sample size is part of what we use in calculating statistical power.
BY MR. LASKER:
Q. My question, though, you have Cocco 11:22 listed as the top study on this table, and the Cocco study is, in fact, the least powerful study in assessing a potential causal association between glyphosate and non-Hodgkin's lymphoma; correct? 11:22

MS. FORGIE: Objection. I object to the form, and asked and answered.
THE WITNESS: You don't like my table?
BY MR. LASKER: 11:22
Q. I'm just asking you a question.
A. The Cocco study is what the Cocco study is, and I actually explain the Cocco study a few pages later. The study by Cocco was limited in how much we can glean from 11:22 its results as only four cases and two controls had ever used glyphosate.
Q. So the Cocco study is, because of that fact, not powerful in assessing an association between glyphosate and 11:23 non-Hodgkin's lymphoma; correct?
MS. FORGIE: Object to the form and asked and answered. This is, like, the fifth or sixth time.
You can answer it again. 11:23
THE WITNESS: The Cocco study has been evaluated by me. It's also been listed in this table. This table shows sample size. The Cocco study is definitely the largest study we have in 11:23

terms of sample size of cases, not controls. The AHS has a lot more controls. So in terms of case number, it is the most -- it is the study with the most cases. However, as I said a 11:23 few pages after on page 18, it is limited because of low exposure prevalence.
BY MR. LASKER:
Q. And just so I understand, the Cocco 11:23 study is the, I believe, least powerful study in being able to answer the question of whether glyphosate is causally associated with non-Hodgkin's lymphoma; correct?
MS. FORGIE: Object to the form. 11:24
Asked and answered. This is number six.
You can answer it again.
THE WITNESS: The Cocco study has a large sample size in terms of cases. The AHS study has the largest sample 11:24 size in terms of controls. One is at the top; the other is at the bottom. We could turn it around if you'd like. However, power, statistical power is determined by a number of parameters. 11:24

One of those is the number of cases. The other is the number of controls. Yet another is the prevalence of exposure, and then power cannot be distinguished on a playing field without 11:24 saying what effect size you actually want to estimate. So once we have agreed what the effect size is, then we can talk about power.
BY MR. LASKER: 11:24
Q. It would not be appropriate for somebody to look at this table on page 15 and conclude that the Cocco study was more powerful than the De Roos study with respect to assessing whether there is an association 11:25 between glyphosate and non-Hodgkin's lymphoma; is that fair?
MS. FORGIE: Object to the form and asked and answered.
THE WITNESS: Again, if we're 11:25 talking statistical power and not validity of the study, which, you know, is another criterion that I would put actually much higher here, the Cocco study has the most cases. The De Roos 11:25

study has the most controls. Both are powerful because of that part of the equation that goes into a power analysis. However, there are more parameters than the number of cases, the number of controls. One of them is exposure prevalence. I explain that when I talk about the Cocco study as not being able to tell us much because it has low exposure prevalence. On the other hand, De Roos has a very high exposure prevalence. 11:25 11:25

BY MR. LASKER:

Q. Dr. --

MS. FORGIE: Wait. Let her finish. 11:26

MR. LASKER: We're going to be here all day, and I'm going to have to mark this and go to the judge because I can't get a yes or no answer to any question I ask. I asked a very simple question, and she's going into a monologue. We're not going to have that happen here. So if the witness is not going to answer the questions, then we'll have to go to the court again to either get 11:26 11:26

instruction for the witness to answer the questions or to provide us more time. I ask yes or no questions and I get a speech.

MS. FORGIE: You know, first of all, part of the problem is you keep putting these long declaratory statements before everything. She is not required to give a yes or no answer. She has answered it very clearly -- 11:26 11:26

MR. LASKER: You're not the witness.

MS. FORGIE: Let me finish.

MR. LASKER: You're not the witness. 11:26

MS. FORGIE: Neither are you. So, you know what? If you want to call the judge, I think you should go ahead.

MR. LASKER: Okay. Well, we're going to start marking these and at a certain point we'll go -- let me mark the last question and answer. I'm going to ask the question again. 11:26

MS. FORGIE: Are you going to call the judge? 11:26

MR. LASKER: I will eventually if this keeps up. I'm going to mark them and we'll come back to the judge if we have to.

BY MR. LASKER: 11:26

Q. Table 15, the table you present on page 15 of your report. It would not be appropriate to look at this table alone to reach a conclusion as to the relative power of the listed studies to determine whether glyphosate is associated with non-Hodgkin's lymphoma; correct? 11:27

MS. FORGIE: Object to the form. Asked and answered. This is like number 7. 11:27

You can answer it again.

THE WITNESS: This is a table that refers to sample size. Sample size is part of statistical power.

BY MR. LASKER: 11:27

Q. It would not be --

A. So --

MS. FORGIE: She is entitled to finish.

THE WITNESS: It is appropriate to 11:27

show parts of statistical power, but, of course, I would not want to infer statistical power from just this table. But it is part of it.

BY MR. LASKER: 11:27

Q. And another way one could look at this would be to calculate the CLRs for each of these studies; correct?

MS. FORGIE: Object to the form.

BY MR. LASKER: 11:27

Q. For the endpoint of Roundup and non-Hodgkin's lymphoma?

A. CLRs is something that we calculate after we have the data and the parameter estimates. 11:28

Q. Right. And we have the data and the parameter estimates for each of these studies; correct?

A. Yeah, but that is not how we're calculating statistical power. Statistical power is something that we are calculating prior to conducting the study. 11:28

Q. Understood. So now it's after the fact we have the data. We could actually calculate a CLR for each of these studies; 11:28

correct?
A. If we can agree on which results to use and, yeah, we can do that.
Q. Have you done that exercise?
A. In my head. 11:28
Q. With respect to -- let's move on. The interpretation of confidence intervals in observational studies requires the assumption of no bias; correct?
MS. FORGIE: Object to the form. 11:28
THE WITNESS: It is correct that confidence intervals and observational studies do not include -- are not estimates of bias.
BY MR. LASKER: 11:29
Q. So the interpretation of confidence interval and observational studies requires the assumption of no bias; correct?
MS. FORGIE: Object to the form. Asked and answered. 11:29
You can answer it again.
THE WITNESS: We make assumptions when interpreting confidence intervals of observational studies, and one of the assumptions is no other biases, yes. 11:29

BY MR. LASKER:
Q. In other words, even if a study reports a positive association and reports a 95 percent confidence interval that excludes 1.0, that study cannot be interpreted as 11:29 evidence of a causal association if there is bias in the study; correct?
MS. FORGIE: Object to the form.
THE WITNESS: It depends on the kind of bias, the size of bias. We are 11:29 talking about bias as a category. We at UCLA try to teach bias in terms of quantitative and so the bias can be so minimal that it's not to be a concern.
BY MR. LASKER: 11:30
Q. One type of bias that you identify in your expert report is recall bias; correct?
A. Yes.
Q. And you also teach your students 11:30 about recall bias, your epidemiology students; correct?
A. Correct.
Q. Let's get the 2017 slide deck on informational bias. 11:30

(Exhibit Number 19-5 was marked for identification.)
BY MR. LASKER:
Q. And, Dr. Ritz, I've handed you as Exhibit 19-5, I believe this is a slide deck 11:31 that you used either last year or you're using currently with your epi 200 B students; correct?
A. I don't know. I haven't reviewed it. It looks like it. 11:31
Q. This is a document I'll represent that you produced in response to our --
A. Oh, okay. Then it must be.
MS. FORGIE: Did you add pages to it? 11:31
MR. LASKER: She's updated.
THE WITNESS: I learn.
BY MR. LASKER:
Q. So at page 61 in your slide deck, you talk about this issue of recall bias. I 11:31 just want to make sure I understand the terminology. So as you explain --
MS. FORGIE: Wait a minute. I don't see page 61.
MR. LASKER: It's actually page 60, 11:31

and then there's no page number on 61.
MS. FORGIE: Right. I don't see the pages.
MR. LASKER: It is the page after 60 which I've called 61 in my simplistic 11:31 way of counting.
BY MR. LASKER:
Q. So you see the slide that has recall bias listed at the top; correct?
A. Correct. 11:32
Q. And recall bias is a form of differential misclassification bias of particular concern in interview-based case control studies; correct?
A. Correct. 11:32
Q. And the issue with recall bias is that cases who are diseased may ruminate about prior exposures and report it more completely than controls; correct?
MS. FORGIE: Object to the form. 11:32
THE WITNESS: It says that that is one way how differential recall can occur.
BY MR. LASKER:
Q. And the other thing that you 11:32

mention and you teach your students is that cases might exaggerate exposure while subjects without the disease under investigation. And I guess there's something missing here. 11:32

A. Yeah. That's why this --

Q. Let me understand this correctly.

A. No, this is an appendix to the class, so it's not edited.

Q. But I think the point -- and let me make sure I'm correct -- the point that without the typo you would be making here is that cases might exaggerate exposure compared to subjects without the disease under investigation; correct? 11:33

A. Yes.

MS. FORGIE: Object to the form.

THE WITNESS: Well, that is one way how differential recall bias can occur and why I'm teaching it is to say that when we do our fieldwork have to avoid that this is going to happen. 11:33

BY MR. LASKER:

Q. And the other issue that you teach your students is that in the case control 11:33

study, controls might not recall exposures since they do not have an incentive to do so; correct?

A. Correct. And, again, that is under the premise that we are doing whatever we can to have everybody recall in the same way. 11:33

Q. A recall bias -- well, recall bias can create another -- there can be another issue with recall bias if a study relies upon next of kin or proxy respondents to provide exposure information; correct? 11:34

MS. FORGIE: Object to the form.

THE WITNESS: That's not -- we can call it recall bias, but it is usually being less informed about the exposure so it's kind of information bias. 11:34

BY MR. LASKER:

Q. As a general matter, exposure data provided by proxies is considered less reliable than exposure information provided by the actual cases and controls; correct? 11:34

MS. FORGIE: Object to the form.

THE WITNESS: That is relative. For example, if it is an exposure that a 11:34

case would not want to report but the wife then tells us, it's actually more reliable. So it really depends on the study.

BY MR. LASKER: 11:34

Q. I'll give you that one. I know that you do this a lot in your work, but with respect to pesticide exposures, as a general matter, exposure data provided by proxies would be considered less reliable than exposure data provided by the cases or controls themselves; correct? 11:35

MS. FORGIE: Object to the form.

THE WITNESS: Again, it depends on the circumstances. For example, if the proxy would be a co-worker, he might be just as able to report the work practices and the type of exposures. If the proxy is a son of the farmer who worked alongside the farmer, he would be very well capable of responding. If it is a wife who never goes out in the fields and doesn't talk to her husband at night at the table -- at the dinner table about what he's been doing all 11:35

day, yes. But if it's a wife who quizzes her husband on how did your day go and what did you do and what are the expenses about these kind of pesticides that I'm seeing on the ledger here because she does the books, she knows very well. 11:35

BY MR. LASKER:

Q. That's why I didn't want to ask in every case because obviously case-by-case can be different. But as a general matter overall, exposure data provided by proxies is considered at least potentially less reliable than exposure data provided by the cases and controls themselves; correct? 11:36

MS. FORGIE: Object to the form and asked and answered.

You can answer it again.

THE WITNESS: Again, it depends. It depends on who the proxy is, how close the proxy is to the individual, how much they communicate, how much they work together, and whether it is actually a proxy who counts while the individual doesn't count, meaning, well, 11:36

we paid so much for all of these pesticides in the last year and the husband doesn't care. He just uses what's there. So sometimes we find in our studies of elderly especially that the wives are much more reliable sources. So you can't really say that it's always the proxy that misreports. 11:36

BY MR. LASKER:

Q. And I understand that. I'm not trying to nail you down on every instance. 11:36

MS. FORGIE: There's no question.

BY MR. LASKER:

Q. But let me -- one of the things you've done, and I've seen this in some of your publications is you can conduct a sensitivity analysis to determine whether or not the inclusion of proxy data affects the results of the study; correct? 11:37

A. Correct. 11:37

Q. And one of the things you're concerned about when you do that analysis is a possibility that the use of a proxy may have introduced some misclassification bias into a study; correct? 11:37

MS. FORGIE: Object to the form.

THE WITNESS: The use of proxies versus the individual themselves may or may not result in information bias, and it may or may not result in differential information bias. So if we are using proxies in cases and controls, then whatever they misreport for cases and controls might be at the same level, and that would be a non-differential misclassification. 11:37 11:38

BY MR. LASKER:

Q. And when you do your sensitivity analysis, you're looking to see whether there's a differential or non-differential including the proxy data; correct? 11:38

MS. FORGIE: Object to the form.

THE WITNESS: Not exactly. If I want to establish the validity of a proxy, I would actually need a gold standard like a record, then interview the case, interview the proxy, and then compare both to the gold standard. 11:38

BY MR. LASKER:

Q. Another type of bias that can arise 11:38

in observational studies is selection bias; correct?

A. Correct.

Q. And case control studies are vulnerable to selection bias and their validity to a large degree hinges on the choice of proper controls; correct? 11:39

MS. FORGIE: Object to the form.

THE WITNESS: It is correct that at -- that there is selection bias in case control studies. There is also selection bias in cohort studies. However, case control studies are usually evaluated more critical in terms of selection bias because we try to avoid it as much as we can. 11:39 11:39

BY MR. LASKER:

Q. And, in fact, in your own publications, you've talked about the fact that this problem of selection bias can be circumvented in the cohort study; correct? 11:39

MS. FORGIE: Object to the form.

THE WITNESS: It's a different kind of selection bias in a cohort study as well as in a case control study. A 11:39

cohort study does not have the kind of selection bias that a case control study has. But it has another type of selection bias that a case control study doesn't have. 11:40

BY MR. LASKER:

Q. And what is that?

A. That's loss to follow-up, differential loss to follow-up.

Q. With respect to loss to follow-up for disease outcome, that is not, as I understand it, correct me if I'm wrong, an issue with the Agricultural Health Study; correct? 11:40

MS. FORGIE: Object to the form. 11:40

THE WITNESS: Not necessarily. The Agricultural Health Study may have selection bias depending on whether or not there's differential loss to follow-up with respect to the exposed and the unexposed. 11:40

BY MR. LASKER:

Q. Okay.

A. So it would depend on what the outcome it is we are talking about. 11:40

Q. The other issue you mention in your expert report is confounding. A confounder is an exposure that is associated both with the exposure of interest and the outcome of interest; correct? 11:41

MS. FORGIE: Object to the form.

THE WITNESS: That is one part of how we define a confounder.

BY MR. LASKER:

Q. So, for example, there was a study a few years back now that reported a positive association between coffee and pancreatic cancer? It's somewhat of a well-known -- 11:41

A. Favorite example. 11:41

Q. And when the investigators looked more closely at that data, they discovered that the reported positive association was actually due to the fact that, if I have this correctly, coffee drinkers were more likely to be smokers and the smoking increased the risk of pancreatic cancer? Do I have that right, or do I have it backwards? 11:41

MS. FORGIE: Object to the form. 11:41

THE WITNESS: That was part of the argument, however, that's not how we are defining confounding. Confounding is an independent risk factor for the outcome that also has an association with the exposure and is not an intermediate in the pathway to disease. 11:41

MS. FORGIE: When you get to a good breaking point.

MR. LASKER: Okay. Let's get through this. 11:41

MS. FORGIE: Thanks.

BY MR. LASKER:

Q. With respect to coffee drinkers and pancreatic cancer, smoking was a confounder; is that correct? 11:42

A. Assuming that smoking really causes pancreatic cancer which I'm not completely sure it's true, but I'm not a pancreatic cancer researcher, and depending on what population we're talking about, for example, there are populations where you have a lot of coffee drinking but no smoking, and there are populations where you have a lot of smoking and no coffee drinking, meaning the 11:42

two are independent.

Assuming that we are in a population where the two are actually dependent and we know that, that coffee drinkers smoke more or vice versa, then that could be defined as a confounder. However, in a cohort study, you can actually assess that. 11:42

Q. In your studies, your epidemiologic studies, you will try to address the possibility of confounding; correct? 11:42

A. Definitely.

MR. LASKER: Why don't we take a break now.

MS. FORGIE: Great. Thank you. 11:43

THE VIDEOGRAPHER: We are off the record at 11:43 a.m.

(Recess taken from 11:43 a.m. to 11:55 a.m.)

THE VIDEOGRAPHER: We are back on the record at 11:55 a.m. 11:55

BY MR. LASKER:

Q. Back on the record.

Dr. Ritz, we were talking about confounding, and I think one of the points 11:55

you made in your report, I think elsewhere, is in analyzing or conducting a study, you'd want to identify as best you can other risk factors for disease that you're studying to be able to see whether or not those are confounders; correct? 11:56

A. It is correct that you're always very worried about confounding no matter what and that you're identifying strong risk factors for the disease that also is associated with exposure. 11:56

In the second step, you have to see whether there are possibly intermediates in the pathway and/or proxies for the exposure, and that's a very important assessment. 11:56

Q. And that can be even more difficult in a situation where you have a disease that has unknown causes; correct? 11:56

MS. FORGIE: Object to the form.

THE WITNESS: It's actually not more or less difficult. A disease that has known causes such as lung cancer, we know that we have to control for smoking, and we may or may not have that data. So that's a very difficult study 11:56

to do if we don't have smoking data.
So difficult in a sense, if I don't have a strong risk factor, then it also cannot be a strong confounder. So I'm actually a little bit out of the woods when there's no risk factor because I can assume that if there was a really strong risk factor, I would know about it. 11:57
So if there was a really strong confounder, I probably would know about it. 11:57
BY MR. LASKER:
Q. You read the deposition of Dr. Blair in this case? 11:57
A. Yes.
Q. Dr. Blair has been studying agricultural exposures and cancer going back probably 40-some-odd years; right?
MS. FORGIE: Object to the form. 11:57
THE WITNESS: I'm not sure, but I know that he's been publishing in the '80s on industrial workers, that he's worked at the NCI and that he was generally also interested in 11:57

agricultural work, and he's a coauthor of some of these early papers.
BY MR. LASKER:
Q. Do you agree with Dr. Blair that there was an association that was found between farming -- farmers and non-Hodgkin's lymphoma that existed prior to the time that glyphosate was on the market? 11:58
MS. FORGIE: Object to the form.
THE WITNESS: Did he say that anywhere in the document? 11:58
BY MR. LASKER:
Q. Yeah. If you want, I can show it to you if you want.
A. Yeah, yeah, please. 11:58
MR. LASKER: We are not going to mark it as an exhibit. It's a transcript.
MS. FORGIE: I think we should mark it. 11:58
MR. LASKER: You want to mark it?
MS. FORGIE: Yeah.
MR. LASKER: Where are we then?
THE REPORTER: 6.
///

(Exhibit Number 19-6 was marked for identification.)
BY MR. LASKER:
Q. On page 80 --
A. Is it the page numbers down here? 11:59
Q. Yeah, the actual --
A. Yeah, okay.
Q. I'm sorry. Page 90. I don't know if you can see the highlighting. And at pages 90, we're talking with Dr. Blair about this issue of an increased or an association between farming and non-Hodgkin's lymphoma dating back to the 1960s. 11:59
Do you see that?
A. Yes. 11:59
Q. And do you agree with Dr. Blair that there was this epidemiological literature pointing to an association between farming and non-Hodgkin's lymphoma dating back to before glyphosate was on the market? 11:59
A. Well, he seems to be saying that. I know those very old studies are very, very broad; so they would ask somebody have you ever farmed, and, you know, find an 12:00

association but, yeah, at the level of that broad types of exposure, it might be the case.
Q. Okay. So with respect to farmers and non-Hodgkin's lymphoma, there is at least something going on that would not be related to glyphosate exposure; correct? 12:00
MS. FORGIE: Object to the form. Asked and answered.
You can answer it again. 12:00
THE WITNESS: I agree that there is a difficulty in assessing exposures that vary over time. So when have we started in agriculture using chemicals? After World War II. Before that, they used arsenicals, et cetera; right? But really manmade chemicals for pest control were introduced during World War II and after World War II and took off in the U.S. in the 1950s. So general exposure to agricultural chemicals dates back to the 1950s. 12:00
Among those chemicals may have been carcinogens. We know that there were waves of chemicals that were being used. 12:01

We started with organic chlorines until we decided that that was a bad idea because they bioaccumulate. And then the organic phosphates got their trial run almost parallel. They were quite acutely toxic; so there were some restrictions on those, and the herbicides, the early ones were 2,4-D.

2,4-D is, for example, a 2B IARC possible human carcinogen. So definitely farmers have been exposed to carcinogens at least since World War II.

BY MR. LASKER:

Q. And you also mentioned earlier that diesel fuel might be associated with non-Hodgkin's lymphoma in farmers; correct?

A. Yes, that has been shown in the AHS. I mean, one study does not make a summer -- one swallow. So we would never just rely on one study, but there's reason to think that certain hematopoietic cancers, possibly also some cancer subtypes of NHL might be related to what is in diesel.

Q. And various types of animal husbandry like chicken farming or certain

types of farming have been, at least in the AHS, associated with non-Hodgkin's lymphoma; correct?

MS. FORGIE: Object to the form.

THE WITNESS: There could be risk factors for Hodgkin's lymphoma, but it has to be reevaluated.

BY MR. LASKER:

Q. For non-Hodgkin's?

A. For non-Hodgkin's lymphoma. However, that doesn't make them a confounder. We now have to also consider whether or not they're related to the exposures.

MS. FORGIE: Wait, let her finish.

MR. LASKER: Understood.

BY MR. LASKER:

Q. So an epidemiologic study, and I think your studies are like this as well, will often report different odds ratios with different levels of adjustment to account for potential confounding; correct?

A. We would try different levels of adjustment for multiple reasons, but the main reason would be to assess confounding.

Q. In your expert report at page 16 -- and this is -- if you have your expert report in front of you, on page 16. In the last paragraph which starts "The IARC working group's monograph on glyphosate."

Do you see that?

A. Yeah.

Q. You state in the second sentence "The most highly adjusted estimates, also known as fully adjusted models, are the estimates that adjust for as many confounding variables as possible such as adjusting for age, sex, race, and also sometimes other pesticide exposures"; correct?

A. Yes.

Q. And then you state that "This is relevant because these fully adjusted models give the reader confidence that the findings are most likely due to glyphosate Roundup exposure instead of other potential causes that act as a confounder"; correct?

A. Correct.

Q. And on page 14 of your report, you present what's called a forest plot of the

various odds ratios or rate ratios in some of the epidemiological studies for glyphosate; correct?

A. You can call it a forest plot. I would just call it a visual representation of results from different studies.

Q. In your visual depiction of the results from different studies, you do not provide or list the most highly adjusted odds ratios or risk ratios from the studies; correct?

A. Not correct. De Roos 2003 is a very highly adjusted for 43 different pesticides.

Q. The most highly adjusted estimate in the De Roos 2003 paper had a report odds ratio of 1.6.

A. No.

MS. FORGIE: Object to the form.

THE WITNESS: Would you show me that?

MS. FORGIE: I don't think there's a question.

THE WITNESS: Yeah, is there a question.

BY MR. LASKER:
Q. There is a question. There are two -- actually, three odds ratios in the De Roos 2003 study.
A. Yes. 12:05
Q. You have reported one of those odds ratios and not the other odds ratio; correct?
A. It's the odds ratio from the logistic regression. 12:05
Q. We'll come back, and we'll circle back to that later when we talk about De Roos 2003, but with respect to the other studies in this paper, for example, in the Eriksson study, you do not provide the most 12:06
highly adjusted odds ratio from the Eriksson study in your chart on page 14; correct?
MS. FORGIE: Object to the form.
THE WITNESS: I would need to see the Eriksson paper because there was a 12:06
multi-varied adjusted odds ratio, and I imagine that we looked at that at some point.
BY MR. LASKER:
Q. Okay. Well, let's pull out the 12:06

Eriksson study right now.
MS. FORGIE: Are we done with these guys?
MR. LASKER: Yeah, for now.
So the Eriksson is -- we'll mark it 12:06
as --
MS. SHIMADO: 7.
(Exhibit Number 19-7 was marked for identification.)
BY MR. LASKER: 12:07
Q. I think you're talking about the multi-variate analysis that's on page 1661 Table 7; correct?
A. Yes.
Q. And the multi-variate odds ratio 12:07
for glyphosate in the Eriksson study is an odds ratio of 1.51 with a confidence interval of 0.77 to 2.94; correct?
MS. FORGIE: Object to the form.
THE WITNESS: Correct. 12:07
BY MR. LASKER:
Q. That is not the odds ratio that you present in your visual depiction on page 14 of your expert report; correct?
A. That is not. 12:07

Q. And if we look at the Hardell study for 1999 -- you have Hardell 2003 listed for hairy cell leukemia. I'm looking at the bottom of your table here.
Do you see that? 12:09
A. Yes.
MR. LASKER: Let's mark Hardell 2002.
(Exhibit Number 19-8 was marked for identification.) 12:09
MS. FORGIE: Are we done with Eriksson?
MR. LASKER: For now. We'll go back to it.
BY MR. LASKER: 12:09
Q. In your visual depiction for Hardell, you're depicting an odds ratio of slightly above 3. That is listed as statistically significant; correct?
MS. FORGIE: Object to the form. 12:09
BY MR. LASKER:
Q. At least as it's depicted on your page 14?
MS. FORGIE: Object to the form.
THE WITNESS: It has a wide 12:09

confidence interval and about 3 from what I see, yes.
BY MR. LASKER:
Q. And if you look at Exhibit 19-8 and you look at page 1047, which is Table 7, 12:09
again, the most adjusted odds ratio in that study is 1.85 with an odds ratio of 0.55 to 6.2; correct?
A. That's what they call them, multi-variate model. 12:10
Q. So again for Hardell, you do not present the most fully adjusted odds ratio according to that study; correct?
MS. FORGIE: Object to the form.
THE WITNESS: For good reasons. 12:10
BY MR. LASKER:
Q. I'm just asking the question in your Table 14 --
A. Yes.
Q. -- for Hardell, you do not present 12:10
the most adjusted -- highly adjusted odds ratio reported by the authors of the study; right?
MS. FORGIE: Object to the form.
Asked and answered. 12:10

You can answer it again.
THE WITNESS: So I'm presenting the odds ratio that I believe has the most validity given what they presented in their paper. 12:10
BY MR. LASKER:
Q. And for the NAPP -- and we'll get to that in a second -- you also have elected in your visual depiction of the study results to report an odds ratio that was not 12:11 adjusted for three pesticides that the NAPP investigators adjusted for in their study; correct?
MS. FORGIE: Object to the form.
THE WITNESS: Again, what I strive 12:11 to do is present odds ratios on confidence interval for what I believe the most valid model is because we're now talking about evaluating the data overall. That does not necessarily mean 12:11 the most fully adjusted model.
BY MR. LASKER:
Q. Just so I understand this, although you state in your expert report that the most highly adjusted estimates reported in 12:11

these studies -- just so we're clear, the -- your comment with respect to the most highly adjusted estimates is specific to the meta-analysis that were conducted of the glyphosate studies; correct? 12:12
MS. FORGIE: Object to the form.
THE WITNESS: It refers to what others considered as their criteria for pulling estimates, not mine, yes.
BY MR. LASKER: 12:12
Q. And you were stating in here that IARC's adjustment or their analysis -- their meta-analysis using these most highly adjusted estimates from the studies was appropriate because it gave the reader 12:12 confidence that the findings are most likely due to glyphosate Roundup exposure instead of another potential cause that acts as a confounder; correct?
A. I'm making no statements about 12:12 appropriateness of these estimates. What I'm saying here is that they did something we call conservative, which is throw the kitchen sink into a model and see what falls out on the other end. 12:12

That is not what I consider the most valid approach.
Q. Okay. The visual depiction that you have of the studies on page 14, you did not -- I mentioned it as a forest plot. You 12:13 weren't --
A. Happy with it.
Q. -- happy with that terminology.
Forest plots, if I understand correctly, are usually depicted on a 12:13 logarithmic scale; correct?
A. Uh-huh.
Q. And the issue with a logarithmic scale, so, for example, in your visual depiction of the Orsi study -- and we can 12:13 look at the actual odds ratios if you want in that study -- but that was a study that had an odds ratio of 1.0 and a lower confidence interval was about 0.5 and the upper confidence interval was about 2.0. 12:13
If you presented that in a forest plot, your line would be about equal distance on both sides of --
A. There --
Q. -- one; correct? 12:14

MS. FORGIE: Wait. Object to the form.
THE WITNESS: There are different ways of depicting results visually, and in a forest plot, you are trying to show 12:14 confidence intervals that are symmetrical, and you can only do that when you use a logarithmic scale.
BY MR. LASKER:
Q. And by using the depiction that you 12:14 use, which is not a logarithmic scale, the visual effect of that is that the confidence intervals will go further out to the right or will appear in this depiction to go further out to the right than if you were 12:14 presenting a forest plot on a logarithmic scale; correct?
MS. FORGIE: Object to the form.
THE WITNESS: That is only the case when you go below 1. As long as you're 12:14 above 1, they are actually symmetric, and you can see that down here Eriksson 2008.
BY MR. LASKER:
Q. Right. 12:14

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But with the -- and we have in this -- in your visual depiction, numerous lines that go below 1 and above 1. When you present it the way that you have in a normal scale as opposed to the way you do it on a forest plot with a logarithmic scale, that has the effect of making those lines extend out further or appear further out to the right than to the left; correct? 12:15

MS. FORGIE: Object to the form and asked and answered. 12:15

You can answer it again.

THE WITNESS: This is not a forest plot. This is just a visualization. I'm giving point estimates and confidence intervals, and the reason for doing this is to have an easy reminder myself, as well as the reader, what the point estimates and the confidence interval widths is. 12:15

It was not to say whether or not it is going more or less beyond the null value, but it clearly indicates when it goes below the null value.

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BY MR. LASKER:

Q. With respect to confounding -- and this is going to be a general question, I think, but epidemiologists use different methods to control for potential confounding; correct? 12:16

A. Yes.

Q. So epidemiologists can control for confounders through model fitting techniques like a regression analysis; correct? 12:16

A. That is one way.

Q. And epidemiologists can also control for confounding by conducting a stratified analysis; correct?

MS. FORGIE: Object to the form. 12:16

THE WITNESS: That is one other way of looking at control for confounding.

BY MR. LASKER:

Q. So in a stratified analysis, an epidemiologist will calculate an odds ratio for subjects with concurrent exposures to two potential risk factors, and then they'll separately calculate the odds ratios for the subjects having only one of those exposures; correct? 12:16

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A. Not necessarily. You can subgroup, but in the end, you want a summary effect estimate that you weigh by the strata. So you're standardizing your estimate according to the weights of the strata in which these individuals fall. 12:17

Q. So in your stratification, for example, you would have if there is current exposures or potential for current exposures, you would have one strata that is exposed only to one of those risk factors, one strata that's exposed to both of those risk factors, and one strata that's exposed to the other risk factor; correct? 12:17

MS. FORGIE: Object to the form. 12:17

THE WITNESS: If you're lucky, you have people in all of those strata, but you have to define the strata, and that's one reason why we use that tool not necessarily when we have better data that's not categorical because, otherwise, within those strata, still have confounding because of categorization. 12:17

So we're trying to use

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multi-variate models rather than stratification.

BY MR. LASKER:

Q. Just so we can agree what -- how this works, let's turn back to 19-4 which is your 2010 slide deck. 12:18

MS. FORGIE: Wait. Let me get it. Okay.

THE WITNESS: Page?

BY MR. LASKER: 12:18

Q. 98. And as you teach your students then, a stratified analysis is a method for controlling for confounders. "We estimate the exposure disease association within categories or strata of the confounders as in the examples given previously or and derive a summary estimate of this association across the strata which often assumes that the association does not vary across strata." Correct? 12:19

A. Correct. That's exactly what I just tried to explain.

Q. In your rebuttal expert report, you state that "Controlling for confounding by other pesticides in the glyphosate NHL 12:19

studies could make it harder to identify an association between glyphosate and NHL."

Do you recall that?

MS. FORGIE: Object to the form.

THE WITNESS: Where do I say that? 12:19

MS. FORGIE: Are we done with 4?

MR. LASKER: For now, yeah. Where are we now?

MS. SHIMADO: 9.

(Exhibit Number 19-9 was marked for identification.) 12:20

BY MR. LASKER:

Q. So pages of 6 and 7, I think and maybe I'm misunderstanding, but I thought what you were stating in pages 6 and 7 of your report is that controlling in the glyphosate NHL studies controlling for confounding by other pesticides can make it harder to identify an association between glyphosate and NHL; correct? 12:20

MS. FORGIE: Object to the form.

THE WITNESS: Well, it depends on what we mean by "make it harder." So what I am trying to say here, what I do remember -- I'm not reading it right 12:20

now -- is that I was trying to identify confounders which is a different concept.

It's the underlying scientific concept behind control for confounding. 12:21

Confounding is something I can assess in data. Confounder is a scientific concept that I need to presume, and that's what we're doing with directed basic little graphs. You saw a lot of 12:21 them in my slides.

And so what that means is we have to convince ourselves that a variable is a confounder, meaning, there's an underlying true association between that 12:21 variable and the outcome as well as that variable and the exposure of interest and that that variable is not just a proxy measure of the exposure that I'm actually trying to evaluate. 12:21

And any kind of proxy measure of the exposure should not be treated as a confounder.

BY MR. LASKER:

Q. I think I was actually looking at 12:22

page 7 where you're talking about this issue of smoking, lung cancer and whether or not radon exposure adds to the background instance of lung cancer. So I think we're talking past each other. 12:22

A. Yeah.

MS. FORGIE: There's no question.

BY MR. LASKER:

Q. We agree in any event.

MS. FORGIE: No, I don't agree that 12:22 we agree. All this smoking stuff is just putting me right off smoking.

BY MR. LASKER:

Q. My question actually goes to the point I think you're trying to make on 12:22 page 7, and maybe I'm misunderstanding it.

But in your example on page 7, you discuss the possibility of another confounder, in this case, I think it's radon, making it more difficult to identify 12:22 an association between an exposure and outcome; correct?

MS. FORGIE: Object to the form.

THE WITNESS: This is really funny in a way because that's exactly what I'm 12:22

trying to teach my students that they should not confuse confounders and effect modifiers. In this case, it's an effect modification and not a confounding. That said, the same factor 12:23 can be an effect modifier and a confounder and/or a proxy. That's why I'm saying confounding is something we do mathematically. We have the data. We throw something in; we take something 12:23 out. But confounder is at the conceptual level. I need to decide is this a confounder? Yes or no? We have our rules for that. Is that a proxy for an exposure and not a confounder, or is 12:23 it acting as an effect measure modifier, and in this case, that was an effect measure modification.

BY MR. LASKER:

Q. So if I understand correctly, 12:23 effect measure modifier in this case is radon?

A. Uh-huh.

MS. FORGIE: Object to the form.

BY MR. LASKER: 12:23

Q. You have to say yes or no, obviously, for the court reporter.
A. Oh, I think that's how I build it. It could be either smoking or radon that I -- but I think it was radon that I called it the effect measure modifier. I'm not saying it, but I think that's correct.
Q. And the reason that in this example radon was an effect measure modifier that could impact the ability to conduct the analysis of smoking and lung cancer was because in your analysis the radon could result in ten extra cases of lung cancer per 100,000 miners; correct?
A. Yes.
Q. And it's the size of that association, if you will, that will determine the extent to which this effect modification could be -- could introduce a problem in conducting your epidemiological analysis; correct?
MS. FORGIE: Object to the form.
THE WITNESS: It is insofar a problem as effect measure modification comes into play when you're comparing

across populations. So you could in one population estimate a relative risk of 2 and another relative risk of 5, and we both would probably agree those are very different numbers. In one population you have an effect modifier present; in another you don't. So it is not that the association was the agent of interest is really different but that the comparison you're making are comparisons to a population at a different risk, baseline risk. And the extent to which the effect modifier could influence the odds ratio that -- of interest in a study will depend on how powerful an effect modification you have; correct.
MS. FORGIE: Object to the form.
BY MR. LASKER:
Q. In other words, let me just reword this. Maybe this would be easier. If the radon exposure added one extra case of lung cancer for 100,000 miners instead of ten extra cases of lung cancer for 100,000, that would have a fairly minimal impact on the

odds ratio that would be reported for smoking and lung cancer; correct?
MS. FORGIE: Object to the form.
THE WITNESS: Fairly minimal is relative, but the number would be smaller.
BY MR. LASKER:
Q. Okay. And in -- and I think you can probably calculate it. It would probably be -- we'd be looking at --
A. 5.05.
MS. FORGIE: There's no question.
BY MR. LASKER:
Q. Instead of -- the 20 out of four, you'd be looking at 31 out of 5 over 5; correct? In that scenario? Or I'm sorry.
MS. FORGIE: No, object to the form.
THE WITNESS: 31 over --
MR. WISNER: 21 over?
MR. LASKER: I think that's right.
MS. FORGIE: What's the question?
BY MR. LASKER:
Q. Instead of 21 over 4 it would be 31 over 5?

MS. FORGIE: Object to the form.
THE WITNESS: Well, 20 over 4 is ignoring radon.
BY MR. LASKER:
Q. Right.
A. So that's the fivefold increased risk due to smoking. So now if radon affects non smokers and smokers in the same way, then we would be adding one case to each.
Q. Right.
A. So we would have 21 over 5.
Q. Okay. 21 over 5?
A. Uh-huh.
Q. So then it would be 4.25 as opposed to 5. It would be a much smaller difference.
MS. FORGIE: Object to the form.
THE WITNESS: 4.25 is pretty big, but there's a difference to 5, yeah.
BY MR. LASKER:
Q. And so to be able to determine or to be -- if the issue is whether other pesticides are effect modifiers in conducting -- in looking at a glyphosate

non-Hodgkin's lymphoma association, one of the issues you can look at is how powerful of an association there is between these other pesticides and non-Hodgkin's lymphoma; correct? 12:28

MS. FORGIE: Object to the form.

THE WITNESS: That is not the only thing I would look at. I would also look at how correlated the exposures are with glyphosate. 12:29

BY MR. LASKER:

Q. But in this instance -- this example is not talking about a correlation?

A. No.

Q. I'm just trying to get the exposure modification aspect of it. 12:29

MS. FORGIE: There's no question.

BY MR. LASKER:

Q. Are we on the same page here?

MS. FORGIE: Objection. 12:29

You're asking if you guys are on the same page?

MR. LASKER: I have to be able to ask the question without you objecting in the middle of it. Let me ask the 12:29

question again.

BY MR. LASKER:

Q. I want to focus on the effect modification point that you're making here, and that does not rely upon any correlation between, in this case, radon and smoking; right? 12:29

MS. FORGIE: Object to the form.

THE WITNESS: This is an example where I'm trying to show in the first part of this example how when you have one risk factor only assessment and you're comparing -- and you're calculating a so-and-so fold risk in the exposed over the unexposed, and you're going to another population where now you have an additional risk factor for the outcome that adds to the baseline risk, and it adds in the same way in the exposed and the unexposed how you would see a different odds at risk or rate ratio. 12:29 12:30

BY MR. LASKER:

Q. And my only point here, I guess -- and my understanding maybe I'm missing it 12:30

was that you were raising the possibility that other pesticide exposures might have an effect modification on glyphosate studies if you're looking at a population that has those other pesticide exposures and that increases the background instance of NHL; is that correct? 12:30

MS. FORGIE: Object to the form.

THE WITNESS: Well, if we agree which pesticides are related to NHL and one population of farmers is exposed to those, then we would presume that those farmers have a larger background rate of NHL. 12:30

BY MR. LASKER: 12:30

Q. Okay. And to be able to assess the extent to which that could create an exposure modification, we would need to consider the strength of that association between the other pesticides and non-Hodgkin's lymphoma; correct? 12:31

MS. FORGIE: Object to the form.

THE WITNESS: No. What we need is enough sample size to then evaluate the effect of glyphosate. 12:31

BY MR. LASKER:

Q. Okay. But if the other pesticide exposures were resulting in one extra case of non-Hodgkin's lymphoma over -- out of a hundred thousand, that would have less of an effect modification than if they were resulting in ten cases of non-Hodgkin's lymphoma out of a hundred thousand; correct? 12:31

MS. FORGIE: Object to the form.

THE WITNESS: That would depend on the correlation of the exposures in this dataset. So the correlation of the pesticides was glyphosate. 12:31

BY MR. LASKER:

Q. And I guess so the effect modification you present on page 7 depends upon the correlation between radon and smoking? 12:31

A. Yes.

Q. Okay. Moving on, we can take a break for lunch now or go on for a little bit longer. 12:32

MS. FORGIE: It's up to you guys. I don't eat; so it doesn't matter to me.

MR. LASKER: Why don't we have 12:32

lunch now. It's a little bit of a short session, but it's probably a good time.

THE VIDEOGRAPHER: We're off the record at 12:32 p.m.

(Recess taken from 12:32 p.m. to 12:33 p.m.) 12:32

THE VIDEOGRAPHER: We are back on the record at 12:33 p.m.

BY MR. LASKER:

Q. Dr. Ritz, let's walk through some of the epidemiologic studies that you discuss in your report. I think the first study you talk about is the Cantor study from 1992. Why don't we mark that. 12:33

(Exhibit Number 19-10 was marked for identification.) 12:33

THE WITNESS: Actually, the Eriksson study that I mentioned first. Doesn't matter.

BY MR. LASKER: 12:34

Q. We'll get to Eriksson as well. 19-10. So the Cantor study reported an odds ratio for glyphosate and non-Hodgkin's lymphoma, and it's on page 2450 in this study in Table 6 of 1.1 with a confidence 12:34

interval of 0.7 to 1.9; correct?

A. Correct.

Q. And the odds ratio was adjusted as indicated in the footnote to the table for vital status, age, sex, smoking, family history of lymphopoietic cancer, high-risk occupations, and high-risk exposures; correct? 12:34

A. Yes.

Q. And as Cantor is defining high-risk exposures, if it meets a certain criteria, those could include exposures to other pesticides; correct? 12:35

A. As far as I remember, but I'm just looking for that definition. 12:35

Q. I think it is page 2448, top of the right-hand column just above "results."

MS. FORGIE: Where did you see it?

MR. LASKER: 2448, top of the right-hand column. 12:35

THE WITNESS: Yeah, it's the odds ratio of 1.5 plus. Is that it?

BY MR. LASKER:

Q. I believe so.

A. Yeah. 12:35

MS. FORGIE: Thank you.

BY MR. LASKER:

Q. Just so the record is clear, in the Cantor study the odds ratio was adjusted for vital status, age, sex, smoking, family history of lymphopoietic cancer, high-risk occupation and high-risk exposures which can include other pesticides; correct? 12:36

A. Other substances it says, but I imagine it's pesticides included. 12:36

Q. And the CLR, if we were to calculate that confidence limit ratio for the glyphosate and non-Hodgkin's lymphoma, is 1.9 to 0.7. So that is slightly below 3.0; correct? 12:36

A. Yeah.

Q. And this is -- and you said you'd done this in your head. I don't know if you recall it in your head, but the CLR for the Cantor study is the smallest CLR for any odds ratio, report odds ratio, where the odds ratio has been adjusted for other pesticide exposures; correct? 12:36

MS. FORGIE: Object to the form.

THE WITNESS: I would need to check 12:37

the other -- De Roos, for example, which includes Cantor. I would imagine that De Roos is at least as powerful as Cantor; so it should actually be shorter. 12:37

BY MR. LASKER:

Q. If you look in your -- and this is an abbreviated short form, but De Roos 2003. You have -- we can get to the actual number if you want, but you have it on -- the number that you used at least has a CLR that is well above 3; correct? 12:37

MS. FORGIE: Object to the form.

THE WITNESS: I wouldn't be able to do that in my head without the numbers right now. I have to guess where this is coming out, and I also need to -- oh, and this is a differently adjusted estimate, plus it's from a larger study. So it doesn't just include Cantor. It also includes the Nebraska and some other study. 12:37 12:38

BY MR. LASKER:

Q. We'll look at the CLR for De Roos when we get there. We can just compare 12:38

them, but I think you stated that you thought the De Roos study might be at least as powerful as the Cantor study. Are there any other case control studies that you believe would be as powerful as the Cantor study, any measuring glyphosate in non-Hodgkin's lymphoma? 12:38

MS. FORGIE: Object to the form.

THE WITNESS: It depends on what the comparison is that I want to do. For example, ever handled is a very bad exposure assessment. So this 1.1 for ever handled I would judge as not very valid because the exposure is probably strongly misclassified non-differentially. 12:38 12:39

BY MR. LASKER:

Q. Except for three of the studies I believe -- let's strike this. Let's strike this. The odds ratio that you present in your expert report on page 14 are for ever/never exposure; correct? 12:39

MS. FORGIE: Object to the form.

THE WITNESS: Page 14? Which one? This? 12:39

BY MR. LASKER:

Q. Yeah.

A. I have to check it whether it's always ever/never. Did I not show any others? No, I guess they would be mostly ever/never. 12:39

Q. Okay. So with respect to that assessment that you have or that measure that you have on page 14 of your expert report, are you aware of -- and I'm going to give you -- talk also, and we'll put it in the NAPP which is a further pooling of the Cantor data and some other data from Canada. But other than that, is there any study that has greater power than Cantor with respect to the ever/never odds ratio for glyphosate-based herbicides in non-Hodgkin's lymphoma? 12:39 12:40

MS. FORGIE: Object to the form.

THE WITNESS: Actually I'm realizing something that I didn't realize before. This table actually says "odds ratios for ever having handled specific herbicides prior to 1965." I thought glyphosate was not 12:40

available prior to 1965.

BY MR. LASKER:

Q. That would be the right column of the table, the left table. Left column is upper. 12:40

A. Oh, okay.

Q. Going back to the question then, other than the subsequent studies that pooled Cantor and included Cantor in the pooling, which would be De Roos 2003 and the NAPP, are you -- are you aware of any study that had a greater power to assess ever/never exposure to glyphosate in non-Hodgkin's lymphoma? 12:41

MS. FORGIE: Object to the form. 12:41

THE WITNESS: I wouldn't be able to tell off my head because I consider ever/never the lowest common denominator across all these studies, and I would hope that we have better measures to assess exposure than ever/never. 12:41

MS. FORGIE: Just so you know, it looks like the lunch is here. I'm not saying we have to break now.

MR. LASKER: We'll probably just 12:41

continue through this.

MS. FORGIE: I agree.

BY MR. LASKER:

Q. And if I understand you correctly, that is because it's your opinion that ever/never analyses are not as informative on whether or not there is an association between glyphosate and non-Hodgkin's lymphoma as measures that try to look at the amount of exposure of glyphosate; correct? 12:41 12:42

MS. FORGIE: Object to the form.

THE WITNESS: An ever/never exposure presumes that any type of exposure I had can be handled in the same way. So somebody looking at a bottle of pesticides and spraying it once gets to be thrown in the same category as somebody applying pesticides on a regular basis in an occupation. And that is the least informative and the most capable of inducing non-differential exposure misclassification by people recalling wrongly. 12:42 12:42

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BY MR. LASKER:
Q. The -- in your expert report you opine, and I think this is at page 17 of your report. I'm sorry. On page 18 of your report. At the bottom of page 18 -- and you were right. This is the bottom of my head. I got it backwards as to which study you were doing first in your report. So bottom of page 18 you're talking about the Cantor study, going over to page 19; correct? 12:43
A. Yes.
Q. And you state that the Cantor study is less informative because the cases are diagnosed with non-Hodgkin's lymphoma between 1980 and 1983 which you state was at most only six to ten years from the first potential glyphosate exposure; correct? 12:43
A. Correct.
Q. And you explain that this would be -- and just so the record is clear, we are talking about here is the concept of latency; correct? 12:44
A. This talks about latency, yes.
Q. And the issue of latency is that you would need to have a certain period of 12:44

time elapse from the time of exposure until the measure of non-Hodgkin's lymphoma for the biological process to take place that would lead to exposure to diagnose disease; correct? 12:44
MS. FORGIE: Object to the form.
THE WITNESS: Latency -- the word "latency" is used in different ways and in epidemiology we are trying to figure out the minimum time between an exposure happening and causing the disease. So in a time-changing exposure and a cumulative or a -- not an exposure like the A bomb that's one time -- right? -- you kind of have to decide when the potential for carcinogenicity has occurred, and from that point of time to when you're actually diagnosing the disease. That may be very different depending on many factors including age of the subject. 12:44 12:45
BY MR. LASKER:
Q. Right. And the point that you're making with respect to Cantor, and I think you state this on page 17 of your report 12:45

about in the middle paragraph -- I'm sorry, in the first paragraph about halfway down, you state that typically we would generally expect a five to ten-year minimum latency between exposure and disease onset for blood system-related cancers; correct? 12:45
A. That's read correctly.
Q. So what that means is even if you have -- let's say if you have a known carcinogen that causes NHL, it would take a minimum of five to ten years from the date of exposure for the regression from cellular insult to result in a diagnosable case of non-Hodgkin's lymphoma; correct? 12:46
MS. FORGIE: Object to the form. 12:46
THE WITNESS: No. I'm using this in terms of epidemiologic latency time which we are estimating was in groups. So we are never estimating for one person. So in one person, it could be happening within a year or two. In another person, it might not be happening until 35 years out. That's why I also refer to age. For example, somebody who is already age 60 and is 12:46 12:46

more susceptible to exposures, that cancer might just happen earlier after exposure than in somebody where the cancer cell is dormant and kept in check by the immune system and other factors for 20 more years. So the latency period is really an average or minimum dependent on what population I'm looking at and whether I allow for that population to age into the time when the cancers would occur. 12:47 12:47
So mostly I would imagine I have higher power in my study when the people are aged into that age when they actually have cancer. 12:47
BY MR. LASKER:
Q. And the concern that you're raising with respect to the Cantor study is that -- well, actually let me just take a step back here. You state -- and I think this is on page 19. You state that one would prefer for NHL cancer epidemiology study, one would prefer a minimum latency period of on average ten years; correct? 12:47
MS. FORGIE: Object to the form. 12:48

THE WITNESS: That's what this says.
BY MR. LASKER:
Q. This is you.
A. Yes, yes, this is what the sentence says. So what I was meaning by this is that a study would be more powerful if we allowed for longer latency because we then would capture more cases due to the exposure. Because if you're only allowing for two years, you would only capture those people who was in those two years come down with the cancer. If you allowing for five years, you can see how that number would increase and then ten years, 20 years out. 12:48 12:48 12:49
So depending on how long we have between the first exposure or the minimum exposure necessary to cause cancer and the events that later occur, the longer the latency, the more chance I have to capture every single case that was actually caused by the exposure because there are these dormant cells. 12:49
Q. Just so I understand also because I think there's a couple things going on, but 12:49

correct me if I'm wrong. One issue is that you want to be measuring the exposures that could have, in fact, resulted in the outcome; correct?
MS. FORGIE: Object to the form. 12:49
THE WITNESS: I'm not sure I understand, but yes, we want to measure exposures as carefully as we can to estimate whether they are causing the outcome. 12:49
BY MR. LASKER:
Q. So, for example, and just take an extreme example, if you were to do an epidemiologic study and you measured an exposure on Tuesday and the individual came -- was diagnosed with non-Hodgkin's lymphoma on Wednesday, whatever the exposure was on Tuesday wouldn't have been a cause of the NHL because there hasn't been a sufficient time that has elapsed for the causal mechanism to take place; correct? 12:50 12:50
A. If I'm assuming that the only exposure the person ever had was on Tuesday.
Q. Right?
A. Yes. 12:50

Q. And one of the issues you're raising in the Cantor study is if you're not looking back sufficiently far in time, then you are not capturing exposures that could have had sufficient time to go through that process whereby they would result in a diagnosable non-Hodgkin's lymphoma; correct? 12:50
MS. FORGIE: Object to the form.
THE WITNESS: So what I'm trying to say here is that exposures have to occur a certain number of, let's say, days, years, months prior to the onset of a cancer before I would think that it is biologically possible or plausible. But that could be a year in a certain circumstance, two years in another, and on average, it might be very different depending on the population I'm looking at. 12:50 12:51
BY MR. LASKER: 12:51
Q. And the point you make here on page 19 is you could have traits that vary but for a study of non-Hodgkin's lymphoma, you'd prefer a minimum latency period of on average ten years to make sure that you are 12:51

capturing the biologically plausible exposures that could account for any reported non-Hodgkin's lymphoma; correct?
MS. FORGIE: Object to the form.
THE WITNESS: That's not correct. That's really not what this says. What this says is that there is an exposure lag time that I would like in order to capture every single case and not just the ones that are the early birds. 12:51 12:52
BY MR. LASKER:
Q. If you have, though, an early bird if you will, one of the issues that you're trying to account for is the possibility that that earlier diagnosed non-Hodgkin's lymphoma would have been related to something that predates any exposure; correct? 12:52
MS. FORGIE: Object to the form.
THE WITNESS: Well, when I have a study that only has a two-year minimum follow-up and no more, then I always have to raise that possibility. That's why I would like a study that has a longer period of time between the 12:52

exposure and the outcome so I can estimate what an average mild latency might be. And if I have a study that only follows for one year, I would probably be concerned. With a study following two years, less, three years, less, et cetera, et cetera. 12:53

BY MR. LASKER:

Q. What you're mentioning here with respect to Cantor is that you have a concern because only six to ten years have elapsed between a potential first glyphosate exposure and an NHL diagnosis; correct? 12:53

A. Well, my concern is not with respect to the biologically relevant latency period but with respect to having really captured all NHLs that might have been caused by the exposure because I presume that, in this case, I only captured the early birds, the people who got their cancer relatively soon after exposure. 12:53

Q. You would have to, though, in determining that those non-Hodgkin's lymphomas that you see are attributable to the exposure, one factor that you would also 12:54

want to consider is whether or not those exposures took place during the time period sufficiently before the diagnosis that you could attribute the exposure to the outcome; correct? Because before you did the study, you don't know there's an association; right? 12:54

MS. FORGIE: Object to the form.

THE WITNESS: Well, it depends on which study I'm conducting, but before this study was conducted, I don't think there was much known about glyphosate. So I agree. So this is certainly a study that is trying to evaluate something we know very little about, and of course, we always want the most information we can get and the longest period between exposures. 12:54

But as a public health official, I want to look right away. I want to look after two years and three years and four years, but if I don't see something after two years or three years, then I want to look after five years because it doesn't mean there's nothing when I 12:54 12:55

don't see something after two years.

And in epidemiology, what we often do in order to remove exposures that are irrelevant is we are discounting exposures within the year before diagnosis, and that's a tool one can use. 12:55

BY MR. LASKER:

Q. And one of the things that you talk about with another study, with the Eriksson study is a lag period of ten years because in that study, that was the demarcation; correct? 12:55

A. Yes, that's correct.

Q. Okay. And that goes to the same issue that you're raising which is that for hematopoietic cancers, you might need a period of ten years before the exposure could actually give rise to diseases so that you can actually measure an effect; correct? 12:55 12:55

MS. FORGIE: Object to the form.

THE WITNESS: That's incorrect. That's actually stating the opposite of what I said. What I'm saying is that you want that -- actually for 12:55

hematopoietic cancers, it's generally in the radiation literature -- and that's where I wrote my dissertation in -- assume that it's two-year minimum. And so what we would do is we would look carefully and critically maybe at around one year or two year, but these are all presumed. 12:56

And they come from the medical literature on radiation effects -- side effects. They are not coming from population studies and workers and the general population. So what we think the case is is that if you say one day or a month, everybody would shake their head. Maybe even one year we would shake our heads and say I'm not really sure. But anything beyond one year would definitely raise concern. 12:56 12:56

Because we are also now talking about initiation of cancer or promotion of cancer, and initiation of cancer might take longer than promotion. Promotion might be the last step in the chain of events, and that might be very 12:56 12:57

soon.
So again, what I'm saying is that I would like to move out from the time of exposure that is relevant for the cause of the disease. I would like to move out as long as I can in order to capture as many cases caused by that exposure as possible.
So ten years out is a good time frame because it makes me more comfortable that I'm not only capturing early birds but that I'm really looking at the chronic consequences of that exposure.
BY MR. LASKER:
Q. Understood.
So with respect to the Cantor study then, if I'm understanding you correctly, your concern was -- with respect to latency was solely a concern about power?
MS. FORGIE: Object to the form.
THE WITNESS: No, it was not about power, but it was a concern about this study not -- being a little bit early in the sense that the chronic effects could

not be assessed as comprehensively as I would have liked to and later studies do a better job.
MR. BAUM: Is this a good time to switch over to lunch?
MR. LASKER: Almost.
BY MR. LASKER:
Q. Now, in your analysis, you were assessing the start date, if you will, of glyphosate as a potential exposure in 1974; is that correct?
MS. FORGIE: Object to the form.
THE WITNESS: Well, we don't really know unless the author tells us exactly when the exposure happened, but the potential for exposure starts in '74, yes.
BY MR. LASKER:
Q. Do you know when glyphosate was first approved for use in agricultural settings?
A. I thought that was about that time.
MR. LASKER: Let's just mark the next exhibit in line.
MR. BAUM: Eric, it's 1 o'clock.

MR. LASKER: We're going to be about five minutes. It's still all in the context of this.
(Exhibit Number 19-11 was marked for identification.)
MS. FORGIE: What number are we on?
MS. SHIMADO: 11.
BY MR. LASKER:
Q. And this will be, and I'll -- obviously, you're going to have to -- well, I'll represent and I'm going to ask you a question on the assumption my representation is correct. I'll represent to you that this December, 1975, letter from EPA marks the first date on which glyphosate-based formulation was approved for use in agricultural settings.
A. Uh-huh.
MS. FORGIE: There's no question.
BY MR. LASKER:
Q. If that assumption is correct for farming studies, and these are -- the Cantor study was specific to farming exposures in calculating that latency period, would I be correct, then, that December, 1975, would be

the starting point for that calculation?
MS. FORGIE: Object to the form.
THE WITNESS: We are presuming that this is the only way to get glyphosate use.
BY MR. LASKER:
Q. This is the first approval for agricultural settings. It would be used as sort of right of way and roadways for road crews. It could have been used before then, but the first approval for farmers for use of glyphosate was in December of 1975.
A. And that --
MS. FORGIE: Wait. There's no question pending.
BY MR. LASKER:
Q. With that assumption in mind, if you're trying to measure farming exposures, which was the exposures in the Cantor study which was the farmers exposure, I think by its definition and by its terms, would December of 1975, then, be the proper start point for determining the potential latency period between exposure and disease outcome?
MS. FORGIE: Object to the form.

Asked and answered. She just answered that exact question.

You can answer it again.

THE WITNESS: Well, I have to make certain assumptions. One was that they actually didn't ask other occupations, such as road worker, and also that these farmers weren't given glyphosate in trial runs because there's a difference, and I thought I'd seen that somewhere listed that actually glyphosate was being tried out in certain farming populations prior to general approval. 01:01 01:01

BY MR. LASKER:

Q. Okay. I'm not sure where you've seen that, but for the purpose of this question, if we assume that December, 1975, was the first date where glyphosate was approved for agricultural uses, for farm uses, and that none of the farmers here were using it for some trial purposes before its official approval, would December, 1975, then, be the proper starting point for then calculating the latency period for the Cantor study? 01:02 01:02

MS. FORGIE: Object to the form. Asked and answered.

You can answer it again.

THE WITNESS: Well, if that is what they are actually assessing, then you would have potential exposure starting at the time this agent became available to the farmers, and then you could use that for a latency period calculation. 01:02

MR. LASKER: Why don't we take a break for lunch. 01:03

THE VIDEOGRAPHER: This marks the end of videotape number 2 in the deposition of Dr. Beate Ritz. We're off the record at 1:03 p.m. 01:03

(Lunch recess taken from 1:03 p.m. to 1:46 p.m.)

THE VIDEOGRAPHER: We are back on the record at 1:46 p.m. This marks the beginning of videotape number 3 in the deposition of Dr. Beate Ritz. 01:46

BY MR. LASKER:

Q. Dr. Ritz, let's move on to the De Roos 2003-case control study. We'll mark that as the next exhibit in line. 01:46

(Exhibit Number 19-12 was marked for identification.)

BY MR. LASKER:

Q. Dr. Ritz, we can walk through this if you'd like, but I feel you probably already have done that. The median latency time for the NHL cases in this study is roughly equivalent to the median latency time for the cases in the Cantor study; correct? 01:47 01:47

A. As far as I know, it went out a little bit longer in Minnesota.

Q. No, I think you're talking Nebraska was longer and Kansas City was shorter.

MS. FORGIE: Wait. Is there a question? 01:48

MR. LASKER: I'm working my way through it.

THE WITNESS: Nebraska is the longest followed by Minnesota and then Kansas. 01:48

BY MR. LASKER:

Q. And Kansas was shorter?

A. Correct.

Q. And Nebraska was longer. So 01:48

roughly the median -- most of the data was the same as Cantor, and then you have some shorter and some longer; right?

MS. FORGIE: Object to the form.

THE WITNESS: It depends on how many people were in each of those studies. 01:48

BY MR. LASKER:

Q. You can look on Table 2.

A. Yeah, Iowa and Minnesota is the biggest chunk of it. 01:48

Q. And then the other two are both about the same?

A. Yeah.

Q. So can we agree the median latency period for the De Roos 2003 study is roughly equivalent to the median latency period for the Cantor study? 01:48

MS. FORGIE: Object to the form.

THE WITNESS: We can calculate it, but it probably would come out similarly, but it's important that we also have longer latency in there, in Nebraska. 01:48

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BY MR. LASKER:
Q. Right. But the median latency is the same. We have shorter latency for the roughly 15 or 16 percent from Kansas and slightly longer latency for the 17.4 percent in Nebraska; correct? 01:49
MS. FORGIE: Object to the form.
THE WITNESS: 21.5 percent in Nebraska.
BY MR. LASKER: 01:49
Q. I was looking at the analysis of multiple pesticides.
A. Oh.
Q. Correct?
MS. FORGIE: Object to the form. 01:49
THE WITNESS: 17.4, yes.
BY MR. LASKER:
Q. Okay. With respect to the Nebraska data which is, as you mentioned, is data that's somewhat longer, that goes out from July 1983 to June 1986? 01:49
A. Correct.
Q. Even in that sub population litigation --
(Interruption in the 01:50

proceedings.)
MR. LASKER: Back on the record.
BY MR. LASKER:
Q. Even for the 17 percent of the data that came from Nebraska, you still would not have a median latency period for glyphosate for ten years; correct? 01:50
MS. FORGIE: Object to the form.
THE WITNESS: That makes assumptions that we're starting to count in 1975 which may or may not be correct. 01:50
But that gives us eight years, I guess.
BY MR. LASKER:
Q. Whether it's '74 or '75, the maximum latency period would be -- maybe the maximum would be 12 years, but we're talking the median latency period. The median latency period even for this Nebraska subgroup would be less than ten years; correct? 01:50
MS. FORGIE: Object to the form.
THE WITNESS: About ten years.
BY MR. LASKER:
Q. Let me make sure I understand the median latency period. This would allow -- 01:51

if everybody had taken glyphosate the very first day that it was available, that would be the latency period, but, of course, that's not going to be the reality in the study; correct? 01:51
A. I don't know --
MS. FORGIE: Object to the form.
THE WITNESS: I don't know what the reality in the study is because it's not stated exactly when these farmers started, and if we are presuming that the EPA date is the earliest one, and you said yourself there were other uses for glyphosate, so who knows? Farmers do all sorts of things including buying things that are not EPA approved. So I don't know. 01:51
BY MR. LASKER:
Q. So there are two parts of this: When you talk about median latency, there is, in this case, a maximum latency period of whenever you want to start measuring 1974, 1975 through to the date of diagnosis. That would be the maximum latency period possible. 01:51 01:52

A. Correct.
Q. The actual median latency for the population that's being studied would be less than the maximum latency period; correct? 01:52
A. It would be somewhere in between the diagnosis dates, and the diagnosis dates are July, '83, through June, '86.
Q. I understand that. That would be when diagnosis was. The exposure -- the median period of exposure would not be ten years before that. It would be somewhat less. At some point in time prior to diagnosis that they're exposed, not the very first day; correct? 01:52 01:52
MS. FORGIE: Object to the form and asked and answered.
You can answer again.
THE WITNESS: Well, it depends what we are presuming about the exposure. So if we are presuming that they really only started using in 1975, and they were using a certain amount of glyphosate that needed to be used in a certain way, they might have used, you 01:52 01:53

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know, a huge amount the first time around because they were told it's very non-toxic and maybe all of the relevant exposure were in the first year. I don't know. They did not investigate that. 01:53

BY MR. LASKER:

Q. Okay. I understand that.

But with respect to, as an epidemiologist if you're looking at this study and you don't have the data on when exposures took place, would you assume then in your analysis of the Nebraska data for purposes of assessing the data that all of the exposures to Roundup took place on the first date that exposures were possible? 01:53

MS. FORGIE: Object to the form. Asked and answered.

You can answer it again.

THE WITNESS: Well, I would probably look at a range of possible times, and then you can, you know, use that in your analysis. 01:53

BY MR. LASKER:

Q. Okay. And if you were to do that 01:53

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analysis, the median latency period, even of the Nebraska data, would be less than ten years; correct?

MS. FORGIE: Object to the form. Asked and answered. 01:54

THE WITNESS: Not necessarily because the Nebraska diagnosis median is 1985. So that's ten years after 1975.

BY MR. LASKER:

Q. I understand that. Let me just make sure I understand this. You mentioned that you had used some sort of range that determined likely first exposure date. 01:54

It wouldn't all be assumed to be 1975; correct? 01:54

MS. FORGIE: Object to the form. Asked and answered. She's testified --

THE WITNESS: That would be a kind of sensitivity analysis you might want to play with. 01:54

BY MR. LASKER:

Q. And if that analysis were conducted, the median latency period for even the Nebraska, 17 percent in this study could be less than ten years; correct? 01:54

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MS. FORGIE: Object to the form. Asked and answered.

You can answer it again.

THE WITNESS: Well, I could define a range that would make it less than ten years, but if I subtract 1985 and 1975, I have ten years on average. 01:54

BY MR. LASKER:

Q. Okay. And you talked earlier about the issue -- we were talking about this in connection with the Cantor study about the power of this study to be able to identify association. So I'd like to ask you about that. 01:55

I'd asked you about the CLR for De Roos, and we now have that data; so I'd like to return to that discussion. The glyphosate data is presented on Table 3; correct? 01:55

A. Correct. 01:55

Q. And for the logistical regression analysis which is the analysis that you report on in your expert report, we have a confidence interval that ranges from 1.1 to 4.0; correct? 01:56

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A. Yes.

Q. So that confidence interval is -- I'm sorry, the CLR for that, and I've done the math, but it's going to be about 3.6, and you can sort of eyeball that; right? 01:56

A. Yeah.

MS. FORGIE: Object to the form.

BY MR. LASKER:

Q. And for the hierarchical regression odds ratio, we have 2.8 over 0.9; so the CLR for the hierarchical regression would be slightly above 3; correct? 01:56

A. Yes.

Q. So the CLR for both of the De Roos 2003 odds ratios for glyphosate are larger than the CLR for the Cantor 1992 study; correct? 01:56

A. What did we have for that again?

Q. You can go back. It's 2.7, but why don't you look at it just to confirm for yourself. 01:56

MS. FORGIE: Do you remember what exhibit it is?

MR. LASKER: It's probably the last one we just did. 01:56

MS. SHIMADO: 10. Exhibit 10.
BY MR. LASKER:
Q. You should have it right there.
A. Yeah.
Q. For the record, I'll ask the question again while you're looking at this. 01:57
The CLR for both of the logistic regression analysis and the hierarchical regression analysis in the De Roos 2003 study is actually larger than the CLR for the Cantor study; correct? 01:57
A. That is correct.
Q. Am I correct, though, in my understanding that the -- your concern -- while you're concerned about the latency period in the Cantor study as making that study less informative, you do not have that same concern for the De Roos 2003 study? 01:57
A. Well, first to the '95 percent confidence interval, the confidence interval widens with the number of adjustments I make. Obviously, De Roos makes a lot more co-adjustments than Cantor, and that's probably the reason why these confidence intervals are wider. So in a way, actually 01:58

her estimate would be the more fully adjusted compared to the Cantor.
With respect to latency, the same rules apply. However, she added some studies that actually had longer latency. 01:58
Again, the latency issue is an issue because I'm missing cases that are truly caused by the exposure, if I believe exposure causes disease, and so it has to do with early studies where I'm catching these early cases 01:58
and not yet the later ones.
Q. Let me just sort of step back, though, because there's a lot in that answer, and I want to make sure I understand that fully. 01:58
Is it your testimony that the logistical regression analysis in De Roos 2003 had more controls, adjusted for more factors than the hierarchical regression?
MS. FORGIE: Object to the form. 01:59
THE WITNESS: No, that's not what I said. The hierarchical regression makes additional assumptions that we can debate and that are debated. You will not see many -- she is actually one of 01:59

the first people to ever use hierarchical regression in a systematic way in the literature.
There are a few more papers here and there. I did it myself in 2002. 01:59
Somehow hierarchical regression has fallen out of favor because you have to make a lot of assumptions, and reviewers actually constantly fight with you over those assumptions whether they're 01:59
correct or not. So generally, we would go back in a consensus manner to a normal logistic regression in which we are adjusting for as many variables that we think make validly sense to adjust 01:59
for.
And this estimate of 2.1 was the confidence interval of 1.1 to 4, had wider confidence interval even though there are more cases and more controls 02:00
in the analysis. The only way this happens is if there is more full adjustment for cofactors to widen these confidence intervals.
So from that, I conclude that she 02:00

must have adjusted for a lot more than Cantor.
BY MR. LASKER:
Q. Let me just step back here because that was my question. The confidence 02:00
interval for the hierarchical regression is narrower than the confidence interval for the logistic regression analysis?
A. Correct, and that's by method. By making more assumptions, you're narrowing 02:00
confidence intervals. That's how hierarchical regression works.
Q. Let me step back so I make sure I understand the question -- understand the answer to my question. 02:00
In the Cantor 1992 study, you raised concerns about a median latency period of less than ten years as making that study which had a 1.1 adjusted odds ratio, in your mind, less informative. And I'm 02:01
just trying to understand if that same concern about the median latency period of less than ten years makes the De Roos 2003 study which has that hierarchy ratio that you cite less informative. 02:01

MS. FORGIE: Objection. Object to the form. Asked and answered.

You can answer.

THE WITNESS: Cantor is part of the study; however, the beauty of pooled studies is that they pool across different studies with different strengths and different weaknesses. It helps for the sample size. It helps for the statistical power. In this case, it helps even to adjust for more variables that you would be happy to adjust for, and overall, it's more powerful because of all of these reasons. 02:01 02:01

BY MR. LASKER: 02:02

Q. That wasn't my question. My question was that you, in your expert report, cited to a median latency period for NHL of less than ten years as a reason why the Cantor study was less informative, and the 1.1 odds ratio in that study was less informative to you. 02:02

The De Roos 2003 study has a median latency period of less than ten years. My question to you is whether that fact makes 02:02

the De Roos 2003 study less informative?

MS. FORGIE: Object to the form. Mischaracterizes her testimony and asked and answered.

You can answer it again. 02:02

THE WITNESS: Again, the latency period in Cantor cannot be different from what the latency period of the part of the data that is Cantor data in this pooled analysis is. So it is what it is. 02:02

However, adding additional states and additional data improves what this study can do over the Cantor study. Plus it overall increases the latency because we have the Nebraska study as well. 02:02

BY MR. LASKER:

Q. Okay. But we also have the Minnesota study which has a shorter latency period; correct? 02:03

MS. FORGIE: Object to the form.

THE WITNESS: It's likely shorter.

Yes.

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BY MR. LASKER:

Q. Just to clarify, the Kansas study has a shorter period?

A. Kansas, yes.

Q. So again, my question is -- and it may or may not -- but does the fact that the De Roos 2003 study has a median latency period of less than ten years, in your assessment, does that, in your mind, make the De Roos 2003 study less informative? 02:03 02:03

MS. FORGIE: Object to the form. Mischaracterizes her testimony. Asked and answered.

You can answer it again.

THE WITNESS: I think De Roos is a really excellent study that did everything we can do in terms of pooling data in terms of relating the exposures that she had access to to the outcomes in adjusting and trying different methods and in actually lengthening the overall latency by including Nebraska. 02:03 02:03

MR. LASKER: Mark that answer. I'm going to ask the question again.

///

BY MR. LASKER:

Q. In your opinion, does the fact that the De Roos 2003 study has a median latency of less than ten years make that study less informative? 02:04

MS. FORGIE: Objection. Object to the form. Mischaracterizes her prior testimony, asked and answered. This is, like, the fifth time you've asked the same question. 02:04

THE WITNESS: Now I'm really confused because I don't know anymore what you mean by "less informative."

BY MR. LASKER:

Q. Okay. Well, that was your terminology with respect to the Cantor study. 02:04

A. Correct.

Q. And you stated that the Cantor study was less informative because it had a median latency period of less than ten years. My question is: Do you believe that the De Roos study is less informative because it has a median latency period of less than ten years? 02:04 02:04

MS. FORGIE: Objection. Object to the form. I object to the mischaracterization of her prior testimony. Asked and answered six times. 02:05

You can answer it again.

THE WITNESS: So the De Roos study generally is a better study than the Cantor study because it pools data. So it's not less informative. It's 02:05 actually more informative, that it cannot go beyond the latency period of one of the studies included for that data is a no-brainer.

However, she added data with a 02:05 longer latency; so she is actually now covering all sorts of latency periods that we can look at. And the longer, of course, we would have a latency period, the more powerful. If she had another 02:05 study to add, it would become more powerful, but it is an incremental step going from one study that may be less informative to two studies that are more informative to three studies that are 02:05

even more informative.

BY MR. LASKER:

Q. And the Nebraska data is from a case control study that was published by Dr. Zahm; correct? 02:06

A. Yes, Sheila.

Q. And Dr. Zahm in her published case control study did not report any association between glyphosate and non-Hodgkin's lymphoma, did she? 02:06

A. Can you show me that?

Q. Sure.

(Exhibit Number 19-13 was marked for identification.)

BY MR. LASKER: 02:06

Q. Again, my question is Dr. Zahm, in her paper, does not report any -- specifically any association or positive association between glyphosate and non-Hodgkin's lymphoma; correct? 02:07

MS. FORGIE: Take as much time as you want reading it.

THE WITNESS: It looks like this is a study specifically analyzed for 2,4-D and some more general pesticide 02:07

exposures.

BY MR. LASKER:

Q. My question to you is: In the published paper addressing the Nebraska data that was pooled in De Roos 2003, the 02:07 investigators, Zahm, et al., do not report any association between glyphosate and non-Hodgkin's lymphoma; correct?

MS. FORGIE: Objection. Object to the form, and asked and answered. 02:08

You can answer it again.

THE WITNESS: So the beauty of pooled studies is that I can do things that I can't do in a single study. I presume that Sheila thought she could 02:08 not analyze certain types of pesticide based on what is 201 cases.

So that would be normal procedure to then make this data available for a larger pooled study for pesticide 02:08 exposures that are less common.

BY MR. LASKER:

Q. My question was -- and I still I'm not sure I've gotten -- I still haven't gotten an answer. Dr. Zahm, in her 02:08

published case control study, looking at that Nebraska data that was then pooled into De Roos 2003, does not report any association between glyphosate-based herbicides and non-Hodgkin's lymphoma; 02:08 correct?

MS. FORGIE: Objection. Object to the form, asked and answered. This is the fifth time she's answered.

You can answer it again. 02:09

THE WITNESS: So the pooled data is not what is being reported on here. There's a difference between a study and a study report. Usually when you do these studies, they're very expensive. 02:09 You collect a lot more data than what you can report in one paper, and for your career, you better publish more than one paper.

There's always the issue of common 02:09 and less common exposures; so when I collect as extensively as I can any kind of occupational exposure, I might or might not have the statistical power to investigate every of those exposures in 02:09

my study that is relatively limited since there are only 201 white males as cases.

So in that case, I provide this data for a collaborative effort and 02:10
Dr. De Roos' paper is such a collaborative effort where then I provide them with a lot more data than I would be -- you see that she is the second author here, and Dr. Blair is the 02:10
last author. So they would have had access to more data than this paper is actually reporting on.

MR. LASKER: I'm going to have the reporter mark that answer again. I'm 02:10
going to ask the question one more time to see if I can get an answer. If not, we'll just have to address this with the Court later.

MS. FORGIE: I object to the 02:10
statements about not getting an answer --

MR. LASKER: That's fine. Just object.

MS. FORGIE: It's unfair. 02:10

BY MR. LASKER:

Q. Dr. Ritz, in her published paper, case controlled paper, looking at the Nebraska data that was subsequently pulled into De Roos 2003, Dr. Zahm does not report 02:10
any association between glyphosate and non-Hodgkin's lymphoma; correct?

MS. FORGIE: Objection. Object to the form and asked and answered. This will be, like, the eighth or ninth time 02:10
she's answered the same question.

You can answer it again.

THE WITNESS: This data in the Zahm publication from 1990 is not the data that was pooled into this pooled study. 02:11
This is data specifically for one type of application. What I imagine Dr. Zahm provided to Dr. De Roos is a much more extensive dataset and the De Roos study is based on that more extensive dataset. 02:11

BY MR. LASKER:

Q. The De Roos study is looking at 187 cases in its pooled analysis and 113 cases in its analysis of multiple pesticides from Nebraska; correct? 02:11

A. 113, yes.

Q. And the Zahm published paper had, would you say, over 200 cases of non-Hodgkin's lymphoma; correct?

A. 201. 02:11

Q. Okay. De Roos and her co-investigators in the 2003 paper discuss their findings with respect to glyphosate in their conclusion -- in the concluding section; correct? Or I guess in their 02:12
discussion section?

A. Yes.

Q. And on page 7 of 9, the paragraph -- sort of the second paragraph from the end of the bottom of the 02:12
second column on page 7 is where De Roos and her co-investigators discuss their findings with respect to glyphosate; correct?

A. This one? The second to the last.

Q. Glyphosate -- 02:12

A. Yeah, yeah.

Q. In that discussion, they talk about the -- they cite to the Hardell paper, and they cite to the McDuffie paper; correct?

MS. FORGIE: Objection. 02:13

THE WITNESS: I see a citation to a Williams paper and a Hardell paper.

BY MR. LASKER:

Q. Number 51 --

A. And 51. 02:13

Q. -- and number 8 is the McDuffie paper; correct?

A. Oh, 8, yes.

Q. So they cite to the McDuffie paper and the Hardell paper; correct? 02:13

A. Yes.

MS. FORGIE: Objection.

BY MR. LASKER:

Q. And they state that these few suggested findings provide some impetus for 02:13
further investigation into the potential health effects of glyphosate; correct?

A. It seems like they are citing Williams here.

Q. I understand that. 02:13

The conclusion that De Roos and her co-investigators provide in their discussion in their paper after reviewing the other epidemiological studies they cite, Hardell and McDuffie, after they've done their 02:14

analysis as well for the pooled data from the U.S. case controlled studies, was that these were suggested findings that provide some impetus for further investigation into the potential health effects of glyphosate; correct? 02:14

MS. FORGIE: Object to the form.

THE WITNESS: The way I read this is that they are commenting on Hardell and McDuffie. 02:14

BY MR. LASKER:

Q. They do not -- De Roos and her co-authors do not anywhere in their paper state that their study in combination with the earlier epidemiological studies supports a conclusion that there has been shown a causal association between glyphosate and NHL, do they? 02:14

MS. FORGIE: Object to the form.

THE WITNESS: Well, they're actually saying, "Our results indicate increased NHL incidents by number of pesticides used only for the subgroup of potentially carcinogenic ones," and then they list them. 02:14 02:15

BY MR. LASKER:

Q. They do not list glyphosate; right?

MS. FORGIE: Wait. She hasn't finished her answer. Please let her finish. 02:15

THE WITNESS: I'm looking for the glyphosate. No, that's the general statement.

BY MR. LASKER:

Q. Okay. 02:15

A. But you would need to look at the list of what she considers potentially carcinogenic which is on Table 1, and you will see that glyphosate was one of them because it got a .3. 02:15

Q. In her -- in De Roos' discussion, if I can direct you to page 6 of 9, she has data there for combined pesticide use, Table 5.

Do you see that? 02:16

A. Yes.

Q. And one of the analyses that they conduct is a combined analysis of atrazine and dicamba; correct?

A. Yes. 02:16

Q. And as it happens, their findings for their logistic regression and their hierarchical regression for atrazine and dicamba combined are almost identical to their findings for glyphosate alone; correct? 02:16

MS. FORGIE: Object to the form.

THE WITNESS: I don't know what you mean by "identical."

BY MR. LASKER: 02:16

Q. Well, for atrazine and dicamba in their logistical regression, they had an odds ratio of 2.1 which is the same odds ratio as glyphosate had in logistical regression; correct? 02:17

A. Yes, but odds ratio of 2.1 or .7 or .3 you can find all over this table.

Q. And the confidence interval for the logistic regression analysis for 2.1 was marginally significant and very similar to the confidence interval for glyphosate alone; correct? 02:17

A. Correct. But you can see that it is based on very different data. It's based on 31 cases and 60 controls in that category 02:17

versus 36 and 61 for glyphosate. So it's not the same people.

Q. Right. I wasn't suggesting it's the same people.

The hierarchical regression analysis, the conclusion for atrazine and dicamba combined was a 1.6 odds ratio which is the same odds ratio reported for glyphosate; correct? 02:17

MS. FORGIE: Object to the form. 02:17

THE WITNESS: Well, yeah, I mean, when we do these kind of analyses, a lot of odds ratios might be the same.

BY MR. LASKER:

Q. And the confidence interval for the hierarchical regression analysis for atrazine and dicamba combined is, again, virtually identical to the odds ratio for the hierarchical regression analysis for glyphosate; correct? 02:18 02:18

MS. FORGIE: Object to the form.

THE WITNESS: Not surprising given the assumptions they made for the hierarchical regression.

///

BY MR. LASKER:
Q. And in discussing those odds ratios, 2.1 for the logistic regression analysis that is just statistically significant and a 1.6 for the hierarchical regression analysis that's not significant in connection with atrazine and dicamba on page 6 in their study, and it is in the text right above the words "Discussion," De Roos states that those findings were "probably misleading due to imprecision of estimates noting that these results did not hold up following shrinkage and hierarchical regression analysis according to our prior distribution of complete exchangeability"; correct? 02:18 02:18 02:19
A. That's what this says. I mean, the text.
Q. And to the extent that -- I take it you would not view the identical -- or not nearly identical odds ratios reported for glyphosate in the same study as being probably misleading; correct? 02:19
MS. FORGIE: Object to the form.
THE WITNESS: You are comparing two 02:19

tables you absolutely cannot compare. The result for atrazine and dicamba both, it's what we call an interaction term, and what she is comparing here is they seem to be indicative super additivity and results from logistic regression. 02:19
And what this next sentence is referring to, such as for atrazine and dicamba, were probably misleading. So the misleading is the super additivity and not the effect estimate. 02:19
BY MR. LASKER:
Q. Let's go on to the Lee study just briefly. That's Lee 2004. 02:20
MS. FORGIE: Are we putting these away?
MR. LASKER: For now, yes.
(Exhibit Number 19-14 was marked for identification.) 02:20
BY MR. LASKER:
Q. The Lee study is another pooled analysis here using two of the three studies that were used in De Roos 2003; correct?
A. Correct. 02:20

Q. The Lee study reporting its results does not adjust for exposures to other pesticides; correct?
MS. FORGIE: Object to the form.
THE WITNESS: I have to check that. 02:21
BY MR. LASKER:
Q. Table 3 on page 300.
A. The Lee study does not give you an effect estimate for glyphosate. It gives you a stratified analysis by asthmatics and non-asthmatics for glyphosate. 02:21
Q. And in that stratified analysis, they do not adjust for exposures to other pesticides; correct?
MS. FORGIE: Object to the form. 02:21
Asked and answered.
You can answer it again.
THE WITNESS: That seems to be correct, and I would be very surprised if they did because they had only six cases among asthmatics. If you throw any more variable into that model, you will explode it. 02:21
BY MR. LASKER:
Q. Well, the adjustment model is based 02:22

upon all the exposures. It's not specific to glyphosate; correct?
A. No. The one for glyphosate has six exposed cases and 12 exposed controls, and you already have age, vital status, and state in there. So if you do it two by two by two table, then you have no more subjects -- 02:22
Q. I'm sorry --
A. -- in one of these. 02:22
Q. We're not connecting here --
A. Table number 3.
MS. FORGIE: Wait, let her finish.
BY MR. LASKER:
Q. All of the adjustments in this entire study, and there's a whole lot of adjustments they do with stratification on Tables 2 and Table 3, none of the odds ratios anywhere in this study are adjusted for exposures to other pesticides; correct? 02:22 02:22
MS. FORGIE: Objection. Object to form. Asked and answered.
You can answer it again.
THE WITNESS: The glyphosate estimates are estimates among 02:22

non-asthmatics and asthmatics. When you split your data in that way, you limit the way you can adjust. In this case, when you have asthmatics with six glyphosate exposed cases and 12 controls, there's absolutely no way -- I don't even know how they adjust for age vital status and state without exploding their model. 02:23

BY MR. LASKER: 02:23

Q. Okay. Dr. Ritz, that wasn't my question, and that doesn't answer my question in the slightest.

MS. FORGIE: I object to that commentary. She's answered it twice. 02:23

MR. LASKER: We'll mark this answer as well.

BY MR. LASKER:

Q. It's a very simple question. There's two tables here, Table 2 and Table 3 with a whole lot of reported odds ratios, not only for glyphosate, but for other pesticides, for other exposures, for combined herbicides. None of those odds ratios include any adjustment for exposure 02:23

to other pesticide; correct?

MS. FORGIE: Objection. Object to the form. Asked and answered.

You can answer it again.

THE WITNESS: None of the pesticide results are concomitantly adjusted, and it's not a surprise because they are stratifying by asthma status, and in order to compare one model with another, they have to adjust for exactly the same variables or else you can't compare the models. 02:23 02:24

And the intent here is to compare models for asthmatics with models for non-asthmatics. If you put different adjustments variables in there, you don't know whether you see a difference or not. 02:24

MR. LASKER: We're going to have to mark that answer again and ask one more time because I can't get a yes or no answer to a question. I'll ask it one more time. 02:24

BY MR. LASKER:

Q. None of the odds ratios in the Lee 02:24

study were adjusted for exposure to other pesticides; correct?

MS. FORGIE: Objection. Object to the form. Asked and answered. As you just stated, this is like the seventh time. 02:24

You can answer it again.

THE WITNESS: This study intends to look at a stratified analysis of non-asthmatics and asthmatics. If I really want to compare the effects estimates between these two groups of people and I want to assess whether glyphosate has the same effect in one group than in the other, I have to automatically adjust for the same variables. They already are adjusting for age, vital status, and state, therefore, there is no way they could also adjust for everything else. 02:24 02:25

BY MR. LASKER:

Q. So if the answer is, yes, that's fine, but I need an answer for the record. Am I correct that the Lee study does not adjust for exposure to other pesticides? 02:25

Yes or no?

MS. FORGIE: Objection.

No. She's not required to give a yes or no answer, and you know that.

MR. LASKER: Frankly, she is. 02:25

MS. FORGIE: No, she's not. Don't do this. Objection. Object to the form. Object to asked and answered for the seventh time.

You're not required to give a yes or no answer. You can answer again. 02:25

BY MR. LASKER:

Q. I'm asking for a yes or no answer. If you can't give a yes or no answer, you can just state that and we'll move on and we'll deal with it later for the judge. 02:25

MS. FORGIE: Objection.

THE WITNESS: My answer will not change.

BY MR. LASKER: 02:25

Q. My question to you is am I correct that the Lee study in reporting the odds ratios for all the odds ratios reported does not adjust for the exposure to other pesticides? 02:25

MS. FORGIE: Objection. Object to the form and asked and answered.

You can answer it again.

THE WITNESS: This is such a general question that it's not answerable. But in order to inform you what is done in this study, I state it again. This study intends to compare effect estimates between asthmatics and non-asthmatics. In order to do so, the authors had to adjust for exactly the same variables in the pesticide models. The variables they adjusted for are age, vital status, and state. 02:26

MR. LASKER: Mark that and we'll move on. 02:26

BY MR. LASKER:

Q. The issue with latency that you raised and we've discussed before from the same pool data would also exist to the extent that it concerns you or not with the Lee study; correct? 02:26

MS. FORGIE: Object to the form.

THE WITNESS: I'm not sure what you mean by issue. However, this study 02:26

includes Nebraska and we seem to have agreed that that has a longer latency and gives you more opportunity to investigate this question.

BY MR. LASKER: 02:27

Q. And it also includes the data in Cantor that has the latency period that you believe is too short; correct?

A. I never said that I believed it is too short, but it does include the Iowa and Minnesota data that's in the Cantor study. 02:27

Q. Let's move on to the McDuffie study.

MS. FORGIE: Are we finished with this? 02:27

MR. LASKER: Yeah.

(Exhibit Number 19-15 was marked for identification.)

BY MR. LASKER:

Q. Dr. Ritz, for the record this is the McDuffie study which is the case control study from Canada; correct? 02:27

A. Yes.

Q. And the authors describe McDuffie, et al., describe their analysis in this 02:28

study as exploratory; correct?

MS. FORGIE: Object to the form.

THE WITNESS: Where do they say that?

BY MR. LASKER: 02:28

Q. On page 1161 in the second column about two-thirds of the way down. Do you see the sentence starting "We report results"?

A. Yes. 02:28

Q. "We reported results."

A. Uh-huh.

Q. And McDuffie, et al., describe their analysis in this study as exploratory; correct? 02:28

MS. FORGIE: Objection. Object to the form.

THE WITNESS: What they're stating is that they investigated a number of different chemicals and exposures and, therefore, some of the analyses to unspecified agents should be considered exploratory. I don't know what they mean by unspecified agents. 02:28

///

BY MR. LASKER:

Q. During the point in time, and I think you mentioned this -- well, at -- in the method section -- strike that.

Do you know based upon your review of this study whether glyphosate was specified in the hypothesis when they were conducting this study? 02:29

MS. FORGIE: Object to the form.

THE WITNESS: I wouldn't know that. 02:29

BY MR. LASKER:

Q. Okay. So you cannot state, then, whether or not the glyphosate findings would be considered by the investigators McDuffie, et al., to be exploratory; correct? 02:29

MS. FORGIE: Object to the form.

THE WITNESS: That's not correct because what I -- when I design a study and a study questionnaire, I have to decide which chemical agents to specify, meaning, to name or to want to investigate. So in my preparation for a study, I have to be very clear about what kinds of pesticides I'm asking about, and I would call that 02:29 02:30

specification.
So if they hadn't been interested in glyphosate, they wouldn't have investigated it, and they wouldn't have asked it in a questionnaire. 02:30
BY MR. LASKER:
Q. They state, however, in presenting the data, and they do present data on various different chemical agents, and they have a whole list of them, that they are 02:30 presenting results for chemical agents and exposures that were not specified in the hypothesis; correct?
MS. FORGIE: Object to the form. Asked and answered. You can answer it 02:30 again.
THE WITNESS: They refer to a number of chemical agents and exposures that were not specified. The way that might happen is that when you have a 02:30 questionnaire, you have open questions and you don't specify the name of the chemical, but people decide to write them in. I have no idea what they mean by unspecified, but that's one way of 02:30

reading it.
BY MR. LASKER:
Q. And you don't know sitting here today whether or not based upon this and based upon however they prepared this 02:31 information, whether the findings that they report with respect to glyphosate should be considered exploratory; correct?
MS. FORGIE: Objection. Asked and answered. Object to the form. 02:31
You can answer it again.
THE WITNESS: All I can tell you I don't consider this exploratory.
BY MR. LASKER:
Q. Okay. The McDuffie case control 02:31 study did not adjust for exposure to other pesticides; correct?
A. In what table?
Q. Any of the tables.
A. That's not correct. Table 6 and 7 02:31 seem to be adjusting for chemicals.
Q. 6 and 7 are dealing with various medical variables?
A. And dicamba and Aldrin and Mecoprop. 02:32

Q. With respect to the tables that report any findings with respect to glyphosate, none of those findings are adjusted for exposures to other pesticides; correct? 02:32
MS. FORGIE: Object to the form.
THE WITNESS: Which table are we talking about?
BY MR. LASKER:
Q. Well, for glyphosate, it would be 02:32 Tables 2 and Table 8 as far as I know. But you should make sure that you agree with that. Take your time.
A. 2 and --
MS. FORGIE: 8. 02:33
THE WITNESS: These tables seem to adjust for age and province.
BY MR. LASKER:
Q. Just so the record is clear in the odds ratios that are reported for glyphosate 02:33 in the McDuffie study, the investigators do not adjust for exposure to other pesticides; correct?
A. That seems correct.
Q. The -- as you note in your expert 02:33

report and just so the record is clear, for the two ever/never odds ratios for the glyphosate that McDuffie reports, they find odds ratios of 1.26 in one model and 1.2 in the other model, and neither of those odds 02:34 ratios are statistically significant by the 95 percent confidence interval; correct?
A. Well, if we want to play the P-value game, that's correct, but the values are 1.26 and 1.20. One adjusted; one not. 02:34 But that's an ever/never.
Q. Right. And the -- you mention in your report that there was separate analyses of the McDuffie data that, first of all, separated out association for glyphosate 02:34 with and without malathion; correct? I think that's your expert report at page 18.
A. Where's that?
Q. In your expert report at page 18.
MR. WISNER: Do you want to go off 02:35 the record while we fix this?
MR. LASKER: If we can. I don't know that we can. Let's wait until the end of this question.
MS. FORGIE: What was the question 02:35

again?
MR. LASKER: Now I'm losing track of these things. Oh, okay.
BY MR. LASKER:
Q. So in your expert report you note that there was a separate analysis of the McDuffie data that separated out the association for glyphosate with and without co-exposure to malathion; correct? 02:35
A. Yes, that's the Hohenadel paper. 02:36
Q. The Hohenadel study is a stratified analysis like we were discussing earlier in your testimony here today; correct?
MS. FORGIE: Object to the form.
THE WITNESS: It's not a stratified analysis. It's what we would call an interaction model testing. 02:36
BY MR. LASKER:
Q. In that interaction model testing when, and I think you report this, you note this in your expert report, when Hohenadel looked at the McDuffie data and looked at exposures -- farmers who were exposed to glyphosate alone without co-exposure to malathion, they found or they reported an 02:36

odds ratio of 0.92 with a confidence interval of 0.54 to 1.55; correct?
A. Correct.
Q. And in your report you also point to a separate analysis that you say McDuffie conducted which looked at glyphosate exposure mixed with dicamba exposure; correct, in your expert report? 02:37
A. Where is that?
Q. Right above -- 02:37
A. Above? Yes.
Q. Okay. And I take it that that -- your discussion there is based upon -- and correct me if I'm wrong -- Table 2 in the McDuffie paper? 02:37
A. It's the McDuffie paper.
Q. Look at Table 2.
MS. FORGIE: You can look at whatever you want.
BY MR. LASKER: 02:38
Q. You'll see the numbers that you cite in your expert report on Table 2 for dicamba and dicamba individual. Do you see those?
A. Yes. 02:38

Q. So in your report when you are stating that there was an elevated odds ratio for dicamba exposure mixed with glyphosate exposure, that is relying upon that footnote G in Table 2; correct? 02:38
A. Correct. That's what it was.
Q. And footnote G states that the odds ratio that you cite for mixed exposure for dicamba and glyphosate also involves mixed exposures to dicamba and 2,4-D and Mecoprop; correct? 02:39
A. That's what it says in the footnote.
Q. And unlike for glyphosate, McDuffie reported statistically significant increased risks of non-Hodgkin's lymphoma separately associated with exposures to each of the three pesticides 2,4-D, dicamba, and Mecoprop; correct? 02:39
A. That's in table -- 02:39
Q. It's actually in Table 2. They have separate odds ratios reported for 2,4-D that is statistically significant in their --
A. Yes. 02:39

Q. -- model, second model for Mecoprop?
A. Yeah, but it's an effect estimate of 1.26 and 1.32, and it's only statistically significant after the adjustment. 02:39
Q. Okay. And then for Mecoprop there is a 2.23 or 2.33 odds ratio --
A. Correct.
Q. -- statistically significant to both measure and for dicamba even in the dicamba alone for their more highly adjusted odds ratio it's 1.68 marginally statistically significant; correct? 02:39
A. Yes. 02:40
Q. And you cannot tell from this data when you're looking at the mixed exposures for dicamba when they're mixed for 2,4-D Mecoprop and glyphosate, you cannot attribute the difference between dicamba alone and this dicamba mixture to glyphosate, can you? 02:40
MS. FORGIE: Object to the form.
THE WITNESS: You can never do that in an individual anyhow. When you're 02:40

doing these kind of analyses, you have mixed exposures. If a person is exposed to two compounds, then it can be either one compound or the other or both together that are responsible for the event. 02:40

BY MR. LASKER:

Q. But in this case, it's not one or the other or two. There's actually four different chemicals when you're stating that there was in your expert report -- and let's go back to your expert report. You state that McDuffie reported that when glyphosate exposure was mixed with dicamba, the risk was increased. 02:41

Do you see that?

A. Yes.

Q. And, in fact, what McDuffie was reporting is that when dicamba exposure also included mixed exposures to glyphosate, 2,4-D and Mecoprop, there was an increase as compared to the dicamba alone; correct? 02:41

MS. FORGIE: Object to the form. Mischaracterizes.

THE WITNESS: That's not what I'm 02:41

saying. I'm saying there is dicamba that is of the kind Banvel and Target which includes glyphosate and then there's dicamba overall. So one is a subgroup of the other. And you can actually see that when you're looking at the number of exposed cases and exposed controls. Dicamba is the all-encompassing over label and then they're breaking it down with and without glyphosate, et cetera, mixtures. 02:41 02:42

BY MR. LASKER:

Q. The et cetera is the important point, but let me make sure I understand. Is it your testimony that or Banvel or Target is a mixed exposure with glyphosate? 02:42

MS. FORGIE: Objection. Object to the form and mischaracterizes her testimony.

THE WITNESS: So it says in the footnote, "dicamba is a major chemical class, includes Banvel and Target and a mixture of dicamba glyphosate, Rustler, or a mixture of dicamba 2,4-D and Mecoprop. 02:42

BY MR. LASKER:

Q. And then Dynel, Killex; correct?

MS. FORGIE: Object to the form.

THE WITNESS: Dynel DS, and Killex.

BY MR. LASKER: 02:42

Q. So the mixed exposure would be in Rustler for dicamba and glyphosate; correct?

A. There are several mixtures. There's the mixture of dicamba and glyphosate in Rustler and then there's the mixture of dicamba with 2,4-D and Mecoprop. 02:42

Q. So for the 1.68 odds ratio, that's dicamba alone; correct?

A. That's the overall dicamba. That's not dicamba alone. That's not -- that's dicamba with everything. 02:43

Q. And your understanding is dicamba with everything is 1.68 and dicamba alone is the 1.88?

A. No. 02:43

MS. FORGIE: Object to the form.

THE WITNESS: It's the opposite.

MS. FORGIE: Okay. That's what I thought.

THE WITNESS: Dicamba overall is 02:43

1.88, and the dicamba, Banvel and Target is 1.68.

BY MR. LASKER:

Q. And the difference -- in your expert report you state that the difference going up to that higher number is because there was including mixtures with glyphosate, but that higher number actually also reflects exposures to 2,4-D and Mecoprop; correct? 02:43 02:43

MS. FORGIE: Objection. Object to the form and asked and answered.

You can answer it again.

THE WITNESS: I'm not sure that I understand what you're trying to get at. In this table, dicamba exposure was the footnote G is the overall encompassing -- all-encompassing exposure. The individual dicamba herbicide Banvel or Target is the one that's reported below. The number of cases is lower, and the number of controls is lower, but, in essence, the number of 26 and 50s included in the larger category above which is 73 and 02:43 02:44

131.
BY MR. LASKER:
Q. My question is very simple. In your expert report, you state that the odds ratio of 1.92 was an odds ratio of glyphosate exposure mixed with dicamba. And am I correct in my reading of this table that that 1.92 odd ratio is, in fact, dicamba with mixtures that include glyphosate but also Mecoprop and 2,4-D? 02:44
MS. FORGIE: Objection. Object to the form and also asked and answered.
You can answer it again.
THE WITNESS: The larger group encompasses everything including glyphosate. 02:44
BY MR. LASKER:
Q. And Mecoprop and 2,4-D; correct?
A. It's the largest group.
Q. Yes. And you have to answer the question or there's no answer on the record. 02:45
A. Yes. It's the larger group.
MS. FORGIE: Wait, wait. So get a format back that's question and answer so I can get my objections in. 02:45

BY MR. LASKER:
Q. So the odds ratio of 1.92 that you cite in your expert report as glyphosate exposure mixed with dicamba is the odds ratio that McDuffie reports for dicamba and dicamba mixtures including glyphosate 2,4-D and Mecoprop; correct? 02:45
MS. FERGIE: Objection. Object to the form. Also asked and answered.
You can answer it again. 02:45
THE WITNESS: Dicamba here is a super category for several mixtures, and it's stated under footnote G. And we can see that that's the case because there are more NHL cases and more controls in that category than in the category below. 02:45
MR. LASKER: I'm going to mark this answer as well.
BY MR. LASKER: 02:45
Q. I'm going to ask the question again because I think it's a simple question, but I'm not getting an answer?
MS. FORGIE: I'm objecting to that commentary. You're badgering the 02:46

witness when you do that.
MR. LASKER: You can object as much as you want.
MS. FORGIE: I will.
BY MR. LASKER: 02:46
Q. The odds ratio of 1.92 that you report in your expert report as the odds ratio for glyphosate mixed with dicamba is as reported, in fact, in the study McDuffie an odds ratio for dicamba and dicamba mixtures with glyphosate but also with 2,4-D and Mecoprop; correct? 02:46
MS. FORGIE: Objection. And I object to the form. And I object to the fact this is the eighth time you've asked her. You're badgering this witness. It's not fair. 02:46
You can answer again.
THE WITNESS: The reason why I'm referring to this is because this is a mixture exposure, and that's very clearly stated in my report. 02:46
BY MR. LASKER:
Q. Your report --
A. The mixture includes dicamba and 02:46

glyphosate under heading G in this footnote.
Q. The mixture also includes which you don't mention in your report 2,4-D and Mecoprop; correct? 02:46
MS. FORGIE: Objection. Asked and answered. Object to the form.
You can answer again.
THE WITNESS: It is a mixture exposure. Some people were exposed to a mixture of dicamba and glyphosate. 02:47
Others might have been exposed to a mixture of dicamba with something else, but it says the major chemical classes included Banvel and Target, and it refers to these two as major and being a mixture of dicamba and glyphosate. 02:47
BY MR. LASKER:
Q. Banvel and Target do not have glyphosate in them, do they?
MS. FORGIE: Objection. Asked and answered. 02:47
You can answer it again.
THE WITNESS: The way it states it dicamba is a major chemical class, includes Banvel and Target and a mixture 02:47

of dicamba and glyphosate. That's what I said.
BY MR. LASKER:
Q. So is it your understanding and the basis of your expert report that Banvel and Target include glyphosate? 02:47
MS. FORGIE: Objection. Object to the form. Asked and answered. You're badgering the witness. This is completely unfair. 02:47
I'll let you answer it again.
THE WITNESS: What I said is that dicamba is a major chemical class and what they refer to here is that dicamba wasn't dicamba alone, but it was under 02:47 this rubric of dicamba G exposed. They subsumed multiple agents that were mixed with dicamba.
BY MR. LASKER:
Q. McDuffie provides an analysis in 02:48 her expert report. I'm not sure that fully answered on the last question but I'm going to move on so I can get through this deposition for now at least.
McDuffie provides an analysis on 02:48

Table 8, I believe, of exposures based upon days, less than two days or more than two days for purposes for glyphosate; correct?
A. Yes.
Q. You do not cite to this analysis, 02:48 unless I missed it, anywhere in your expert report; correct?
A. I think I'm referring to it in my Bradford Hill analyses. Yes. However, the effect as to -- 02:49
Q. Can you show me where you are?
A. Yes. Page 23. Bradford Hill evaluations.
However, the effect estimates for longer or more extensive use in several 02:49 studies were larger between two and three, and that includes this estimate.
Q. So if you were referring to this at page 23, you would need to refer to the McDuffie paper? 02:49
A. Yes.
Q. You do not in your discussion of the McDuffie paper --
A. Point that out.
Q. Point that out; correct? 02:49

A. I guess I didn't.
MS. FORGIE: When you get to a good breaking point, let's take a short break, please.
MR. LASKER: Okay. Let's just get 02:50 through this.
MS. FORGIE: That's fine.
BY MR. LASKER:
Q. In your opinion, does this analysis on Table 8 of less than or equal to two days 02:50 versus greater than two days provide evidence of a dose response for glyphosate?
A. This is not supposed to give a dose response. This is an analysis where you're trying to separate out people who are 02:50 completely unexposed to this agent and people who had minimal exposure versus reasonable exposure two days per year. And in doing so, you can actually see that there's very little confounding due to any 02:50 other variable because for minimal exposure the effect estimate is 1. So even if I would compare as done in De Roos, the people with more than two days of exposure to the people of less than two days, I would still 02:51

get the same kind of effect estimate.
Q. I'm not sure I got the answer to my question, though.
In your opinion, does the analysis that McDuffie provides in Table 8 of less 02:51 than or equal to two days' exposure versus greater than two days, in your opinion, does that provide evidence of a dose response for glyphosate?
MS. FORGIE: Objection. Object to 02:51 the form. Also asked and answered. She just answered that.
You can answer it again.
THE WITNESS: The intent of this analysis is not dose response. The 02:51 intent of this analysis is to distinguish between types of people who use and did not use glyphosate.
BY MR. LASKER:
Q. And do I understand correctly then 02:51 that you do not interpret the data reported in this table as providing evidence of a dose response?
MS. FORGIE: Objection. Asked and answered. 02:51

You can answer it again.
THE WITNESS: I see this as an indicator that a better exposure assessment that defines glyphosate use not as ever/never which is the worst or the most simple category you can get but as a reasonable amount, more than two days per year, we don't know how many days those are, but that that category provides you with some indication that there is an effect. 02:51 02:52
BY MR. LASKER:
Q. So I think I understand you, but I just want to make sure that I'm clear. Am I correct then in my understanding that you do not interpret the data on Table 8 in McDuffie as presenting evidence of a dose response glyphosate and non-Hodgkin's lymphoma? 02:52
MS. FERGIE: Objection. Object to the form. Also asked and answered. 02:52
You can answer it again.
A. There's no formal analysis of a dose response. However, the more than two days per year category suggests that there 02:52

is a dose effect.
BY MR. LASKER:
Q. And so I get your opinions because that what we're here for. In your opinion, does the data presented on Table 8 for glyphosate provide evidence of a dose response for glyphosate and non-Hodgkin's lymphoma? 02:52
MS. FERGIE: Objection. Asked and answered. This is the fifth time. 02:53
You can answer it again.
A. So, again, this is not a formal dose response analysis, but it is a very clever analysis and one that I really enjoy looking at because, first of all, they are splitting up people who don't use glyphosate and then the group of people who do use it and the casual users, whether -- versus the more frequent or more intense users, and in that sense, you can say that at the higher doses there is actually an effect. 02:53 02:53
BY MR. LASKER:
Q. Okay. I'm still trying to get an answer to this question because I don't think I have it. 02:53

In your opinion, does the data presented in Table 8 in the McDuffie paper provide evidence of a dose response for glyphosate and non-Hodgkin's lymphoma?
MS. FORGIE: Objection. I object to the form, and especially I object to the fact that she's answered this five or six times now. Again, you're badgering the witness just because you don't like the answer. 02:53 02:54
You can answer it again.
THE WITNESS: Okay. So clever analysis, splitting up unexposed and exposed, selecting out people who are maybe occasional users, looking at those who have probably regular intense use. Among those with regular and intense use, we see an effect for glyphosate. 02:54
BY MR. LASKER:
Q. That wasn't my question. My question is: Does this data in Table 8 from McDuffie, in your opinion, present evidence of a dose response for glyphosate? 02:54
MS. FORGIE: Objection. Asked and answered. 02:54

THE WITNESS: I have criteria for those response. You may have your own. In this case, there is a high use of glyphosate associated clearly with an odds ratio of 2.12 with NHL. 02:54
BY MR. LASKER:
Q. Does this Table 8 in the McDuffie meet your criteria to be interpreted as providing evidence of a dose response for the glyphosate in non-Hodgkin's lymphoma? 02:55
MS. FORGIE: Objection. Asked and answered.
THE WITNESS: This results provides evidence that with intensity and frequency, whatever this means, two days per year, there is indeed an effect for glyphosate compared to people who are using either none or using occasionally less than two times a year. 02:55
MR. LASKER: I'm going to mark this answer, and again, I'm going to ask the question again because I still don't get answers to my questions. 02:55
BY MR. LASKER:
Q. Based upon your criteria, whatever 02:55

criteria you use in your professional work, does the data presented in Table 8 in the McDuffie paper provide evidence of a dose response effect for glyphosate in non-Hodgkin's lymphoma? 02:55

MS. FORGIE: Objection. This is, like, the eighth time you've asked the same exact question, and she's answered it seven or eight times. This is really badgering the witness. I'm going to let her answer it one more time. 02:55

THE WITNESS: I just repeat myself. We are distinguishing unexposed people from irregular users, minimal users, and regular users. In the regular use group, we see an effect. 02:56

MR. LASKER: Okay. Mark that answer.

Let's take a break.

THE VIDEOGRAPHER: We are off the record at 2:56 p.m. 02:56

(Recess taken from 2:56 p.m. to 3:13 p.m.)

THE VIDEOGRAPHER: We are back on the record at 3:13 p.m. 03:13

BY MR. LASKER:

Q. Dr. Ritz, we were talking about Table 8 in the McDuffie paper, and I'm correct, am I not, that the McDuffie paper does not provide any analysis of the intensity of the exposures to glyphosate in this population; correct? 03:13

MS. FORGIE: Object to form.

THE WITNESS: That is incorrect. They are actually distinguishing between irregular and regular users, and in the category of regular users, they see an increased risk. 03:14

BY MR. LASKER:

Q. So regular users is greater than two days per year; correct? 03:14

A. Yes.

Q. So if somebody were to use glyphosate for a half-hour in the spring in the driveway and then a half-hour in the fall and another half-hour in the summer, that would be three times a year, and they would be greater than two days a year; correct? 03:14

A. I don't venture to say that because 03:14

they're measuring here in days, and when I do my pesticide studies, we actually ask how many hours per day, and then we average across to come to eight-hour workday and add all of that up. How they exactly did that is not described here, but that's how we would do it. 03:14

Q. Okay. But you don't know how the investigators in this study calculated day of exposure; correct? 03:15

MS. FORGIE: Objection. Asked and answered.

THE WITNESS: These investigators give you a more than two day per year category, and I imagine they did this in order to distinguish between irregular users who they classify as more than zero and less than two days. 03:15

BY MR. LASKER:

Q. My question, though, is these investigators do not indicate and you don't have any information as to how they determine a day of exposure; correct? 03:15

MS. FORGIE: Objection. Asked and answered. 03:15

You can answer it again.

THE WITNESS: These investigators asked people to report occupational exposures, and when you ask about occupational exposures, you usually refer to a workday. So I would interpret this as two workdays per year. 03:15

BY MR. LASKER:

Q. Okay. So your interpretation -- it's not set forth in the study, but your interpretation of this table is that greater than two days means a full two-day -- each day would be a full workday of exposure? 03:15

MS. FORGIE: Objection. Asked and answered. Also mischaracterizes her testimony. 03:16

THE WITNESS: I, as a pesticide exposure assessment epidemiologist, would specifically ask people to report how many hours, how many days, how many weeks, how many years they would be having used these specific agents and then categorize it according to the days or hours or years. 03:16

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BY MR. LASKER:
Q. I understand what you would do. That's not my question. I'm trying to find out what McDuffie and her group did.
They do not state in their paper -- they do not define a day as being an eight-hour exposure day, do they?
MR. FORGIE: Objection. Asked and answered.
THE WITNESS: I have to check. They actually asked extensive questions including histories, pesticide spill, protective equipment, et cetera. So given that they asked all this, and they were after workplace exposures, I would interpret this as two workdays.
BY MR. LASKER:
Q. McDuffie does not, anywhere in this paper, state that they define a day as a workday of exposure, do they?
MS. FORGIE: Objection. Asked and answered. She just testified as to exactly how she interprets that meaning.
MR. LASKER: Okay. That's not the question I asked. I'll ask the question

again.
MS. FORGIE: Yes, it is.
BY MR. LASKER:
Q. McDuffie and her investigators in this published paper never state that they defined a day of exposure as a full workday of exposure; correct?
MS. FORGIE: Objection. Asked and answered. You're badgering the witness. She's already told you how she interprets it.
You can answer it again.
THE WITNESS: Yes, actually they're saying on page 1157, "We created dose response levels based on days per year of personally mixing or applying selected herbicides, insecticide, fungicides, and fumigants."
So days per year of personally mixing or applying, that's workplace types of exposures.
BY MR. LASKER:
Q. I understand, but they don't state a minimum time period in a day for it to be quantified as a day of exposure; correct?

MS. FORGIE: Objection. Asked and answered. She's told you exactly two or three times how she interprets that.
You can answer it again.
THE WITNESS: I think I answered it.
MS. FORGIE: You can answer it again.
THE WITNESS: So they are trying to distinguish between regular users and occupational regular users who are mixing and applying pesticides and people who might be for one day in their life applying glyphosate.
BY MR. LASKER:
Q. Dr. Ritz, let's talk about the North American pooled project analysis by Pahwa in 2015.
MS. FORGIE: Are we putting this away?
MR. LASKER: For now, yeah.
BY MR. LASKER:
Q. And this is analysis which was a pooled analysis of the case control studies that were pooled in De Roos 2003 and also

the Canadian case control study that was analyzed by McDuffie; correct?
A. Can I have the exhibit?
Q. Sure.
A. Thank you.
Q. This is 19-16.
(Exhibit Number 19-16 was marked for identification.)
THE WITNESS: It's called the North American Pooled Project. On page 5, we see that it is encompassing those states, yes.
BY MR. LASKER:
Q. And this is the analysis at that 2015 ISEE conference that you cite to in your expert report; correct?
A. Yes.
Q. When did you -- you provided this slide deck or at least it was provided to us as an additional material considered after your rebuttal expert report.
When did you first see this slide deck?
A. I saw it after the deposition of Dr. Blair, and there was reference to this.

Q. Did you -- had you seen this slide deck prior to the time you prepared your initial expert report in this case?
A. No.
Q. Okay. And I take it you saw it then sometime before you reviewed the rebuttal -- I'm sorry, before you prepared your rebuttal exert report, your second expert report? 03:20
A. Yes. 03:20
Q. Have you read Dr. Neugut's deposition?
A. Yes.
Q. Did you see this slide deck before you read Dr. Neugut's deposition or after? 03:20
A. I wouldn't be able to tell.
Q. So may have been before or may have been after, you're not sure?
A. I don't know.
Q. If I can refer you to page 10 of this presentation, the NAPP presentation, they provide data or odd ratios for their ever/never analysis both overall for the glyphosate and non-Hodgkin's lymphoma and also for various subtypes of NHL; correct? 03:21

A. Correct.
Q. And they have two analyses that they present in this table. Their odds ratio A which is adjusted for age, sex, state, province, emphatic or hematopoietic cancer in a first-degree relative, use of a proxy respondent, and use of personal protective equipment; correct? 03:21
A. Yes.
Q. And then odds ratio B would adjust for those factors just listed and also adjusts for 2,4-D, dicamba and malathion; correct? 03:22
A. Correct.
Q. For the ever/never analysis of the pooled data from the U.S.-based and Canadian-based case control studies, when adjusted for the use of 2,4-D, dicamba and malathion, they report an odds ratio of 1.13 with a confidence interval of 0.84 to 1.51; correct? 03:22
A. Yes.
Q. And for their various subtypes of non-Hodgkin's lymphoma, in their adjusted model adjusting for the use of 2,4-D, 03:22

dicamba, and malathion, they report varying odds ratios, one of which is below 1, three of which are above 1, but all of which are not statistically significant; correct?
A. Well, I wouldn't evaluate this according to statistical significance especially in a subgroup analysis where I'm splitting the data in this way. The way I would evaluate it is whether there's considerable change in effect estimates and width of the confidence interval. 03:23
Q. Okay. So follicular lymphoma for their odds ratio that's adjusted for the use of 2,4-D, dicamba, and malathion, they find an odds ratio of 0.69; correct? 03:23
A. That's what they state, yes.
Q. And that was a reduction in the odds ratio when they adjusted for these exposures to other pesticides; correct?
A. Correct. 03:23
Q. For diffuse large B cell lymphoma when they adjusted for 2,4-D, dicamba, and malathion, they report an odds ratio of 1.23. That's not statistically significant; correct? 03:24

MS. FORGIE: Objection. I object to the form.
MR. LASKER: That's fine.
THE WITNESS: That's an odds ratio that's lower than 1.6 and the confidence interval includes the 1. 03:24
BY MR. LASKER:
Q. Okay. So when they adjusted for the use of 2,4-D, dicamba, and Malathion, their odds ratio for diffuse large B cell lymphoma went down and was no longer statistically significant; correct? 03:24
MS. FORGIE: Objection. Object to the form.
THE WITNESS: It fluctuated. It went from 1.6 to 1.23, but the confidence interval basically overlapping. 03:24
BY MR. LASKER:
Q. And for the odds ratio with adjustment for 2,4-D, dicamba, and Malathion, the confidence interval went from .81 to 1.88 including a null hypothesis of 1.0; correct? 03:24
A. Including the null value in a 03:24

formal statistical test.
Q. And SLL, I knew I was going to get to this one. What does SLL stand for?
A. Small lymphocytic lymphoma.
Q. For that odds ratio there is not a meaningful change when they adjusted for exposures to other pesticides; correct? 03:25
MS. FORGIE: Objection. Object to the form.
THE WITNESS: It almost -- it basically stays the same. The confidence interval widens as one would expect when you put additional variables in a model. 03:25
BY MR. LASKER:
Q. And then for the other category you have an odds ratio that drops from 1.66 to 1.51 with adjustments for 2,4-D, dicamba, and Malathion, and that adjusted odds ratio is 0.87 to 2.6 which includes the null value of 1.0; correct? 03:25
MS. FORGIE: Object to the form.
THE WITNESS: Well, the odds ratio changes from 1.66 to 1.51 which is almost the same. And as I stated 03:26

before, the confidence intervals widen when you add other variables into the model, and it does include null to null value.
BY MR. LASKER: 03:26
Q. And in your original expert report before you had seen this data, you had discussed the fact that the Pahwa NAPP data should be considered in conducting any meta-analysis of the website data; correct? 03:26
MS. FORGIE: Object to the form.
THE WITNESS: Where is that stated?
BY MR. LASKER:
Q. That is on page 16, 15 and 16, where you're talking about the NAPP data. 03:26
And, first of all, just to be clear, in your expert report for the NAPP data you are reporting data that is not adjusted for exposures to 2,4-D, dicamba, and Malathion; correct? 03:27
A. I have to go to the abstract to confirm that.
So what's the question?
Q. In your expert report before you had seen the data adjusted for exposures to 03:27

2,4-D, dicamba, and Malathion, you had suggested that the NAPP data had not been included in the meta-analysis that had been performed for glyphosate and non-Hodgkin's lymphoma; correct? 03:27
A. That is correct. They have not been included anywhere, and that's what this sentence says.
Q. And under the methodology that both Chang and Delzell used and that the IARC scientists used in conducting their meta-analyses, when there was a subsequent pooled analysis of case control data, they included that subsequent study, and they removed the earlier studies from their meta-analysis; correct? 03:28
MS. FORGIE: Object to the form.
THE WITNESS: That would usually be how you do it.
BY MR. LASKER: 03:28
Q. And in both the Chang and Delzell meta-analysis and the analysis that IARC did with its working group for their meta-analysis, they used the odds ratios that were -- where they had them that were 03:28

adjusted for exposures to other pesticides; correct?
A. I think they did, but can you show me where that's stated.
Q. In your expert report actually at page 16. We went through that earlier. 03:29
A. Okay.
Q. Correct?
A. Yes.
Q. If we were to conclude the NAPP data into the meta-analysis using the methodology that was used by Chang and Delzell and using the methodology that was used by IARC, we would use the odds ratio for the NAPP of 1.13; correct? 03:29
MS. FORGIE: Object to the form.
THE WITNESS: No. This is not a valid model in my mind because you have to show me that 2,4-D, dicamba, and Malathion are actually related to glyphosate use and also are independent risk factor for NHL. So if you're telling me dicamba is an independent risk factor for NHL, then yes. Also it should be removed. 03:29 03:30

Also I would not accept this model because we would not want to adjust for the use of proxy respondents or personal protective equipment because those two variables are indicators for exposure mismeasurement. You cannot adjust a model for exposure mismeasurement. These are confounded and shouldn't be in the models. 03:30

BY MR. LASKER:

Q. I understand, and I'm going to get to your opinions about the NAPP and how they did their analysis. The IARC in conducting its meta-analysis did not reach any conclusions with respect to the individual studies as to whether or not they found those studies to be internally valid; correct? They just used the data that was presented? 03:30

A. I don't -- 03:30

MS. FORGIE: Object to the form.

THE WITNESS: I don't believe that IARC would use estimates that they don't believe are valid. I wouldn't.

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BY MR. LASKER:

Q. In their methodology the both for the IARC meta-analysis and for the NAPP, they used the data point presented in each of the studies that were available for glyphosate and non-Hodgkin's lymphoma; correct? 03:31

A. That's how you conduct meta-analysis.

Q. They did not exclude any of the analyses; correct? 03:31

MS. FORGIE: Object to the form.

THE WITNESS: They did not exclude one of the studies.

BY MR. LASKER: 03:31

Q. And they did not -- so for their purposes -- and I understand you will have your own interpretation how you do a meta-analysis when we talk about that in a moment, but following their methodology, if this study was available to them, they would use as they did with every other study what was reported as the most adjusted odds ratio which in this case was reported as 1.13; correct? 03:31

MS. FORGIE: Object to the form.

THE WITNESS: I don't want to venture into what people would be doing if. I would not recommend to use this preliminary data that has obvious problems to replace studies that have been published and peer-reviewed. 03:32

BY MR. LASKER:

Q. I'm sorry. This is the data except for the fact that we now have adjusted odds ratios which you had not seen when you prepared your expert report. This is the same NAPP analysis that you had put forth as a basis for your expert opinion; correct? 03:32

MS. FORGIE: Objection. Mischaracterizes her report. 03:32

THE WITNESS: I have not used these slides. I have used an abstract.

BY MR. LASKER:

Q. But it was an abstract that resulted in the presentation at the exact same conference where the abstract was presented, and this is -- the exhibit we have, 19-16, is a presentation that went along with that abstract at that conference; 03:32

correct?

MS. FORGIE: Object to the form. Mischaracterizes.

THE WITNESS: When we are scientists to present results, we sometime like to present results that are provocative and also have discussions. So I would consider this one of those slides where we can then discuss how to run the analysis one way or another. 03:32

These kind of discussions often feed into final analyses that are published in the literature because the authors then are aware of criticism from the scientific community. That's the whole reason to present these. 03:33

BY MR. LASKER:

Q. I'm just a little confused now because prior to seeing this data adjusted for the pesticides, you were opining, and you had earlier in this deposition I thought, that the NAPP data presented at Brazil at that ISEE conference should be considered as part of the analysis of the 03:33

epidemiologic literature, didn't you?
A. The abstract I saw, yes. But I'm not referring to this table.
Q. Okay. So while you believe that the NAPP data that was prepared and 03:33
presented in a one-paragraph abstract for this presentation should be considered, you do not believe that it would be appropriate to consider the full data that was actually presented at that conference because it is 03:34
preliminary; is that correct?
MS. FORGIE: Object to the form.
THE WITNESS: So any data that we are presenting and not putting into a paper version is preliminary including 03:34
the abstract that went to this conference. The only reason why I like the abstract is because it referred to existing data, existing studies that I had read that I understood. The 03:34
methodology and the way they were performed. However, when we are presenting tables at conferences, what we are doing is allowing input into analyses from a scientific audience that 03:34

is informed. That's what this table is all about, and had I been there, I would have made comments about this kind of table.
BY MR. LASKER: 03:35
Q. I just want to be clear now if I understand your position. Is it your position, then, that the NAPP data is too preliminary to be considered as part of an expert analysis, or is it your opinion that 03:35
the NAPP data in the abstract that came out before this conference should be considered but that the data presented at the conference should not?
MS. FORGIE: Objection. 03:35
Mischaracterizes her testimony.
THE WITNESS: It's all the same data. It's just a question of which analyses you believe more or not.
BY MR. LASKER: 03:35
Q. And is it my -- is it your testimony then that while you believe in the data that was presented in the abstract and you think that should be considered as reliable evidence, epidemiological evidence 03:35

for glyphosate and non-Hodgkin's lymphoma, you do not believe that the data that was actually presented at that conference should be considered as reliable evidence, separate epidemiological evidence regarding 03:35
glyphosate and NHL?
MS. FORGIE: Object to the form.
THE WITNESS: Again, I want to say the same data.
BY MR. LASKER: 03:36
Q. So in your expert report, you stated that we should consider the NAPP data in our analysis; correct?
A. Yes.
Q. Okay. And so it's fair to say that 03:36
you also agree that we should consider the data that was actually presented from the NAPP in its conference in our analysis; correct?
MS. FORGIE: Object to the form. 03:36
THE WITNESS: That's different. The data, the way it's presented, contains a lot of what we would call sensitivity analyses and ways of presenting the data that I would as a 03:36

reviewer agree or not agree with.
BY MR. LASKER:
Q. And am I correct in my understanding that your concern with respect to presenting the data from the NAPP for -- 03:36
as compared to data that controls for 2,4-D, dicamba, and Malathion versus data that does not control for 2,4-D, dicamba, and Malathion, that you believe it is more reliable to look to the data that does not 03:37
control for 2,4-D, dicamba, and Malathion?
MS. FORGIE: Object to the form and object to mischaracterizing her testimony.
THE WITNESS: I never talked about 03:37
reliability. That's not at issue here. What is at issue is validity of the model, and I disagree with the validity of this model, and I would suggest additional sensitivity analyses 03:37
concerning this.
BY MR. LASKER:
Q. And am I correct in my understanding that -- well, let me ask this: Do you have concerns of the validity of the 03:37

NAPP model for all of the data presented or only for the data presented that adjusts for exposures to 2,4-D, dicamba, and Malathion?

MS. FORGIE: Object to the form.

THE WITNESS: I have validity concerns about this one table, and I would like to see additional analyses before I would make up my mind. 03:37

BY MR. LASKER:

Q. Do you have validity concerns for the data presented in the abstract that you relied upon in your expert report before you saw this data? 03:38

A. The validity concerns are not considering the data. The validity concerns are with respect to this one subanalyses that I consider a sensitivity analysis. 03:38

Q. Which subanalyses are you talking about?

A. The one adjusting for three additional pesticides. 03:38

Q. So that's -- so I understand. So you do not have -- I'm just making sure I understand this. You do not have validity concerns with respect to the NAPP data that 03:38

does not adjust for dicamba, 2,4-D, and Malathion; is that correct?

MS. FORGIE: Object to the form.

THE WITNESS: I have validity concerns about this whole table as I just told you because I would suggest that, first of all, proxy respondents and personal protective equipment should not be entered in the model to begin with. 03:38 03:38

BY MR. LASKER:

Q. That information, and I'll just -- I don't have time to go through this, but if that information was in the abstract that they controlled for that, would you have concerns with the data and the information presented in the abstract that you relied upon in your original expert report? 03:39

MS. FORGIE: Object to the form and also asked and answered. 03:39

You can answer it again.

THE WITNESS: I can only refer to this table in front of me that states very clearly what they adjusted for, and I would have asked as a conscientious 03:39

reviewer to remove these two variables and tell me whether it makes a difference.

BY MR. LASKER:

Q. And do you have greater concern for the validity of the odds ratios that adjusts for 2,4-D, dicamba, and Malathion than for the odds ratios that do not? 03:39

MS. FORGIE: Objection. Object to the form. Asked and answered. 03:39

You can answer it again.

THE WITNESS: That's a question I cannot answer because I don't know what the results would be if we did this differently. 03:39

BY MR. LASKER:

Q. Okay.

A. And that's what we do in epidemiology. We try all sorts of things and see how the data behaves. 03:39

Q. Okay. For the analysis for duration of exposure and days of exposure, the NAPP basically had data on duration -- if you look at page 7.

A. Page 7? 03:40

Q. Yeah.

A. Oh, yeah.

Q. So the duration and frequency and lifetime days analysis for the NAPP is drawn from the Nebraska and the Canadian case control data because we don't have all -- we don't have the full data for Iowa, Minnesota. We don't have any data for Kansas to conduct those analyses; correct? 03:40

MS. FORGIE: Object to the form. 03:40

THE WITNESS: If those Xs mean there's no data, then that seems to be the case.

BY MR. LASKER:

Q. Okay. If we can go then to page 26, and I want to start just with the first column which is proxy and self-respondents, and we'll talk about the self-respondents only in a second. But for the -- they provide information in this table for frequency with respect to days per year, duration, and also lifetime days; correct? 03:41 03:41

A. Yes.

Q. And when we do the frequency 03:41

analysis -- and this is not particularly surprising since the Canadian case control study was a large driver of this -- we have a somewhat similar finding to what is reported in the McDuffie paper; correct? 03:42

MS. FORGIE: Object to the form.

THE WITNESS: Frequency more than two days per year and odds ratio of 1.73 or 1.77 counts as similar to 2, yes.

BY MR. LASKER: 03:42

Q. For duration -- so it's a different measure -- correct? -- of how many years they actually used glyphosate; correct?

A. Yes.

Q. McDuffie does not provide any 03:42 indication of the duration of use in her analysis in her study; correct?

MS. FORGIE: Object to the form.

THE WITNESS: She doesn't provide tables. That doesn't mean that they 03:42 didn't have it. Did they have it?

BY MR. LASKER:

Q. In the McDuffie paper?

A. No. In the data.

Q. They did have it in the data, yes. 03:42

A. Yes.

Q. But in the McDuffie paper they don't report duration; correct?

A. No.

Q. When they look at that data for 03:42 duration, we find that there is a lower incidence of NHL with a, at least numerically, with greater duration of use of glyphosate; correct? Goes from either 1.28 to 0.94 or 1.17 to 0.78; correct? 03:43

A. There's basically no difference.

Q. When we look at lifetime days, so this is actually figuring out the total amount of exposure that an individual in the study would have -- correct? -- that last 03:43 category?

A. It's not the total amount. It's duration times intensity, and that could be seven years used minimally or -- and that would give you a seven or seven days used at 03:43 the two workdays per year as we discussed. We don't know.

Q. Just to be clear because your answer had the word "seven years," and I want to make sure we understand this. The 03:44

lifetime days analysis is less than seven days in a lifetime of exposure to glyphosate or greater than seven days of exposure to glyphosate in the lifetime; correct?

MS. FORGIE: Object to the form. 03:44

THE WITNESS: What they call lifetime days is similar to pack years. So it's a product of the number of years times the days per year.

BY MR. LASKER: 03:44

Q. And when they did this analysis using that same McDuffie data and also the Nebraska data was added to it, and they looked at total lifetime days of exposure to glyphosate and they looked at that higher 03:44 category, the highest category they reported of greater than seven lifetime days of exposure to glyphosate, they had an odds ratio of either 1.08 or 1.06 for glyphosate and non-Hodgkin's lymphoma; correct? 03:44

A. They call it lifetime days, but it's not days in a lifetime. It's this product of years times number of days per year; so it's more like a pack year, and I'm not surprised because duration, number of 03:45

years, had no effect. So if you're using duration as number of years, you are very likely to wipe out any intensity effect.

Q. Well, the intensity just to be fair, the duration would include all the 03:45 days within each year -- the lifetime days has both factored into it. It has the days per year, and it has the duration of time; correct?

MS. FORGIE: Objection. Object to 03:45 the form.

THE WITNESS: It's not correct because number of days per year has two categories. It has the greater than zero and less than two which we agreed 03:45 on were the occasional users and then the two or more or better two -- more than two. So when you're calculating number of years times number of day per year, you're actually mixing a lot of 03:45 different things together. It's a really bad measure. So if you don't believe it is duration low level chronic exposure, if you think it's intensity, you have to have a high level of 03:46

exposure, then lifetime days is really not a good measure.
BY MR. LASKER:
Q. Is it your opinion that there could be intense exposure to glyphosate that is less than seven days of exposure in a lifetime? 03:46
A. Yes.
Q. And, in your opinion, when you look at this analysis -- 03:46
A. It's not seven days per lifetime. It's seven lifetime days as defined by this product.
Q. Okay. And you would agree that when this data is analyzed for pack year type analysis or lifetime days analysis, there's no indication of any greater risk of non-Hodgkin's lymphoma in the group that has the greater than seven days lifetime exposure; correct? 03:46 03:47
MS. FORGIE: Object to the form. Mischaracterizes her testimony.
THE WITNESS: Well, lifetime days seem to be a measure that doesn't show a dose response here. However, frequency 03:47

of years -- days per year which is not really a frequency but an intensity, seems to have an effect.
BY MR. LASKER:
Q. And your belief that this is an intensity is based upon your understanding of what a day of exposure means? 03:47
A. Correct.
MS. FORGIE: Objection.
BY MR. LASKER: 03:47
Q. And for day of exposure, would that be different -- defined differently for a lifetime day, each day and that day of exposure as compared to a frequency day?
MS. FORGIE: Object to the form. 03:47
THE WITNESS: So these frequencies go from zero to who knows what; correct? Number of days per year. And when you multiply those by years, then you could have very high intensity days with a low 03:48 number of years landing in the lower category, or you could have the opposite. So there's a lot of potential for exposure misclassification in terms of who's a regular user and who is not. 03:48

BY MR. LASKER:
Q. And without knowing more about how a defined exposure for frequency days, there could be exposure misclassification throughout this entire analysis in duration, in frequency, and in lifetime days; correct? 03:48
MS. FORGIE: Object to the form.
THE WITNESS: Well, duration is defined as duration, but we don't know what the intensity is. So that would 03:48 just be a measure of duration. It could be a very low intensity; it could be a very high intensity. It's just duration.
On the other hand, frequency which 03:48 I call intensity in this case distinguishes the high use from the low occasional use. There's no duration in this. We can only assume how it relates to duration, but they're not showing us 03:49 data that relates frequency and duration. And then this made-up lifetime days is a product of years, number of years times number of days per year. So a product of the two above. 03:49

And the one with the larger span will weight the other to nothing or to whatever that is.
So what we're seeing in duration year gets reflected in lifetime years 03:49 only in lifetime years it's even more misclassified because it mixes intensity with duration.
BY MR. LASKER:
Q. At the time you prepared your original expert report in this case, were you aware of the fact that the NAPP had conducted this further analysis of duration and lifetime days exposure to glyphosate? 03:49
MS. FORGIE: Object to the form. 03:49
THE WITNESS: At what time?
MS. FORGIE: Asked and answered.
BY MR. LASKER:
Q. At the time you prepared your expert report in this case. 03:49
A. I hadn't seen this.
Q. Okay. Also on this page there is a sensitivity analysis for proxy respondents, use of proxy respondents; correct?
A. You mean the same table? 03:50

Q. Yes.
A. The same table distinguishes between proxy and self and self-respondents. So it's not really a stratified analysis. It's a sensitivity analysis.
Q. Right. That's what I said. It's a sensitivity analysis; correct?
A. Yeah, yeah.
Q. When they conducted their sensitivity analysis, they found that for the never/ever category the odds ratio for self-respondents only for glyphosate and non-Hodgkin's lymphoma and all of the case control studies pooled in North America, U.S. and Canada, was 0.95 with a confidence interval of 0.69 to 1.32; correct?
A. That's what they're reporting.
Q. And that is, in fact, the -- if we're looking at the -- just a second. Okay. Let's talk about the Eriksson paper.
Let's change. I'm sorry. I got this note. I just completely ignored it.
THE VIDEOGRAPHER: This marks the end of videotape number 3 in the deposition of Dr. Beate Ritz. We're off the record at 3:51 p.m.
(Recess taken from 3:51 p.m. to 4:02 p.m.)
THE VIDEOGRAPHER: We are back on the record at 4:02 p.m. This marks the beginning of videotape number 4 in the deposition of Beate Ritz.
BY MR. LASKER:
Q. Dr. Ritz, I'd like to direct you to Exhibit 19-7, which is the Eriksson study. I just have a few questions.
MS. FORGIE: Do we have it?
MR. LASKER: She's got it.
BY MR. LASKER:
Q. We previously discussed the fact that --
MS. FORGIE: Hold on a second.
MR. LASKER: Let's go off the record.
THE VIDEOGRAPHER: We're off the record at 4:03 p.m.
(Recess taken from 4:03 p.m. to 4:03 p.m.)
THE VIDEOGRAPHER: We are back on the record at 4:03 p.m.
BY MR. LASKER:
Q. We were talking about the Eriksson study. I think earlier we established that the only odds ratio in this paper or the only table that includes odds ratios in this paper that were adjusted for the pesticide exposure is table 7 where the multi-variate analysis is presented on page 1661; correct?
A. Yes.
Q. Now, when you look at the other odds ratios in these other tables that are not adjusted for other pesticide exposures, virtually every odds ratio for every compound and every chemical that is analyzed is reported at above 1.0; is that correct?
A. That's a very simplified statement because a lot of the odds ratios are right around 1.
Q. Virtually every single one of the odds ratios that are reported in this paper are above 1.0; correct?
MS. FORGIE: Object to the form.
THE WITNESS: Again, there are lots of odds ratio hover above 1. There are odds ratio below 1, and there are odds ratios above 1, and there are lots of analyses that are including the same subjects. So if you want to do odds ratio counting, you need to discount the ones that are using the exact same data on the exact same people.
BY MR. LASKER:
Q. Correct. And when you do that, the vast majority of these odds ratios reported in Eriksson are above 1.0; correct?
MS. FORGIE: Object to the form.
THE WITNESS: Again, that's not how I look at this. I look at this as odds ratios reported for different agents for different purposes. One is a yes/no, ever/never. Other purposes are intensity or duration measures, and splitting up groups into less and higher intensity, you can see how nicely dose response patterns are starting to emerge. And the lower odds -- the lower exposure odds ratios usually include a close to 1, and the confidence intervals include 1.

BY MR. LASKER:
Q. Let me ask you this question generally: If you have a case control study, and you are -- I think you refer to this in your expert report at page 8 when you're talking about the fact that the De Roos 2003 study had odds ratios below 1 and above 1. And one of the things you stated there is that if you have odds ratios in a case control study for multiple agents and they're all above 1, you would have a concern for -- about recall bias; is that correct? 04:07
MS. FORGIE: Object to the form.
BY MR. LASKER: 04:07
Q. And you can look at page 8 on your expert report.
A. Where is it?
Q. At the very top you stated, "If recall bias existed, you would expect all pesticides reported to show an association with the outcome and not just one among many since the tendencies to recall better and more exposures than controlled would not be expected to be specific to one chemical." 04:07 04:08

Correct?
A. Yes.
Q. So if you have all chemicals in a study where you have elevated odds ratios, one of the things you would be concerned about, in general, is the possibility of recall bias; correct? 04:08
MS. FORGIE: Object to the form.
THE WITNESS: In general, if it's all chemicals, yes, but in this study I see a lot of odds ratios that are around 1 or even below 1 reported, and many of the odds ratios are duplicate analyses in terms of a dose response. So there's an analysis of an ever/never, and then for the same people we are now categorizing them in several categories to explore a dose response. 04:08
In that case I would expect that the overall estimate is somewhere a weighted average of the categories that I'm looking at. And in many cases you can see that the specificity increases. That's why we do this. So the specificity of exposure increases with 04:09 04:09

intensity or duration of use, and that's informative. When it doesn't, then it actually dissuades me that this agent is actually contributing.
BY MR. LASKER: 04:09
Q. Dr. Ritz, if you look at Table 5 in the Eriksson study which looks at insecticides total, DDT, mercurial seed dressing, pyretrine, other, every single odds ratio reported in that table is above 1; correct? 04:09
MS. FORGIE: Object to the form.
THE WITNESS: The confidence intervals, many of them include the 1, and it is a table of subtypes meaning we're now going into very, very small subgroups with very low exposures. So essentially a lot of these estimates are non-informative. 04:10
BY MR. LASKER: 04:10
Q. Let's skip over to --
A. And some are actually below 1. Clearly below 1.
Q. Let's skip over to the De Roos 2005 cohort study. First of all, I'd like to 04:10

mark as --
MS. FORGIE: Are we putting this away?
MR. LASKER: Yeah.
MS. FORGIE: Thank you. 04:10
MR. LASKER: So this is 19-17.
(Exhibit Number 19-17 was marked for identification.)
BY MR. LASKER:
Q. Dr. Ritz, this is a slide deck that unfortunately we received in this form. It's a little bit difficult to read, but this is a slide deck you produced to us in response to our document subpoena. 04:11
I take it this is a slide deck you've used in training in teaching of your class; correct? 04:11
A. Yes.
Q. And the glyphosate case control studies that we've been discussing are what are called retrospective in that they take individuals with NHL or without NHL, and then they look back in time and ask them about their prior exposures; correct? 04:11
MS. FORGIE: Object to the form. 04:11

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THE WITNESS: They are case control studies in which cases and controls report their lifetime use of pesticides.
BY MR. LASKER:
Q. So retrospective analyses; correct? 04:12
MS. FORGIE: Object to the form.
THE WITNESS: It's not an analysis that's retrospective. It's the exposure assessment that's retrospective.
BY MR. LASKER: 04:12
Q. So the exposure amendment in the case control studies are retrospective; right?
A. Correct. Not always. In this one. In these because they're questionnaire 04:12 based. They're case control studies that follow records, and they not retrospective.
Q. In the case control studies, is it your testimony that there are glyphosate case control studies that are not 04:12 retrospective in their gathering of exposure data?
A. Not in the literature that I reviewed.
Q. Okay. Strike that. Or don't 04:12

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strike that. Let me just make clear. In the literature you reviewed, in the case control studies you reviewed for glyphosate, are all of those containing exposure information retrospective? 04:12
MS. FORGIE: Object to form. Asked and answered.
You can answer it again.
THE WITNESS: They had questionnaire that were sent out to 04:13 cases and controls asking them about lifetime exposure. In that sense it's a retrospective exposure assessment.
BY MR. LASKER:
Q. And it is true as you teach your 04:13 students -- and this is on page 2. It's the top slide on the right -- that retrospective often is considered a less reliable design in an epidemiologist study; correct?
MS. FORGIE: Object to the form. 04:13
THE WITNESS: Well, that is a very broad statement.
BY MR. LASKER:
Q. I'm just asking about the statement you make in your slide presentation -- 04:13

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A. Where is it?
Q. -- to your students. It is the top slide on the left on page 2. "Retrospective is often considered a less reliable design." Is that correct? 04:13
A. Yes. And that does not refer as a judgment to case control studies but to the term "retrospective," and this is not to say that it really is a lesser way and a less reliable design. That's why it's in quotes. 04:14 This is to stimulate my students to think about the advantages of this kind of exposure assessment.
Q. And on page 5 in your slide deck for your students in the top right for 04:14 discussing cohort studies, you state that cohort studies are generally most accepted in scientific community; correct?
A. Again, that is to stimulate discussion about is that really a criterion 04:14 we should be using as epidemiologists even if the scientific community equates cohort studies with higher study quality. One of the things I do in my class is I start with this where there is that validity ranking 04:14

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highest to lowest, and I try to debunk it.
Q. And just to be clear, the "this" because that won't be on the record, you start on page 1 with your Table 1, which is a listing of validity ranking from highest 04:15 to lowest, and this is, I take it, what is generally presented in the scientific literature as the ranking of study designs by validity; correct?
A. Correct. 04:15
MS. FORGIE: Object to the form.
THE WITNESS: Well, this is how many people think about epidemiologic or medical trials and designs, yes.
BY MR. LASKER: 04:15
Q. And in this ranking, randomized clinical trials are the highest, and prospective cohort studies are directly below that; correct?
A. That's correct. 04:15
Q. And there is a term for "nested case control study." That is a case control study that is conducted within a cohort; correct?
A. Yes. Sometimes it's used for 04:15

population-based case control study as long as you know what the source of controls was.
Q. Okay. And in this sort of general ranking in the scientific community of design validity, where would a non-nested case control study fit in this ranking? 04:16
A. Right below case control study.
Q. So a case control study would be below nested case control study and above time series analysis? 04:16
A. Correct.
Q. Okay. The one cohort study that we have for glyphosate and non-Hodgkin's lymphoma or the one cohort analysis is from the Agricultural Health Study; correct? 04:16
A. Correct.
Q. So let's look to that now.
A. Just for the record, I'm using this to stimulate discussion because I disagree with this ranking presented in Table 1. 04:16
Q. So this is 19-18.
(Exhibit Number 19-18 was marked for identification.)
BY MR. LASKER:
Q. And for -- so Exhibit 19-18 is the 04:17

2005 published AHS study of glyphosate by De Roos; correct?
A. Yes.
Q. You mentioned this study in your report at page 21. You can go to that. And 04:17
you present right above that chart the odds ratio for the De Roos 2005 study for glyphosate and non-Hodgkin's lymphoma as 1.2; correct?
A. Yes. 04:17
Q. And if you look at De Roos in Table 2 on page 51, the odds ratio that you report in your expert report is the odds ratio that is minimally adjusted, only adjusted for age; correct? 04:18
A. I report two -- I report 1.2 and next to it the 1.1.
Q. I'm sorry. Got it. My mistake.
And you mention in your expert report that the confidence interval for the 04:18
finding in the De Roos study is wide, 0.7 to 1.9, which you describe as a wide confidence interval; correct?
A. Yeah. And they're exactly the same. 04:18

Q. And this confidence interval, if you were to calculate the CLR for the De Roos study to measure the width of the confidence interval, for the De Roos study 1.9 to 0.7. That is, again, somewhat below 04:19
3; correct?
A. Slightly, yeah.
Q. And that confidence limit ratio is actually narrower than the CLR for the case control studies for adjusted odds ratios 04:19
that we've been reporting that we've been talking about; correct?
MS. FORGIE: Object to the form.
THE WITNESS: Again, that's not the only criteria to evaluate statistical 04:19
significance or confidence interval or any meaning that these estimates might have.
BY MR. LASKER:
Q. I understand. I'm just trying to 04:19
get an understanding because in your report you discuss this confidence interval as being wide, and, in fact, this confidence interval is narrower than the confidence interval that appears in the case control 04:19

studies that we've been discussing; correct?
MS. FORGIE: Object to the form.
THE WITNESS: For a cohort study this is a rather wide confidence interval especially if you look at some 04:19
more common cancers. It should be better. Yes, the one for all cancer. It's .9 to 1.1. That's a nice confidence interval.
BY MR. LASKER: 04:20
Q. I understand that. But I'd like to ask you with respect to the case control studies. Would it be correct to my understanding that the confidence interval for glyphosate and non-Hodgkin's lymphoma in 04:20
the De Roos 2005 study is not wide as compared to the odds ratios for glyphosate and non-Hodgkin's lymphoma reported in the case control studies?
MS. FORGIE: Object to the form. 04:20
Asked and answered.
You can answer it again.
THE WITNESS: These confidence intervals might be comparable. However, it's even more important that the 04:20

confidence interval safely includes the overall meta-analytic point estimate of 1.45.
BY MR. LASKER:
Q. I'm sorry. I have no idea what that is. It seems like a meta conference interval that was reported by -- 04:20
A. No, I'm talking about the point estimate falling nicely into this wide confidence interval for NHL. So this study does not contradict the meta-analysis. That's what I'm saying. 04:21
Q. So the meta-analysis number you're reporting, you're discussing here, is the meta-analysis number from the -- 04:21
A. From several --
MS. FORGIE: Wait for the question.
BY MR. LASKER:
Q. -- from the IARC meta-analysis and the Chang and Delzell meta-analysis that did not include the NAPP data; correct? 04:21
MS. FORGIE: Object to the form.
THE WITNESS: Yes, that's correct.
BY MR. LASKER:
Q. And the De Roos 2005 study in and 04:21

of itself fair to say does not report a positive association between glyphosate and non-Hodgkin's lymphoma; correct?
MS. FORGIE: Object to the form.
THE WITNESS: A 1.2 to 1.1 is still a positive association. 04:21
BY MR. LASKER:
Q. In your opinion, does the De Roos 2005 cohort study provide evidence that supports the hypothesis that glyphosate causes non-Hodgkin's lymphoma? 04:22
A. It contributes very little.
Q. Okay. But that's not quite answering my question.
Do you believe that the De Roos 2005 cohort study provides some evidence, even if you think it's little, in favor of an opinion that there's an association between glyphosate and non-Hodgkin's lymphoma? 04:22
MS. FORGIE: Object to the form. Also, asked and answered.
You can answer it again.
THE WITNESS: This study does not, in the way it's reported here and in the 04:22

way I see these data, does not contribute very much to the discussion.
BY MR. LASKER:
Q. Okay. And the Table 3 analysis, I take it, which sets forth the various risk ratios based upon two measures of exposure, either cumulative exposure days or intensity weighted exposure days, am I correct in my understanding that you do not believe this data contributes much to the analysis of glyphosate and non-Hodgkin's lymphoma? 04:22 04:23
MS. FORGIE: Object to the form. Also, asked and answered.
You can answer it again.
THE WITNESS: These tables are much more complex to analyze because we're now getting into a discussion over appropriate exposure assessment which I don't think is -- the exposure measures that are used here to derive these total cut points are most likely misclassified. 04:23 04:23
BY MR. LASKER:
Q. Now, these exposure measures are the same exposure measures the Agricultural 04:23

Health Study has used in numerous different epidemiological studies that were being published at the same time that you were serving on that outside advisory committee; correct? 04:23
MS. FORGIE: Object to the form.
THE WITNESS: An exposure measure for one pesticide is not exactly the same as an exposure measure for another pesticide, and I think we agreed today that it depends on when these pesticides were used and where they were used and whether use changed. There's no other pesticide for which use changed in the same way that I can think of, at least as for glyphosate, during the general baseline enrollment of these farmers. 04:24 04:24
THE REPORTER: I'm so sorry. My computer just rebooted.
MR. LASKER: How much did we miss and what do we have to do?
THE REPORTER: No, I've got it all the writer. I just need to go off and reboot.
MS. FORGIE: Why don't we take a

short break.
THE VIDEOGRAPHER: We're off the at 4:23 p.m.
(Recess taken from 4:23 p.m. to 4:47 p.m.) 04:47
THE VIDEOGRAPHER: We are back on the record at 4:47 p.m.
BY MR. LASKER:
Q. Dr. Ritz, we were looking at De Roos 2005. I'd like to actually direct you to Table 1 on page 50. 04:47
A. Yeah, I'm there.
Q. And that table, at the bottom, presents data from this cohort on co-exposures for glyphosate and other common pesticides or exposures in individuals not exposed to glyphosate; correct? 04:47
A. Yes.
Q. Okay. And for every pesticide in this cohort, they found that as there was increased use of glyphosate, there was also increased use of these other pesticides; correct? 04:48
MS. FORGIE: Object to the form.
THE WITNESS: I'm confused. Should 04:48

I answer.
BY MR. LASKER:
Q. Yes.
MS. FORGIE: If you understand the question, you can answer. 04:48
THE WITNESS: So you're saying there's correlation between pesticide use and the AHS?
BY MR. LASKER:
Q. I'm saying that for every pesticide that they looked at, and there's, I think, ten pesticides listed on Table 1, they found that with glyphosate use and with greater glyphosate use, there was greater use of these other pesticides; correct? 04:48
MS. FORGIE: Object to the form.
THE WITNESS: These pesticides correlate with glyphosate, yes.
BY MR. LASKER:
Q. So you have a correlation between increased glyphosate use and use of these other pesticides; correct? 04:49
A. That's how it looks like.
Q. And if I understand correctly, if any of these other pesticides are, in fact, 04:49

risk factors for NHL, that would introduce a differential confounding so that you'd have a greater confounding of your glyphosate measure with higher glyphosate exposure as compared to lower glyphosate exposure; correct? 04:49
MS. FORGIE: Object to the form.
THE WITNESS: Not necessarily. This really depends on how you look at glyphosate data in terms of, first of all, is it -- is any of these other pesticides really a -- you said that, NHL risk factor. 04:49
(Simultaneous cross-talk interrupted by the reporter.) 04:50
MS. FORGIE: Wait, wait.
THE WITNESS: Are they correlated with glyphosate exposure, but then couldn't you imagine that even a true risk factor for NHL that's correlated with glyphosate has two different meanings. One, it might be a risk factor that's on its own, but it also could be an indicator for pesticide use, glyphosate, and that's what this is also 04:50

showing.
So all of these pesticides are perfect indicators of glyphosate use.
BY MR. LASKER:
Q. Okay. My question -- I'm going to try to understand this, your answer, but let me just make sure I understand this. 04:50
Given this data showing that there is increased correlation between glyphosate exposure and exposure -- strike that. 04:50
Given this data that there's an increased correlation with use of other pesticides and glyphosate with increasing use of glyphosate, is one possibility given this data that there is -- if any of these other pesticides are associated with non-Hodgkin's lymphoma, that there is increased confounding for higher doses of glyphosate exposure? 04:51
MS. FORGIE: Object to the form. 04:51
THE WITNESS: So it's not increased confounding. It's some -- it can be some type of confounding. It can also be a proxy for the exposure. It was all highly correlated exposures. That's the 04:51

case. You have to decide whether it's a confounder or a proxy.

BY MR. LASKER:

Q. Okay. And if the pesticides are confounders and we determined that, for the purposes of this question, that they are independent causes of non-Hodgkin's lymphoma, and you were to compare the odds ratio for glyphosate exposure for the lowest exposed to the highest exposed, you could have confounding -- if you don't control -- adjust for those other exposures, you could have confounding that would inflate the odds ratio for the higher glyphosate exposure as compared to the lower glyphosate exposure. 04:51 04:51 04:52

That's possible; correct?

MS. FORGIE: Object to the form.

THE WITNESS: So confounding is always a possibility especially with highly correlated exposures. So the intellectual challenge here is to decide how to treat these variables. Are they truly confounders in the sense that we are assuming that glyphosate has no effect and all the effect comes from the 04:52 04:52

other pesticide, or are there one or two or three carcinogens, all of them contributing to the risk of NHL, and how do we put those together in a model if we -- if they're highly correlated, we put them all three in the model, then they will just split variance, and none of them will show anything. 04:52

BY MR. LASKER:

Q. And if we have that situation, the real challenge we have, if I understand you correctly, is, let's say, if we have four pesticides, we have glyphosate and we have three other pesticides, and they are often used together, and you have this situation with a correlated, and you have positive associations popping out with each of the different chemicals, then am I correct in my understanding that it is difficult to reach a determination as to whether all of them are, in fact, associated with increased risk of NHL or one of them is and which one is; correct? 04:52 04:53 04:53

MS. FORGIE: Object to the form.

THE WITNESS: That's not what I'm 04:53

saying. I'm saying that the data and the mass will not help you. What you have to do is design a study in which you can distinguish between these three exposures -- four exposures, and make up your mind what to call these individual agents. Are they truly risk factors increasing the risk of NHL, or are they not. 04:53

If all four of them are risk factors, and they are highly correlated so every time one person is exposed to one, they're also exposed to all three others, then you don't have a study that you can actually -- from which you then can come with a conclusion on one of them. 04:54 04:54

All you can say is all four of them seem to increase risk of NHL.

BY MR. LASKER: 04:54

Q. And has there been a study, to your mind, that has allowed -- that would allow one to parse that out?

A. Yes.

Q. Which study would that be? 04:54

A. That would be the hypothetical study in glyphosate production workers.

Q. I'm sorry. I misspoke. My question was: Has there been, in fact, an epidemiological study conducted that you've reviewed that would allow you to tease out that fact between the different pesticide exposures? 04:54

MS. FORGIE: Object to the form.

THE WITNESS: That depends on which study we are talking about because confounding is a study-specific issue. So in some studies, one of these pesticides may be a confounder. In another study, it might not be, and that would depend on the timing of exposure. 04:54 04:55

So for this study, the AHS where we only have farmers who are coming for a pesticide exam at baseline. Right? That's how they were enrolled. They came to an exam in Iowa or North Carolina to get their pesticide application license. 04:55

So we know from the beginning that this is a cohort that will have multiple 04:55

pesticide exposures, and a lot of them will be highly correlated. In other populations, it might not be as much of a problem because certain farmers may just use glyphosate and nothing else. 04:55

BY MR. LASKER:

Q. I understand.

My question to you, though, is: You've reviewed all the epidemiologic literature; so if there is a study, that's 04:55 fine. You can let me know what study that is.

Is there an epidemiological study that you've identified in the literature that allows you to distinguish between 04:55 glyphosate and other pesticides that are potentially being used by that population to determine whether all of them are risk factors, one of them is a risk factor, or distinguish between them? 04:56

MS. FORGIE: Object to the form. Also asked and answered.

THE WITNESS: Well, I think the De Roos 2003 study is actually a very good example where even after we adjust for 04:56

40-some pesticides, the effect of glyphosate is still apparent.

BY MR. LASKER:

Q. And is that in the hierarchical regression analysis? 04:56

A. That is in the logistic regression, and I stated before that I do not think that the hierarchical is the way to go for many reasons because it makes all these assumptions about carcinogenicity of 04:56 substances we don't know anything about.

Q. Other than De Roos 2003, is there a study that you believe allows you to tease out the effects of glyphosate versus another pesticide to determine which of those are 04:56 risk factors and which of those are just correlated?

A. I believe that the Eriksson study also made multiple adjustments and glyphosate survived those, but it is real 04:57 study to study. We could go through all of them.

Q. The De Roos 2005, in their dose response analysis, as they performed their analysis for cumulative exposure days, they 04:57

reported risk ratios of below 1 for the higher tertiles of exposure for cumulative exposure days and also intensity-weighted exposure days; correct?

A. That's how it looks like. 04:57

Q. The number of days of exposure to glyphosate in the exposed members of the AHS cohort in the highest exposure group was significantly higher than the reported days of exposure to glyphosate in any of the case 04:58 control studies; correct?

MS. FORGIE: Object to the form.

THE WITNESS: I'm actually very surprised to see this number. I can't imagine anybody was spraying glyphosate 04:58 on a daily basis for seven years.

BY MR. LASKER:

Q. The data in this study for De Roos would span 27 years of potential glyphosate use; correct? 04:58

MS. FORGIE: Object to the form.

THE WITNESS: It would be -- no. It would be use between -- let's see.

BY MR. LASKER:

Q. Between -- 04:58

MS. FORGIE: Wait, let her finish.

THE WITNESS: -- whatever we're assuming is the introduction of glyphosate and the first person in this cohort having used it. Some of these 04:58 farmers -- or actually the bulk of these farmers were less than 45 -- 40 years -- 50 years of age when they were enrolled. So I don't think they might have used glyphosate -- well, depends on the age 04:59 they started farming; right?

BY MR. LASKER:

Q. Yes.

A. So it could be 1975 to enrollment. So that would be -- the latest enrollment is 04:59 1997; so we have 22 years maximum.

Q. Okay. And is it your testimony that you believe that the data presented in this table with the maximum, and it is the single maximum exposure of 2,678 days, do 04:59 you believe that that data point is incorrect?

MS. FORGIE: Object to the form.

THE WITNESS: I have no idea, but I'm very surprised to see it. On the 04:59

other hand, these are farmers who are high intensive users of pesticides; so maybe there's something to it.

BY MR. LASKER:

Q. Am I correct that the 2005AHS data presents data for exposures that are significantly more intense than any of the exposures that are assessed in any of the case control studies that we've talked about; correct? 04:59 05:00

MS. FORGIE: Object to the form.

A. So now we are coming to the exposure assessment that was done in 1993 to 1997. As we know in 1995-'6 there was a big change in glyphosate use due to genetically modified crops. So the individuals who were enrolled in 1993 would report general use among farmers where glyphosate is just one among several herbicides; right? Could be 2,4-D. Could be atrazine, could be all sorts of thing. And then we have this big, big switch in 1995, and you're still enrolling these farmers, and now they have started to use modified crops, and they're using glyphosate at a huge amount. And what 05:00 05:00 05:00

you're now having is a situation where you don't know anything about what people in 1993 did. You know who changed in 1995 to glyphosate-intensive farming, but you would not know who was interviewed in 1993 also changed to glyphosate-intensive farming. You would keep them in the low exposure even though they may have changed to a much higher level. 05:01

Q. My question was not that, though; so let me ask my question again and see what the answer is. Am I correct in my understanding that the cohort that was analyzed in the De Roos study had significantly more intense exposures both by cumulative exposure days and to intensity measure to glyphosate than any of the individuals who were assessed in the case control studies we've been discussing? 05:01 05:01

MS. FORGIE: Object to the form. Also asked and answered. 05:01

You can answer again.

THE WITNESS: So I'm having a hard time comparing them because the other studies had more than two days. That 05:02

could also be a hundred days; right? So plus those were days per year. Here we have a cumulative exposure meaning this could be an average that's actually less than what was reported in the other studies depending on the number of years. 05:02

BY MR. LASKER:

Q. The two data points we have from Eriksson, it was ten days -- more than ten days or less than ten days; correct? 05:02

A. Yes, but I'm not sure that it was ten days per year or ten days cumulative.

Q. Okay. I'll represent, and if I'm wrong, the court will know and everybody will know that it was ten days cumulative. 05:02

The NAPP data we just looked at reported seven days cumulative as the cutoff point; correct?

MS. FORGIE: Object to the form. 05:02

THE WITNESS: That was the cumulative, yes.

BY MR. LASKER:

Q. So we have a cutoff of seven days cumulative for the NAPP U.S.-based case 05:03

controls. We have a cutoff of 10 days cumulative for the Eriksson study, and we have a cutoff in the De Roos 2005 cohort that goes 1 to 20 days cumulative for the low exposure group, 21 days to 56 days for the mid exposure group, and 57 days to 2,678 days in the high exposure group; correct? 05:03

A. Correct.

MS. FORGIE: Object to the form. 05:03

THE WITNESS: Over 22 years.

BY MR. LASKER:

Q. And my question -- and for the Eriksson study, you'd have that same time period generally, the number of years of exposure -- of potential exposure; correct? 05:03

MS. FORGIE: Object to the form.

THE WITNESS: That was --

BY MR. LASKER:

Q. The 2008 study? 05:03

A. I have to look. When did they get their cases? 1993? So it's shorter. It's actually shorter because the cases were ascertained in the early '90s and these cases were ascertained after. 05:04

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Q. And we're not going to go back. I don't think that's correct, but we'll move on and address that later.

The cumulative exposure in the De Roos study, measured in the De Roos study for glyphosate associated with non-Hodgkin's lymphoma was significantly greater than the cumulative exposure measures in any of the case control studies; correct? 05:04

MS. FORGIE: Object to the form. 05:04

THE WITNESS: Again, this is a measure that's cumulative over 22 years, and it is not a measure of intensity.

BY MR. LASKER:

Q. Okay. And the intensity-weighted exposure days that was presented, that is based upon an analysis of intensity in the AHS that looks at mixing status, application method, equipment repair status, and personal protective equipment; correct? 05:04

A. Yes.

Q. And that is a measure that has been looked at and validated through the De Roos -- through the AHS to try and measure the intensity of exposures not only 05:05

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to glyphosate but to all the pesticides that they analyzed; correct?

MS. FORGIE: Object to the form.

THE WITNESS: What was that.

BY MR. LASKER: 05:05

Q. The measure of intensity that the Agricultural Health Study uses is a measure that they have validated not only for glyphosate but for all the different pesticides that they're analyzing; correct? 05:05

MS. FORGIE: Object to the form.

THE WITNESS: They actually did not validate that for all the pesticides. They used two or three pesticides for the validation procedure, and I wouldn't 05:05 call that validated because they are only measuring biomarkers over a very short period of time, and they are saying that these short time periods cannot be set to be the same as a 05:05 lifetime exposure.

In fact, we tried in my own studies for occupational exposures to pesticides to reproduce these intensity measures and compared them with very simple 05:06

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measures. So we went through all the trouble of weighing in exactly the same way. We asked the same questions, and it made just about no difference whether you used a very simple measure such as 05:06 in Eriksson and Hardell, et cetera, or you used this very complicated measure.

BY MR. LASKER:

Q. When you say the measure that was used in Eriksson and Hardell you're assuming 05:06 the measure they used because they don't report it in those studies; correct?

MS. FORGIE: Object to the form. Mischaracterizes her prior testimony. Asked and answered. 05:06

You can answer it again.

THE WITNESS: No, because what Eriksson describes is very similar to the methods that I know I used. So we had several measures that we tried with 05:06 and without protective equipment, with and without frequency of applications, et cetera. We are using -- we tried to use everything in the same way as the AHS and going back to fairly simple 05:06

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measures of, you know, how many times per year did you apply, or how many days per year did you apply made no difference.

BY MR. LASKER: 05:07

Q. In your discussion of the 2005 De Roos dose response analysis in your expert report at page 23, you state that the investigators' decision to conduct their dose response analysis with comparisons only 05:07 between low, mid, and high exposure without an unexposed group reduces the exposure contrast between the three dose groups; correct?

A. Where do I say that? 05:07

Q. Page 23. Right above industry-sponsored studies.

A. Yes.

Q. "This type of approach also reduces any remaining exposure contrast." 05:08

A. Yes.

Q. The exposure contrast, though, in the De Roos study were greater than the contrast between the exposure groups in the McDuffie study and the Eriksson study; 05:08

correct?
MS. FORGIE: Object to the form.
THE WITNESS: That's an assumption, and the assumption is that there's not a major exposure misclassification in the way I described before. 05:08
BY MR. LASKER:
Q. Okay. This exposure misclassification, to the extent that Eriksson analyzed data exposures going into the 1990s, if that's the case, they gathered their data after 1997, would that same issue arise with the Eriksson study? 05:08
A. If they gathered it after 1997, no, because then they would have actually already gotten past the change. 05:09
Q. Well, they --
MS. FORGIE: Wait. Let her finish.
THE WITNESS: The problem is that this study had the change happen in the middle of the enrollment period. 05:09
BY MR. LASKER:
Q. The Eriksson study would be looking back over time so it would be a questionnaire and be asking about prior 05:09

exposures over time; right?
MS. FORGIE: Object to the form.
THE WITNESS: It's a case control study so they would ask cases and controls to remember their lifetime exposure which, by definition, would be prior to the onset of the cancer, yeah. 05:09
BY MR. LASKER:
Q. So if the Eriksson study is asking that question after 1997 for all past exposures and using that data for their analysis, would they have the same misclassification problem that you believe exists for the AHS study? 05:09
A. No, it would not. 05:09
Q. The -- there has been a further analysis of the Agricultural Health Study data, and you address this in your rebuttal report. This is the document we received from Dr. Blair presenting data from 2013. 05:10
Let me ask first at the time that you prepared your initial expert report in this matter, had you seen that 2013AH analysis?
A. First time I was aware of it was in 05:10

that attachment to Dr. Blair's statements.
Q. Okay. But were you -- did you see that attachment -- had you seen that attachment at the time you prepared your initial expert report in this matter? 05:10
MS. FORGIE: Object to the form.
THE WITNESS: I don't believe so or else I would have known because the deposition was after -- when was it? Do we have a date? 05:10
BY MR. LASKER:
Q. We do have a date. I'll represent, and counsel can correct me if I'm wrong, the deposition was taken before your expert report was submitted. That doesn't mean you saw it then? 05:11
A. No, exactly. I don't think I saw any depositions prior to my expert report, so that's fine.
Q. And do you recall whether you saw the AHS2013 data prior to -- you obviously saw it prior to the time you did your rebuttal report. 05:11
A. Yes.
Q. Do you recall if you saw it prior 05:11

to the time you read Dr. Neugut's deposition?
MS. FORGIE: Object to the form.
THE WITNESS: I really don't know.
BY MR. LASKER: 05:11
Q. The 2013 -- why don't we mark that analysis.
(Exhibit Number 19-19 was marked for identification.)
MS. FORGIE: Tell me which version you're using.
MR. LASKER: March, 2013.
MS. FORGIE: So the earlier one.
MR. LASKER: The later one.
MS. FORGIE: Oh, the later one, I'm sorry.
THE WITNESS: Are there more than one.
MR. LASKER: There's February and March. The data doesn't change. 05:12
MS. FORGIE: I object to that comment. It does change. You know it.
MR. LASKER: I don't think it changes actually, but maybe I'm wrong.
///

BY MR. LASKER:
Q. The -- Dr. Blair in his deposition testified that the 2013 data, although for the glyphosate it is reported in a dose-response analysis that includes a never exposure category and then three exposure categories, he calculated that the ever/never risk ratio for glyphosate and NHL in this 2013 data would be about 0.9. Do you recall that? 05:12 05:13
MS. FORGIE: Object to the form. Mischaracterizes the testimony.
THE WITNESS: I don't recall that.
BY MR. LASKER:
Q. Okay. Let's look at Dr. Blair's deposition. I think we marked it as an exhibit. 05:13
MS. SHIMADO: 6.
BY MR. LASKER:
Q. I'm going to hand it to you. It's Exhibit 6 after we find it. 05:13
And Dr. Blair on page -- it's 172. We're looking at the 2013 cohort study data; correct?
MS. FORGIE: Well, she's not there 05:14

yet. She needs some time to read a couple pages before and after, so give her a minute, please.
THE WITNESS: What are we talking about? 05:14
BY MR. LASKER:
Q. On page 172 Dr. Blair is -- I'm asking him some questions about the 2013 data.
Do you see that? 05:14
A. Yes.
Q. I ask him the question at line 11. "This 2013 cohort study finds no association -- no evidence of association between exposure to glyphosate and non-Hodgkin's lymphoma; correct?" 05:14
And Dr. Blair answers, "Correct."
Do you see that?
A. Yes.
Q. And then I ask Dr. Blair, "And based upon the data that's set forth here, if you look at individuals who had no exposure to glyphosate, which is that first row, and you look at the three categories of individuals who did have exposure to 05:14 05:14

glyphosate, if we were to do an ever/never analysis of glyphosate and non-Hodgkin's lymphoma, the relative risk here would be something below 1.0; correct? About 0.9?"
"Answer: That's a reasonable guess I think, yes." 05:15
Do you see that?
A. Yes.
Q. Do you have any reason to disagree that if one were to do an ever/never analysis of the 2013AHS data for glyphosate, the risk ratio that would be reported would be something on the order of 0.9? 05:15
MS. FORGIE: Object to the form.
THE WITNESS: I would have to look at the data, but, in general, I don't believe any of those analyses because I don't believe the exposure assessment. So it doesn't matter. 05:15
BY MR. LASKER: 05:15
Q. I understand that, but let me just make sure I understand and see if you agree with what the numbers would be, and obviously others will decide whether or not those numbers are the -- the significance of 05:15

those numbers. But if we were to look at page 34 in the 2013 study for glyphosate, do you see that data?
A. Yes.
Q. And if we were to calculate from this data an ever/never risk ratio for glyphosate and non-Hodgkin's lymphoma, do you agree with Dr. Blair that the risk ratio would be about 0.9? 05:15
MS. FORGIE: Object to the form. Asked and answered. 05:16
You can answer again.
THE WITNESS: Again, it would be hovering somewhere around the 1. However, I don't think that these categories are sufficiently well established to even make this comparison. 05:16
BY MR. LASKER:
Q. Okay. But just so the record is clear, we have the non- -- the never use is the reference of 1.0; correct? 05:16
A. That's the reference, correct.
Q. And in the exposure groups, we have odds ratios of either below 1 or just at 1; 05:16

correct?
MS. FORGIE: Object to the form.
Asked and answered.
You can answer it again.
THE WITNESS: Well, the relative risks here which they are not odds ratios --
BY MR. LASKER:
Q. I'm sorry.
A. -- are actually hovering around the 1.
Q. So the relative risks are either 0.8, 0.9, or 1.0 for use of glyphosate as compared to non-use of glyphosate as the data is reported here; correct?
MS. FORGIE: Object to the form.
Asked and answered.
You can answer again.
THE WITNESS: Well, the relative risks are rate ratios hover around the 1 and the confidence intervals include the 1, but they go out to 1.4.
BY MR. LASKER:
Q. The -- in your rebuttal report, you state one of the main concerns you have

about the 2013 analysis relates to the imputation method that was used; correct?
A. That's correct.
Q. And the AHS investigators -- and just to be clear, the issue with the imputation method is in their second phase of gathering information on pesticide exposures. They had, I think, 36 percent of individuals who responded to the first survey who didn't respond to the second; correct?
MS. FORGIE: Object to the form.
THE WITNESS: So the AHS is a cohort study that has, because there's so many people to be interviewed, a long period of enrollment which is about four or five years. And by the time the last person was enrolled, they pretty much decided they had to update their exposures because they realized that exposures change.
So in the next phase starting in 1999, I believe, through 2003, they tried to recontact all these farmers who they enrolled in the first phase, and

yes, among those that they reached again, that was about 62 percent.
BY MR. LASKER:
Q. And because of that, the AHS investigators used an imputation method to impute what the values would be, the exposure values would be for the individuals who did not respond to the second phase questionnaire based upon the prior information that they had from those individuals and the information they had from the 60 plus percent of subjects who responded to both questionnaires; correct?
MS. FORGIE: Object to the form.
THE WITNESS: From what I understand is they basically used the baseline information to impute the follow-up.
BY MR. LASKER:
Q. So is it your understanding then that they did not use data from the 60 some odd percent who responded to both questionnaires --
A. Oh, yes, because they used the baseline for all of them.

Q. Used that as well to impute for them?
A. Yes.
Q. And the AHS investigators have used that same imputation method for every pesticide study that they have published that includes data from the phase 2 surveys; correct?
MS. FORGIE: Object to the form.
THE WITNESS: Yes. They used a general method of imputation for all pesticides, whether or not these pesticides were actually still in use or not, and whether or not the use changed over time specifically between the first and the second survey.
BY MR. LASKER:
Q. So every publication that has come out of the AHS that looks at pesticides since they've had this phase 2 exposure information, all of the published studies, all the peer-reviewed published studies from the AHS have used this same imputation method that was used in the 2013 analysis included glyphosate; correct?

MS. FORGIE: Object to the form. Asked and answered. It mischaracterizes her prior testimony.

You can answer it again.

THE WITNESS: They used one single imputation method to apply to every single pesticide whether the pesticide has been banned and supposedly not been used since '72 which is DDT and lindane shortly after, or whether it's a pesticide that came on the market and went and was gone by 1993 when they started this study or whether it's a pesticide which is unique such as glyphosate that changed use in the middle of their inrollment period. And they're using the same method for all of these pesticides. 05:21

BY MR. LASKER:

Q. Just so I understand, every publication that's come out of the AHS since the second phase data was incorporated into their analysis, every peer-reviewed published study has made use of this general imputation method that was used in the 2013 05:21

study; is that correct?

MS. FORGIE: Object to the form. Also asked and answered. She's answered this twice.

You can answer it a third time. 05:22

THE WITNESS: Again, this imputation method is one and the same imputation method for every single exposure, and there are big differences between the exposures, the timing of the exposure and, therefore, the validity of this method. So every other paper that comes out has to be judged by how valid this method is, not only for the pesticide but also the outcome. 05:22

BY MR. LASKER:

Q. I understand that. But I just want to make sure that I'm clear that every paper that has come out of the AHS and including all the papers that have been peer-reviewed and published from the AHS have used the same imputation method that is used in the 2013 study; is that correct? 05:22

MS. FORGIE: Object to the form. Asked and answered. She's answered it 05:22

four times now.

You can answer it again.

THE WITNESS: So it's a perfectly fine imputation method for something like DDT that supposedly hasn't changed since 1972, and it's a perfectly fine method for any pesticide that was discontinued in use since 1993 because what would change over time since 1993? Nothing. Right? Because supposedly all the exposures you could ever have had for this pesticide would have been recorded at baseline. This is not the case for any exposure that changed and especially not for an exposure that changed dramatically. There's only one I'm aware of in this study, and that was glyphosate for which that changed. 05:22 05:23

BY MR. LASKER:

Q. Just so I understand this correctly, and I think you'll agree with me on this, but I just need to understand this for the record, am I correct that every study that has been published by the AHS, every peer-reviewed published paper from the 05:23

AHS looking at pesticides since that second survey was conducted has used the imputation methodology that is used in the 2013 study?

MS. FORGIE: Objection. I object to the form also. You are badgering the witness now. This is the sixth time you've asked the exact same question, the exact same question. 05:24

MR. LASKER: And one of these times I'll get an answer. 05:24

MS. FORGIE: Wait. Don't do that. You've gotten answers. You're badgering the witness. I object to that. Don't do that.

MR. LASKER: Mark the record here. 05:24

MS. FORGIE: Good. Please do.

MR. LASKER: I'm going to ask it again because it's a pretty simple question.

BY MR. LASKER: 05:24

Q. Am I correct -- and it's a question that has a yes or no. There may be an explanation you want to give afterwards. But it's a yes or no question. Am I correct that every peer-reviewed publication from 05:24

the AHS that has come out since that phase 2 exposure data was collected has used the same imputation that is used in the 2013 study that included the glyphosate data?

MS. FORGIE: Objection. You are really badgering this witness. This is now like the eighth time. I'm counting. Objection. Asked and answered. 05:24

You can answer it again.

THE WITNESS: There is no yes or no answer to this. And, also, I don't know. Because, for example, if you're assessing lindane and DDT, you don't need an imputation method because you have all the data you want which is the data you collected at baseline. 05:25

However, for any pesticide still in use where you have no updated pesticide information, you would use this imputation method. Whether that's an appropriate method is a totally different question. For glyphosate, I don't believe so. 05:25

BY MR. LASKER:

Q. And the AHS investigators actually 05:25

did a study in which they tried to test their imputation methodology and to look at how well it performed with respect to the different pesticides; correct?

MS. FORGIE: Object to the form. 05:25

THE WITNESS: It was a very special type of pesticide they looked at. It wasn't glyphosate from what I recall.

BY MR. LASKER:

Q. Let me ask you about the study. 05:25

Maybe we're not talking about the same study. The Heltshe study?

A. Yeah, Heltshe.

(Exhibit Number 19-20 was marked for identification.) 05:26

BY MR. LASKER:

Q. This will be Exhibit 19-20. This Exhibit 19-20 by Heltshe entitled, "Using Multiple Imputation to Assign Pesticide Use for Non-Responders in the Follow-Up Questionnaire in the Agricultural Health Study"; correct? 05:26

A. Yes.

Q. And in this study, they reported that their imputation methodology, and they 05:26

report this in their abstract, that the distribution of prevalence and days per year of use for specific pesticides were similar across observed and imputated in the holdout sample. 05:26

Do you see that?

MS. FORGIE: Take your time.

BY MR. LASKER:

Q. It's towards the bottom in the abstract. 05:27

A. Oh, in the abstract.

Yes, they're using the data to predict the data.

Q. Right. And what they did in this analysis is they took of the people who had responded to the second phase, they randomly selected 20 percent of them; correct? 05:27

MS. FORGIE: Object to the form.

THE WITNESS: Yes.

BY MR. LASKER: 05:27

Q. And then they used their imputation method to predict what the imputation method would say was the exposure experience of that 20 percent holdout sample; correct?

A. That's correct. 05:27

Q. And they compared that to the actual data because they had actual data from those individuals; correct?

MS. FORGIE: Object to the form.

THE WITNESS: They have actual data from those individuals that they are putting in the holdout sample, correct. 05:27

BY MR. LASKER:

Q. And they then used that analysis to check on the accuracy of their imputation method. And if you look at figure 2 on page 414, they measure the relative errors on page 414 for -- it's got to be 40 maybe, I didn't count them, but 40 different pesticides starting with methyl bromide on the top down to coumaphos on the bottom; correct? 05:27

A. Yes.

Q. And for each of those pesticides they checked to see how well their imputation methodology worked; correct? 05:28

A. Correct.

Q. And for glyphosate, they found that their imputation methodology worked about in the middle of the pack for all of these 05:28

specifically identified pesticides as far as how well their imputation methodology works; correct?

MS. FORGIE: Object to the form.

THE WITNESS: Well, it's not the middle of the pack. It's in relative error on the left of the zero. So they are underestimating. 05:28

BY MR. LASKER:

Q. But there's also one, two, three, four, five at the top. I've done the counting. I think there's maybe 17 that are more relative error, maybe 20 that have less relative error. But if you want to do the counting, you can. 05:29

A. But this is a prevalence, and we are talking about a relative error to predict a ever/never, and 75 percent of all people at baseline already reported use. So you can get, you know, this number very easily just because of the high prevalence. 05:29

Q. But my question to you is: In this published paper from the AHS in which they're checking the validity of their imputation methodology for the individual 05:29

pesticides that they were analyzing, they found that glyphosate was about in the middle of the pack for prevalence as far as how well the imputation methodology worked; correct? 05:29

MS. FORGIE: Object to the form and asked and answered.

You can answer it again.

THE WITNESS: I don't think this answers to what I've just tried to explain. They can only use to predict from data they actually have; so we don't still know anything about the people for whom they don't have the follow-up data. 05:29 05:30

They are just assuming that those people behaved in the same way as the people they have data for.

BY MR. LASKER:

Q. I understand. 05:30

And the people they have data for would be people who cover this period that you're concerned about where glyphosate exposure increased. The folks who responded to the second survey and the first survey, 05:30

that's the hold-out sample; correct? The 20 percent?

MS. FORGIE: Objection. Object to the form. And asked and answered.

You can answer it again. 05:30

THE WITNESS: This was done within the 62 percent who answered twice.

BY MR. LASKER:

Q. Right.

A. These 62 percent, as they describe in here, are actually different in many ways from the 30-some percent that did not -- 38 percent that did not answer. So they are using the 62 percent who are very different in many ways, and they actually acknowledging that they're also different in pesticide use to predict what would have happened to 38 percent that they did not have that second answer from. 05:30

It's easy to predict from people who are answering and are -- and are captured because they want to be captured. They could be younger. They could be more educated. All of that is described in here. So the people, 62 percent is not a 05:31

representative sample of the 38 percent.

Q. Okay. I understand that. That's a different question, but I want to get at this issue of changes in glyphosate use over time. 05:31

The individuals who responded to the first survey and the second survey would obviously have gone through that period for glyphosate -- correct? -- where there was expanded use? 05:31

A. Only a small number would have gone through -- no. Okay. We have 1993 through 1997. So the 62 percent supposedly come from that whole time period; correct?

Q. And the second phase because they responded to the second phase as well. 05:32

A. Right.

Q. So '97 to 2001 as well. So for 62 percent, they have exposure data that spans before that first phase period and then also into the 1990s during that period where glyphosate use was impacted by GMOs; correct? 05:32

A. So some of these people, at baseline, would have reported use prior to 05:32

1995, and some would have responded past 1995.
Q. And they had that data?
MS. FORGIE: Wait. Let her finish her answer. 05:32
MR. LASKER: Well, I mean --
MS. FORGIE: No. She gets to finish her answer.
THE WITNESS: So some people changed, and other people didn't. Some 05:32 of this error is because some people changed, and it was a very simple change. So what they're talking about here is a change from yes, no.
There's only 25 percent at baseline 05:32 who did not report glyphosate use. So that's the only group that could have actually reported a change. Everybody else stayed the same if you say yes, no. That tells us nothing about the amount 05:33 of use.
BY MR. LASKER:
Q. Okay. Let me just break this down. First of all, in the original phase 1 study, we are looking at exposures over -- for 05:33

glyphosate, potentially, I think we talked about 20-plus years; correct?
MS. FORGIE: Objection. Mischaracterizes the testimony, and I'll object to the form. 05:33
THE WITNESS: So potential for exposure. We really don't know how far it goes back because none of the Eghal study papers actually describe for glyphosate how much in, you know, the 05:33 past these people reported use.
BY MR. LASKER:
Q. Okay. And what they're trying to measure in the second phase is how much exposure there was from the end of the first 05:33 phase to the second phase -- correct? -- which is a much shorter time period?
MS. FORGIE: Objection. Mischaracterizes the study itself.
THE WITNESS: So what they're 05:33 trying to do is to update the exposure information. Of course, the update is much more drastic in terms of amounts that somebody who reported in 1993 still use glyphosate but increased use in 1995 05:34

enormously and then responds again. Right.
BY MR. LASKER:
Q. And so for the 62 percent that responded to the questionnaire, that would 05:34 be information that you'd get from their second survey response; correct?
MS. FORGIE: Objection. Asked and answered and object to the form as well.
You can answer again. 05:34
THE WITNESS: You get updated information from these people who respond. However, to then use that data to predict how many people would use what who did not respond is a big step. 05:34
BY MR. LASKER:
Q. And I understand that step, and that's a step that we have for all of the pesticides, but for glyphosate, in looking at the individuals who responded at least 05:34 and who had gone through that period of increased use that you're talking about, that introduced whatever error it would introduce into the imputation methodology, and for those people, that error is 05:35

reflected in Table -- or Figure 2 on page 414; correct?
MS. FORGIE: Objection. Object to the form. Also asked and answered. She's answered this question at least 05:35 three times.
You can answer again.
THE WITNESS: And there are at least two wrong statement here. First of all, that's not correct for all the 05:35 pesticides. The pesticides that did not have this extreme change don't have this problem. This problem only has occurred because glyphosate use changed dramatically. 05:35
Second, this imputation method is a method that not only is used for a prevalence of glyphosate yes/no, but to also impute the amount used. And what they're showing you in this little graph 05:35 is just a prevalence yes/no. That's the least you could do and the least piece of information you can have about this method actually working.
Plus it makes the assumption that 05:36

the 62 percent are representative of the 38 percent, and we have to make that assumption, and it's not right. They're stating that in this paper that it's not correct. 05:36

BY MR. LASKER:

Q. Within the 62 percent that responded when the AHS investigators looked to see for prevalence how well the imputation methodology worked, including the 05:36 fact that for those 62 percent, it spanned over that period when glyphosate use was expanding, the -- they found that the error in that 62 percent through the use of that imputation method when they tested it for 05:36 glyphosate was somewhere in the middle of the pack for all the pesticides that they analyzed, and that's reflected on Figure 2; correct?

MS. FORGIE: Objection. Object to 05:36 the form. You're badgering the witness. This is now about the fifth time you've asked that same exact question.

You can answer it again.

THE WITNESS: I don't believe you 05:37

can say that because when you have such a high prevalence of use to begin with, 75 percent, then it is like a couple value where you're asking, well, how much agreement is there in a measure 05:37 when 98 percent say no, I never used this pesticide, and 2 percent do use it, and then you're, you know, getting -- okay, now next time around 4 percent say yes, but the 94 percent or the 05:37 75 percent are the overwhelming group that is consistent.

So because they already said yes at the baseline, they will consistently be predicted in the future because a yes is 05:37 a yes.

BY MR. LASKER:

Q. The concern that you are raising now about glyphosate and this imputation methodology is not raised as a concern by 05:37 the investigators, Dr. Heltshe and others, who presented the data for their validation study of the imputation method in which they presented glyphosate data along with the other pesticides; correct? 05:38

MS. FORGIE: Object to the form.

THE WITNESS: I don't understand this question. Could you repeat?

BY MR. LASKER:

Q. The AHS investigators, including 05:38 Dr. Heltshe, conducted a validation test of their imputation methodology in this publication; correct?

MS. FORGIE: Object to the form.

THE WITNESS: What? A validation 05:38 method? No.

BY MR. LASKER:

Q. The investigators of the AHS study, including Dr. Heltshe, published this paper in 2002 presenting their data on how well 05:38 the imputation methodology worked through the analyses that they conducted in this paper for various pesticides; correct?

MS. FORGIE: No. Object to the form. 05:38

THE WITNESS: This is a 2012 paper.

BY MR. LASKER:

Q. Sorry.

A. And they conducted this method under lots of assumptions. The assumptions 05:39

they made might be holding for most of these pesticide, but they themselves actually say that certain assumptions might be incorrect, including the missing at random assumption that they're making in this imputation, and 05:39 I'm saying that for glyphosate because of the time -- the exposure period change and the huge increase in glyphosate and that happening in the middle of the first enrollment period, this is not the method to 05:39 test this.

Q. I understand that that's what you're saying.

My question is: Dr. Heltshe and the other investigators who published this 05:39 analysis and presented the data on glyphosate in Figure 2 and also the findings for the other pesticides -- so in glyphosate relative error to be in the middle of the pack, they do not anywhere in this 05:39 publication state that this finding for glyphosate alone is not reliable; correct?

MS. FORGIE: Objection. That's the exact question you just asked twice. She's answered -- 05:40

MR. LASKER: It's not the exact question. You're coaching the witness. You're coaching witness. I'm asking a different question.

MS. FORGIE: I'm not coaching the witness. I object. I object to the form. Asked and answered.

You can answer it again.

MR. LASKER: I'll ask the question again because I can't imagine how you're going to remember it at this point. 05:40

BY MR. LASKER:

Q. Dr. Heltshe and her co-investigators who presented this analysis in checking on the validation -- checking on the imputation methodology that they used and reported the relative errors for all of these various pesticides, including glyphosate, showing glyphosate to be in the middle of the pack for the different pesticides looked at in the AHS, nowhere in this publication do they state that there is a different concern about glyphosate that should be taken into account in analyzing the results that they present; correct? 05:40 05:41

MS. FORGIE: Objection. Object to the form. Asked and answered.

You can answer again.

THE WITNESS: These authors investigated lots of pesticides. They are not making any reference to any single pesticide. They are just treating them as if they are equal in terms of their method. 05:41

BY MR. LASKER: 05:41

Q. They do not state that their method does not work for glyphosate in this analysis; correct?

MS. FORGIE: Objection. Asked and answered. 05:41

You can answer again.

THE WITNESS: In this paper, they are not stating anything specific for any of the pesticides.

BY MR. LASKER: 05:41

Q. Well, that's not true. In Figure 2, they have specific information on each of the pesticides. In Figure 1, they report specific information -- or Table 3, I'm sorry. They present specific 05:41

information for specific pesticides; correct?

MS. FORGIE: Objection. It's not appropriate to tell the witness one of her answers is not true. 05:41

Objection. Also object to the form. Asked and answered.

You can answer again.

THE WITNESS: I may have misspoken. What I tried to do is answer your questions in terms of whether the authors actually commented on glyphosate being different. They did not comment on these pesticides being one or the other different. They are, of course, producing all of these data for all of the pesticides they imputed. 05:42 05:42

BY MR. LASKER:

Q. And the data that they presented and they decided to present to the world in this peer-reviewed publication so that people could understand their imputation methodology when they're reading these AHS studies that all now use this imputation methodology, the data they presented showed 05:42

a relative error for glyphosate that was in the middle of the pack for all the pesticides that they are -- for which they're using the imputation methodology; correct? 05:42

MS. FORGIE: Objection. You're badgering the witness. You've asked her the same question so many times.

You may answer it again.

THE WITNESS: I think you don't understand what I'm getting at, and I'm sorry that I can't express myself in more lay terms or whatever I need to do, but this is not the same as a validation study of the imputation method, and the authors clearly state that this multiple imputation makes lots assumptions and that, you know, for simplicity of modeling, they only used a single set of observed complete data, et cetera, et cetera. 05:42 05:43 05:43

So it is not -- and they also say that some of these assumptions may not be correct and may have to be updated.

///

BY MR. LASKER:
Q. Can you point to anything in the published literature, in the AHS website, anywhere, anyone other than you has stated that the imputation methodology that the AHS 05:43
study is using is uniquely inappropriate for glyphosate?
MS. FORGIE: Object to the form.
THE WITNESS: Well, I haven't looked; so I don't know. 05:43
BY MR. LASKER:
Q. You're not aware of any statement from any of the AHS investigators that the imputation method that they are using for their phase 2 results are not appropriate 05:44
for glyphosate; correct?
MS. FORGIE: Object to the form.
THE WITNESS: I don't understand why they should be doing this if they haven't published on glyphosate. 05:44
BY MR. LASKER:
Q. Are you aware -- and I deposed Dr. Blair. In Dr. Blair's deposition when I deposed him, did he at any point state that the imputation method that was being used in 05:44

the 2013 study was not appropriate for glyphosate?
MS. FORGIE: Object to the form.
THE WITNESS: I can't remember.
BY MR. LASKER: 05:44
Q. In the -- in your role on the executive -- I'm sorry. Not the executive, the external advisory committee for the AHS to the present, have you ever heard anybody say that the imputation method that they're 05:45
using for the phase 2 respondents is not appropriate for glyphosate?
MS. FORGIE: Object to the form.
THE WITNESS: This is a 2012 paper. We have not met since they started doing 05:45
this. So nobody could have objected.
BY MR. LASKER:
Q. And there is nothing in the draft, the 2013 document that you've reviewed, that includes the glyphosate data that says 05:45
anything about the imputation methodology being inappropriate for glyphosate; correct?
MS. FORGIE: Objection to the form. Mischaracterizes the draft manuscript.
THE WITNESS: As far as I know, 05:45

this manuscript actually does refer back to the imputation method, and there was some back and forth between authors about how to present it.
BY MR. LASKER: 05:45
Q. Right.
But in that back and forth, is there any specific discussion that for glyphosate the method is not appropriate?
MS. FORGIE: Objection. Do you 05:46
want her to review to find it?
MR. LASKER: If you want to take a break, we can do that.
MS. FORGIE: No, we're not going to take a break. 05:46
THE WITNESS: So am I supposed to look.
MR. LASKER: Let's take a break.
MS. FORGIE: You're not going to look during the break, though. 05:46
THE VIDEOGRAPHER: We're off the record at 5:46 p.m.
(Recess taken from 5:46 p.m. to 5:54 p.m.)
THE VIDEOGRAPHER: We are back on 05:54

the record at 5:54 p.m.
BY MR. LASKER:
Q. Dr. Ritz, in your role as the chair of the external advisory committee to the AHS, have you spoken with anyone at the AHS 05:54
to share the opinion that you've been offering here today that the imputation method that they're using is inappropriate for glyphosate?
MS. FORGIE: Objection. Asked and 05:54
answered.
You can answer again.
THE WITNESS: I have not talked to them about glyphosate.
BY MR. LASKER: 05:55
Q. In your rebuttal report at page 7, you're talking about -- bottom of page 7, you're talking about the differences between peer-reviewed and unpublished -- a peer-reviewed paper and the unpublished 05:55
manuscript for the Agricultural Health Study 2013 analysis; correct?
A. I think I do. Where is it?
Q. Bottom of page 7, continuing to page 8. 05:55

A. Oh, yes.
Q. All right. One of the things that you state is that there is a footnote in the 2013 AHS analysis that includes glyphosate that states that numbers do not sum to totals due to missing data; correct?
A. Correct.
Q. Now, the manuscript that was the 2013 draft was subsequently published without herbicide data, so without the glyphosate data in 2014; correct?
A. There is a 2014 paper, and I went to that, yes.
MR. LASKER: So let's mark that. This is 19-21.
(Exhibit Number 19-21 was marked for identification.)
BY MR. LASKER:
Q. And 19-21 -- Exhibit 19-21 is the 2014 publication that was the subsequent revisions to the actual -- the 2013 study but without the herbicide data and substituted in fungicide and fumigant data; correct?
MS. FORGIE: Object to the form.

THE WITNESS: This is the insecticide paper. Fungicide and fumigant, right.
BY MR. LASKER:
Q. And if you look at the corresponding tables in the peer-reviewed published literature -- published study in 2014 and you look at the same footnotes that you were looking at in the 2013 study on those same tables, the peer-reviewed published article in 2014 likewise has the footnote that says that the number of cases do not total -- do not equal the total NHL cases because of missing data; correct?
A. Where is that?
Q. If you look at page 6, footnote 2.
A. The subtype, yeah. The subtypes due to missing data.
Q. If you look at page 10 for the dose response analyses of NHL, in general, footnote 2, the same statement, "The number of cases do not sum the total number of NHL cases because of missing data"; correct?
A. Yes.
Q. So that statement which appears

both in the peer-reviewed published 2014 paper and the 2013 draft; correct?
MS. FORGIE: Object to the form.
THE WITNESS: Well, it probably refers to different types of data because missing data are defined by what you're looking at, and this manuscript looked at the subpopulation of pesticides; so the missing data must be different.
BY MR. LASKER:
Q. This study looked at some of the same pesticides -- I know that the herbicides are dropped out, but it looked at some of the same pesticides as the 2013 draft; correct?
A. Yes. It overlaps in terms of all pesticides, but this paper should have less missing data because it dropped out the herbicides. The missing herbicide data should not be affecting this.
Q. So is it your testimony, just so I understand, is that you think that the herbicide, there's more missing data for the glyphosate than there were for other

pesticides that stayed in the analysis?
MS. FORGIE: Object to the form.
THE WITNESS: That's not what I said. I said that it's not exactly referring to the same data or missing data because, by definition, they have to be different.
BY MR. LASKER:
Q. Okay. But the fact that there is missing data noted in the 2013 paper is not something that will prevent that paper from being published in a peer-reviewed literature; correct?
MS. FORGIE: Object to the form.
THE WITNESS: It depends on what missing data does, and obviously here nobody in the peer review community thought that it was an issue.
BY MR. LASKER:
Q. Okay. You also state in your expert report on page 8, you talk about page 19 in the March 15, 2013, draft, and if you can go to that --
A. Well, we --
Q. I'm sorry. In your rebuttal report

on page 8 as another concern that you raise about the unpublished 2013 paper, you point to a comment that appears on page 19 about -- in the section that starts "although this is a large prospective study, there are limitations," and then there is a reference in the 2013 draft that you talk about need to add a paragraph of exposure assessment, discuss the information on our exposure scale in relation to the monitoring work, discuss the likely magnitude of misclassification and its likely impact on the estimates of relative risk"; correct. 06:00

A. Correct.

Q. And you mention this as another indication of why the 2013 analysis was not something that would have withstood peer review; correct? 06:00

MS. FORGIE: Objection.

THE WITNESS: This I cite because I'm asked to review glyphosate. 06:00

BY MR. LASKER:

Q. Okay. You stated that in the next paragraph for the above-stated reasons including the fact that there's this 06:00

question raised in the draft if you would have pointed out the above-mentioned problems -- and let me make sure, let me see if this is one of them. This data I had gotten closer to publication. So let me first ask this. The comment that you're pointing out in the March 15, 2013, draft following "although this is a large prospective study," is that a comment that in your mind will lead you to conclude that this study should not be published in peer-reviewed literature, specifically that comment? 06:01

MS. FORGIE: Object to the form. Asked and answered. 06:01

You can answer it again.

THE WITNESS: This statement was specific to glyphosate, not to anything that's published.

BY MR. LASKER: 06:01

Q. The comment in the draft that you're referring to is not discussing glyphosate; correct?

MS. FORGIE: Object to the form.

THE WITNESS: The comment is 06:01

probably more general, but my idea is that they took glyphosate out because that was the one that had most of the problems.

BY MR. LASKER: 06:02

Q. And if you can look at the 2014 paper again, and you can go to the very end of the paper on page 15 above the section -- above the conclusion, do you see where conclusion is in the same column? 06:02

A. Yeah, uh-huh.

Q. The paragraph above that which starts, "Although this is a large prospective study."

Do you see that? 06:02

A. Yes.

Q. And that is the same language that appeared in the draft in 2013, the same start of that paragraph; correct?

MS. FORGIE: Object to the form. 06:02

THE WITNESS: What was the question?

BY MR. LASKER:

Q. The phrase that starts in the peer-reviewed published study, "Although 06:02

this is a large prospective study" is the same statement that appears in the draft at page 19 where you are mentioning this concern that was being raised -- this comment that was raised in the draft document; correct? 06:02

MS. FORGIE: Object to the form. Misstates the draft.

THE WITNESS: There are two things conflated: One is the statement that was commented on, and the other is the comment. 06:03

BY MR. LASKER:

Q. The comment that you note that appears in the draft of potential limitation in the 2013 study, that is, in fact, discussed in the peer-reviewed published study in 2014; correct? 06:03

MR. BAUM: Object to the form. Again, mischaracterizes the draft.

THE WITNESS: So, again, the statement I pulled out, I'm referencing this early -- this sentence that starts on this paragraph in order to tell you which comment I'm referring to. The 06:03

comment I'm referring to states, "Need to add a paragraph of exposure assessment, discuss the information on exposure scale in relation to monitoring work, discuss the likely magnitude of misclassification and its likely impact on the estimates of RR." None of that could be done in this publication because they're not publishing on glyphosate. 06:04

BY MR. LASKER:

Q. But the comment that they're saying -- the note they're saying about what needs to be added to the manuscript was, in fact, added to the manuscript as it was published in 2014; correct? That's what the rest of that paragraph does. It responds exactly to that comment. 06:04

MS. FORGIE: Object to the form.

THE WITNESS: I have -- 06:04

MS. FORGIE: Wait. Also asked and answered.

You may answer it again.

THE WITNESS: I can't read it this fast. I would have to read the whole 06:04

paragraph, plus what this statement or this comment requests inserts in the message section, and I haven't reviewed the message section.

BY MR. LASKER: 06:04

Q. In making this criticism in your expert rebuttal report of the 2013 draft, am I correct that you did not compare this comment with what was actually included in the 2014 peer-reviewed published study? 06:04

MS. FORGIE: Object to the form.

THE WITNESS: I would not need to do that because the peer-reviewed study does not address glyphosate, and it is with glyphosate that I have this problem and not with these other pesticides. 06:04

BY MR. LASKER:

Q. Okay. The -- I want to make sure I talked about it. I think there's one study that I did not talk about. I don't think I'm going to have time to go through it in detail, but there was a case control study in France by Dr. Orsi, and that I know you have certain concerns about that I don't think we'll have time to go through in 06:05

detail. But am I correct that that case control population in France, the investigators reported an odds ratio for glyphosate of 1.0 that was not statistically significant? 06:05

MS. FORGIE: Object to the form.

THE WITNESS: They are reporting that for NHL. They also had other outcomes for which the odds ratios were slightly different including multiple myeloma and some sub groups. 06:05

BY MR. LASKER:

Q. But for NHL in the French case control study, they reported an odds ratio of 1.0; is that correct? 06:05

A. With a wide confidence interval and very few exposed subjects.

Q. Okay. And then for the NAPP data which would be the pooled data of all the case control studies in Canada and the U.S. for their ever/never analysis when they adjusted for three pesticides, they reported an odds ratio for glyphosate and non-Hodgkin's lymphoma of 1.13 or for self-respondents only an odds ratio of 0.95; 06:06

correct?

MS. FORGIE: Object to the form.

THE WITNESS: I remember that table, and my problem was that self -- was excluding the proxies is that you're actually excluding the sickest individuals who died before they could be interviewed. So the difference between the two estimates might be that you're actually throwing out the people who are the sickest. 06:06

BY MR. LASKER:

Q. Just so I understand for the NAPP data for pooling together all the case control studies in U.S. and Canada control adjusted for those three other pesticides, the odds ratios and the two ways that they reported it were either 1.13 or 0.95; correct? 06:07

MS. FORGIE: Object to the form. Asked and answered. 06:07

You can answer it again.

A. Those are reported for models that included three pesticides that I am questioning whether or not they should be 06:07

included, and the model that didn't include these pesticides was 1.43 and also for a subgroup analysis with intensity of exposures more than two days per year it actually didn't change at all. 06:07

Q. I understand that you have --

MS. FORGIE: Let me ask a question. How much time do we have left, please?

THE VIDEOGRAPHER: 11 minutes.

MS. FORGIE: Okay, so you'll let us know when seven hours is up, please. 06:07

BY MR. LASKER:

Q. For the De Roos 2005 cohort study, they reported a never/ever use risk ratio adjusted for other exposures of 1.1; correct? 06:07

A. Yes.

Q. And in the 2013 AHS data the never/ever odds ratio, you said, would be somewhere around 1.0. Dr. Blair said it would be around 0.9; correct? 06:08

MS. FORGIE: Objection. Mischaracterizes her testimony.

THE WITNESS: So I would not rely on De Roos, and I would not rely on the 06:08

new data unless somebody can show me that the exposure assessment for glyphosate was not severely misclassified.

BY MR. LASKER: 06:08

Q. I understand that. But the odds ratio reported in that data, and I understand you have reasons why you don't want to rely upon that was, according to Dr. Blair, around 0.9 and you agree it's somewhere around 1.10; correct? 06:08

MS. FORGIE: Object to the form. Also asked and answered.

You can answer it again.

THE WITNESS: That was my answer. I don't think I have to repeat myself. 06:08

BY MR. LASKER:

Q. And for the Swedish study for Eriksson in the multi-regressional analysis, they had an odds ratio of glyphosate non-Hodgkin's lymphoma of 1.5; correct? 06:09

MS. FORGIE: Object to the form.

THE WITNESS: It was about 1.5 in a multi-variated adjusted, yes. 1.53, yes. 06:09

BY MR. LASKER:

Q. We discussed now there was -- the Cocco study very small. The Hardell study was very small. But the four largest study populations then would be that French study, the NAPP study, the Eriksson study, and the De Roos or the AHS cohort. Those are the four largest datasets; correct? 06:09

MS. FORGIE: Object to the form.

THE WITNESS: Orsi is the wrong one to mention. I don't think that Orsi is one we should be looking because the power was very low and it's a case control study that's hospital-based. There are lots of problems with hospital-based controls. 06:09

BY MR. LASKER:

Q. Okay. You would -- and I know you don't agree with -- you have concerns about all of those numbers. But for all of these adjusted odds ratios you have as they're reported by the investigators, you have odds ratios that are bordering around 1.0 when adjusted for other exposures to pesticides; correct? 06:09 06:10

MS. FORGIE: Object to the form. Mischaracterizes the testimony -- the studies.

THE WITNESS: That's not correct. We would have to go study by study. For example, 1.35 is not hovering around 1. 06:10

BY MR. LASKER:

Q. 1.13, 1.0, 1.1 --

A. There was a 2 --

MS. FORGIE: Wait, wait. There's no question. 06:10

BY MR. LASKER:

Q. For ever/never use; correct?

MS. FORGIE: Object to the form. Asked and answered. 06:10

THE WITNESS: Can we go back to De Roos 2003 and check that?

BY MR. LASKER:

Q. Let's -- well, the NAPP includes -- pools all the data that's in De Roos and in McDuffie; correct? 06:10

A. Well, you asked me about all these substudies before.

Q. In your expert report you discuss biological plausibility; correct? 06:10

A. Yes.
Q. And you discuss in there data points for some studies on genotoxicity and oxidative stress; correct?
A. Where's that? 06:11
Q. It's the last page of your expert report, I believe.
A. It's the regular expert?
Q. Yes.
A. The first one. 06:11
MR. WISNER: Second to last page?
MR. LASKER: Yes.
THE WITNESS: Yes.
MR. WISNER: Page 24.
BY MR. LASKER: 06:11
Q. First of all, let me ask you, and I don't know if you've read Dr. Portier's deposition. He goes through the genotox studies in some detail. Dr. Portier testified that in his review of all of the 06:11 glyphosate studies, he did not find evidence from those studies showing that glyphosate is mutagenic. Do you agree with his assessment?
MS. FORGIE: Object to the form, 06:11

and I believe that mischaracterizes the deposition testimony, but you can show her a portion from that.
THE WITNESS: Do you want to show me? 06:11
BY MR. LASKER:
Q. No.
MS. FORGIE: Object to the form.
THE WITNESS: Then I can't comment.
BY MR. LASKER: 06:11
Q. Do you have an independent opinion as to whether or not the glyphosate mutagenicity studies present evidence that glyphosate or glyphosate-based formulations is mutagenic? 06:12
MS. FORGIE: Object to the form.
THE WITNESS: It has never been a point of discussion. It's genotoxicity, not mutagenicity.
BY MR. LASKER: 06:12
Q. So sitting here today, do you have any opinion one way or the other as to whether or not glyphosate is mutagenic?
MS. FORGIE: Object to the form.
Asked and answered. 06:12

You can answer it again.
THE WITNESS: It's beside the point because the topic here is genotoxicity and oxidative stress and not mutagenicity. 06:12
BY MR. LASKER:
Q. Do you have an opinion as to whether glyphosate is mutagenic?
MS. FORGIE: Objection. Asked and answered. 06:12
You can answer it again.
THE WITNESS: Mutagenicity is affect in bacteria. Genotoxicity we can assess in human cells and animals, and I believe that the studies that looked at 06:12 genotoxicity showed that there is genotoxicity as I report.
BY MR. LASKER:
Q. Do you have any opinion one way or the other as to whether or not glyphosate is 06:12 mutagenic? Yes or no.
MS. FORGIE: Objection. She doesn't need to give yes or no. You're badgering the witness. You've asked her three times now. 06:13

You can answer it again.
A. I was not evaluating mutagenicity here. I was evaluating genotoxicity, and my statement is about genotoxicity, not mutagenicity. 06:13
Q. Okay. And last document I'll show you -- and we'll have a statement for the record -- is the 2017 slide deck.
MR. LASKER: Has been marked as an exhibit? 06:13
MS. SHIMADO: Yes.
MR. LASKER: This will be my last question. I have a question on one of the slides in there.
MR. WISNER: Exhibit 5. 06:13
MR. LASKER: Yeah, 19-5.
THE WITNESS: My slide deck?
BY MR. LASKER:
Q. Yeah, it's this one.
A. Got it. 06:13
Q. And slide 16 in your slide deck --
MS. FORGIE: You mean page 16?
MR. LASKER: Page 16, slide 16. The number 16 on the slide.
THE WITNESS: Oh, yeah, the Ames 06:14

test.
BY MR. LASKER:
Q. Right.
So you present data here on the Ames test for assessing carcinogens, and you report data that for truly carcinogenic compounds and truly non-carcinogenic compounds and positive and negative on the Ames test; correct? 06:14
A. That's correct. 06:14
Q. My question is: The data in this table, is that data that you made up, or is that data --
A. Not even my data. It's actually Dr. Olson who loves to make these up. 06:14
Q. So this is all made-up data?
A. Yes.
MR. LASKER: Okay. Let's take a break. I've got about four minutes left. I'm going to see if I've got any questions after that point, and I've got a comment for the record. 06:14
THE VIDEOGRAPHER: We're off the record at 6:14 p.m.
(Recess taken from 6:14 p.m. to 06:14

6:32 p.m.)
THE VIDEOGRAPHER: We are back on the record at 6:32 p.m.
BY MR. LASKER:
Q. Dr. Ritz, in your opinion, can scientific studies looking at the issues of genotoxicity and oxidative stress standing alone provide evidence that can establish that a compound causes cancer in humans? 06:32
MS. FORGIE: Object to the form. 06:32
THE WITNESS: These are two criteria that are used by IARC to establish carcinogenicity, but they are just two criteria within the animal study -- within the mechanistic study section. There are several others. 06:32
BY MR. LASKER:
Q. And you would agree that genotoxicity and oxidative stress studies by themselves would not be sufficient for you to be comfortable reaching an opinion of carcinogenicity; correct? 06:32
MS. FORGIE: Object to the form.
THE WITNESS: I cannot subtract from what I know about animal studies, 06:32

mechanism, and human studies, and I would never start with a genotoxicity study. Because I'm an epidemiologist, I always start with human data.
MR. LASKER: I want to make a statement for the record, and then I'll suspend my questioning. There's a couple of issues here. 06:33
One is I mentioned earlier on the record, Dr. Ritz earlier in the deposition suggested, and I don't know whether she does or she does not, that she might have opinions regarding the animal cancer bioassays. 06:33
I have reviewed her expert reports multiple times. I don't see any mention of animal cancer bioassays. To the extent that plaintiff's counsel -- and we don't have to discuss this now -- but if there's going to be the position of plaintiffs that they're reserving the right for Dr. Ritz to offer opinion testimony regarding animal cancer bioassays, we'll move to strike all that testimony. 06:33

MS. FORGIE: I'm not going to respond to that. I believe her expert report speaks for itself.
MR. LASKER: You just responded.
MS. FORGIE: That's not a response. Just a statement. 06:34
MR. LASKER: Second, we marked a number of points in the transcript where the witness would not respond to a simple yes-or-no question and kept going into soliloquies on issues that were not part of the question. We marked that in the transcript numerous times. 06:34
By doing so, the witness, I think, intentionally was eating into our questioning time. As a result of that, we have not had sufficient time to explore Dr. Ritz's opinions both on the studies that we actually at least mentioned or discussed somewhat in passing or in connection with some of the studies, some of the smaller studies like Hardell and Cocco and also the Orsi study where we did not have time to ask questions pretty much at all, and also 06:34

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the numerous issues dealing with the Eriksson study in particular and the other studies where because of the witness' refusal to answer questions, we did not have time to go through all those questions.

I will raise an option for plaintiff's counsel that if plaintiff's counsel is agreeing to further questioning at this time for us to ask those questions, we are prepared to stay longer to do so.

If plaintiff's counsel is not prepared to provide us the time necessary to ask those questions and get Dr. Ritz's opinions, we reserve our right, and I'm only going to be suspending my questioning at this point in time to go back to the Court to get additional time because significant portions of time, in our opinion, were taken up because the witness would not answer a simple yes-or-no question, and we've marked those in the record, and the Court can reach its own conclusions 06:35

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about them.

MS. FORGIE: And for the record, how much time is left of his seven hours, or has he used it all? He's out. Could I just have a statement on the record that he's out? 06:35

THE VIDEOGRAPHER: Yeah. He's at seven hours.

MS. FORGIE: Okay. Of course, we don't agree at all with your characterization. In fact, there were multiple times, I would guess hundreds of times where you asked the same question over and over and over again, and that's what ate up into your time. 06:36

I wrote down at least three times where you asked the same question ten times.

Simply because you don't like the answer doesn't give you the right to ask the same question over and over again. That's what ate up your time, and I'm not going to agree to any further time. You can do whatever you want. 06:36

That's outrageous.

MR. LASKER: As I said, the Court 06:36

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will be able to look at the transcript. The witness didn't answer the questions; so of course, I had to ask them again.

MR. WISNER: Just for the record, a large portion of the time during this deposition was eaten up by yourself commenting on the proprietary or responsiveness of the witness' answer, which, quite frankly, is both argumentative, a waste of the testimony because it would never be admissible in court, and a large portion of your commentary was also eaten up. 06:36

So I think at this point -- how much time are you saying you want? Just curious. What's the amount of time you're asking for? 06:36

MR. LASKER: I probably need another two hours or so.

MR. WISNER: Okay. 06:37

MS. FORGIE: All right. So I have a few questions.

MR. LASKER: And further commentary, I'm going to respond to. It's in the transcript. The Court will 06:37

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be able to read that, and the Court will be able to decide whether or not the witness was responsive to questions.

MS. FORGIE: The court certainly will. 06:37

MR. LASKER: Also one more thing I want on the record as well. There was objections to virtually every question, other than what is your name, by plaintiff's counsel which also ate into the time. 06:37

MS. FORGIE: And I'll respond to that. You make incredibly compound, complex questions which are objectionable. I have to object to questions as to form if I want to preserve them, which I do, and you make these declaratory statements beforehand about all kinds of things; so that's why I had to object, and the Court can look at that as well. 06:37

Okay. I have a few questions, Doctor.

EXAMINATION 06:37

BY MS. FORGIE:
Q. Dr. Ritz, can you explain how you went about arriving at your opinions as expressed in your report?
A. Yes. When I'm asked to write a report of a review paper, I use standard methods common to epidemiology which is I go to PubMed, and I put in search terms, multiple search terms to find the biggest amount of literature that I can on PubMed. 06:38
However, I know that certain search terms don't work as well on PubMed; so we also go to Google Scholar which usually gives you a larger number of papers, and a lot of those then have to be weeded out 06:38 because they're not relevant for the question, but it at least allows you to check the literature very thoroughly. So it's a lot of work, but you, you know, go through it. 06:38
Then in addition, you're going to the published literature that is meta-analyses, pooled analyses to cross-reference and make sure you haven't missed anything that's mentioned in one of 06:39

the meta-analyses pooled analyses. You also go to the original literature and check all the references they have because normally every paper refers to papers in this same area prior -- that was published prior. So 06:39 you do that to make sure that you have all the information that you need.
In addition, I, of course, read not only the meta-analyses, the pooled analyses but also previous reports. I also read all 06:39 of the different meta-analyses that kind of keep repeating information about the singular studies. I read the singular studies. I read the IARC report, and I read the EPA CARC report, and all of it together 06:39 I used for my opinion.
Q. And you mentioned that you read the CARC report. How did you decide how much weight, for example, to give the CARC report? 06:39
A. The CARC report was not weighted very heavily because the epidemiology section was rather cursory, and the animal section, that one I actually studied more intensively, seemed to make a lot of use of 06:40

criteria that were contradictory in terms of which studies they were throwing out or throwing in, but it stimulated me to go back to some of the original studies they are citing, but overall, it did not make a big 06:40 impact on my assessment.
Q. You mentioned you reviewed the IARC monograph; is that correct?
A. That's correct.
Q. Did you rely on the IARC monograph, 06:40 or did you form your own opinions?
A. I formed my own opinion. It is very interesting to read the IARC monograph because it summarizes information in an interesting way. However -- and I use it to 06:40 cross check, and I use it to understand their argumentation.
It was published in 2015. There is additional data that came out since.
Q. Are you familiar with something 06:40 known as the Bradford Hill analysis?
A. Of course, yes. We teach that.
Q. Can you explain briefly what it is?
A. Well, Dr. Bradford Hill in the early 1960s, wrote a commentary in which he 06:41

describes viewpoints, he calls them, according to which one can review the scientific literature. It's not just epidemiology. It's all of science more or less. 06:41
Although he meant it for observational studies in order to help us gauge how the data is performing, how the studies are performing in terms of causal assessments because, as you may have 06:41 gathered while I was talking today, there is more to data than just, you know, numbers. We have to put these data into context, and that's what his viewpoints do. They put these data into context of validity, 06:41 biologic plausibility, et cetera.
Q. And with regard to glyphosate-based formulations and non-Hodgkin's lymphoma, did you perform a Bradford Hill analysis?
A. I did, and I talked about it in my 06:42 report.
Q. And what conclusion did you reach after performing your Bradford Hill analysis?
A. After that, I concluded that there 06:42

is reasonable scientific certainty that NHL is associated with glyphosate use in these data.

Q. And did you also -- are you aware as to whether or not IARC also performed a Bradford Hill analysis? 06:42

A. I would presume they did. Actually, they are talking about it; so I think they did.

Q. Okay. And what is your understanding of the conclusion that the IARC reached with regard to their Bradford Hill analysis? 06:42

A. Well, they used their Bradford Hill analysis in the way I just described to put the different pieces together. First, they might have done it work group for work group, but they also do this as a whole group in which they are putting together the human data, the animal data, the mechanistic data and put that in context of these criteria that Bradford Hill suggested. 06:42

Q. Is there a difference between hazard assessment and risk assessment?

A. Absolutely. 06:43

Q. What is the difference?

A. So a hazardous assessment is an assessment in which we are categorizing an agent according to its ability to be toxic including being carcinogenic, but you can also assess reproductive toxicity or other types of toxicity. 06:43

While a risk assessment is something that regulatory agencies use in order to come up with standard setting methods. 06:43

Q. So would it be accurate --

THE VIDEOGRAPHER: I'm going to have to change tapes.

This marks the end of videotape number 4 in the deposition of Dr. Beate Ritz. We're off the record at 6:43 p.m. 06:43

(Recess taken from 6:43 p.m. to 6:45 p.m.)

THE VIDEOGRAPHER: We are back on the record at 6:45 p.m. This marks the beginning of videotape number 5 in the deposition of Dr. Beate Ritz. 06:45

BY MS. FORGIE:

Q. Doctor, we are discussing the 06:46

difference between -- we were discussing what a hazardous assessment is.

Do you recall that before we changed tapes?

A. Yes, I do. 06:46

Q. Would it be fair to say that a hazardous assessment gives you an idea, in general, as to whether or not a particular product is capable of causing a disease?

MR. LASKER: Object to the form. 06:46

THE WITNESS: A hazard assessment is a general evaluation of an agent's potential to be toxic in different ways.

BY MS. FORGIE:

Q. And in this case, would it be accurate to say that a hazard assessment determines whether or not glyphosate is capable of causing non-Hodgkin's lymphoma? 06:46

MR. LASKER: Objection to form.

THE WITNESS: So, in fact, this what IARC is performing is a hazardous assessment. They are making a categorical -- they're taking a categorical approach with a conclusion of carcinogenicity. 06:46 06:47

BY MS. FORGIE:

Q. And did you read the deposition of Dr. John Acquavella in this case?

A. Yes, I did.

Q. From reading that deposition, is it your understanding that Dr. Acquavella is an epidemiologist? 06:47

A. Yes.

Q. Is it also your understanding that Dr. Acquavella was a -- is a former employee of Monsanto? 06:47

A. Yes.

Q. And is it also your understanding that he is a -- that Dr. Acquavella is a current consultant to Monsanto? 06:47

MR. LASKER: Objection to form.

THE WITNESS: I read that in the deposition, I believe, and I met him while he was an employee of Monsanto at some of these meetings. 06:47

BY MS. FORGIE:

Q. Do you recall reading what Dr. Acquavella said about IARC's hazard assessment?

A. Yes. I understood his testimony as 06:47

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stating that IARC got the hazard assessment right but that there are questions about the risk assessment.
MR. LASKER: Objection to form.
BY MS. FORGIE: 06:47
Q. So Dr. Acquavella's testimony was that IARC got it right in that in categorizing glyphosate as 2A; is that correct?
MR. LASKER: Objection to form. 06:48
Mischaracterizes the testimony.
THE WITNESS: I did understand from reading his testimony that he actually referred to a correct hazard assessment, and if he meant correct, then he would 06:48 have included the assessment of carcinogenicity in terms of a 2A.
BY MS. FORGIE:
Q. And likewise, it would be correct that in agreeing with IARC's hazard 06:48 assessment, he would have agreed that glyphosate is capable of causing non-Hodgkin's lymphoma; is that correct?
MR. LASKER: Object to the form.
Mischaracterizes testimony. 06:48

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THE WITNESS: So since IARC based its evaluation on NHL and quotes a positive association with NHL, I assume that that was what he meant.
BY MS. FORGIE: 06:48
Q. Can you look at Exhibit 16, please.
MR. LASKER: Which one is that?
MS. FORGIE: It's the Brazil slide show, slide deck, PowerPoint, whatever you want to call it. 06:49
THE WITNESS: Yeah.
BY MS. FORGIE:
Q. And on that, can you turn to the Section 26, page 26, "Proxy Versus Self-Respondent," please. 06:49
A. Yes.
MR. LASKER: Page 26?
MS. FORGIE: Yes. This one. "Proxy Versus Self-Respondents."
MR. LASKER: Thanks. 06:49
MS. FORGIE: Do you have it?
MR. LASKER: I do.
BY MS. FORGIE:
Q. Okay. Do you see the section where they're talking about frequency of greater 06:49

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than two days per year?
Do you see that?
A. Yes.
Q. And what is the odds ratio there for proxy and self-respondents? 06:49
A. So for proxy and self-respondents, meaning for everyone, it's 1.73 with a confidence interval of 1.02 to 2.94.
Q. And is that odds ratio controlled for use of 2,4-D, dicamba, and malathion? 06:50
A. Yes, it is.
Q. And are those the only three pesticides that you're aware of that are associated as risk factors for non-Hodgkin's lymphoma? 06:50
A. I am aware that 2,4-D is a 2B category according to IARC. Malathion is a 2A. I'm not aware that dicamba is categorized.
Q. Okay. And with the 1.73 odds 06:50 ratio, is that statistically significant?
A. It is.
Q. And is the greater than two days of use per year category there more important than the never/ever use category that was 06:50

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discussed earlier by the defense counsel?
MR. LASKER: Objection to form.
THE WITNESS: Absolutely. It's much more important to look at higher intensity because oftentimes that is 06:50 where we see effects when we're evaluating carcinogens.
BY MS. FORGIE:
Q. And with regard to the seven -- the category greater seven lifetime days, years, 06:51 number of years times number of days per year.
Do you see that?
A. Yes.
Q. And it looks like the odds ratio 06:51 has actually gone down in that section.
Do you see that?
A. Yes. The odds ratio hovers around the 1.
Q. Can you explain why the odds ratio 06:51 is lower for that category than for the greater than 2 category where the odds ratio is 1.73?
A. Yeah. These are two different -- very different measures. One is the 06:51

intensity, and the other is duration, and the lifetime days is the product of duration and intensity meaning that, in essence, I am watering out any intensity via duration.

I can get the same numbers with a very low intensity over long duration as with a shorter duration and a higher intensity. So that measure really is more closely related to duration than to intensity. 06:51 06:52

Q. And does that explanation -- how does that tie into whether or not this information tells you -- what information this gives you about glyphosate-based formulations causing non-Hodgkin's lymphoma? 06:52

A. So in terms of occupational epidemiology, we are very interested in high level exposures which we often have a much better way in assessing a much more reliable way in assessing and also believe that high intensity exposures are really what we have to worry about, and we have to protect workers from. 06:52

So I would think that the high intensity more than two days per year is 06:52

what really is an interesting finding in terms of worker health.

Q. And one last question. You see there's two categories here, proxy and self-respondents category A and self-respondents only category B. 06:52

Do you see that?

A. Yes, I see that.

Q. Do you see that under greater than two days of use per year, while the odds ratio goes up from 1.73 for proxy and self-respondents to 1.77 for self-respondents only, it is not statistically significant for self-respondents only. 06:53 06:53

Do you see that?

A. Yes, I see that.

Q. Is there any way to -- what happens when you take out the proxy group?

A. You are pretty much reducing sample size, and when you reduce sample size, you automatically lose statistical power to show a statistically significant effect. So that's what happens here. 06:53

Q. With regard to if you remove 06:53

proxies from the category, is there any reason you would want to include proxies?

A. Well, the one reason I can think of is that proxies are responding because the self-respondent isn't available which means the self-respondent would be too sick to answer or dead. 06:53

So what you're doing is you're pretty much removing the sickest individuals if you're removing the proxy respondents. 06:54

Q. Okay. And then can you turn -- oh, a couple more questions about the NAPP study.

You were shown Exhibit 16. Do you see at the bottom where it says, on the front page, it says Sao Paulo Brazil? 06:54

A. Yes.

Q. Okay. So is it your understanding this is a PowerPoint presentation that accompanied the Brazil presentation? 06:54

A. That's what I understand.

Q. Were you also made -- or have you also seen slide shows with regard to a presentation in Canada?

A. Yes, I was shown that. 06:54

Q. And you also have seen abstracts and posters with regard to a Canadian presentation?

A. Yes.

Q. Have you also seen a slide show, abstracts, or posters related to an IARC presentation? 06:54

A. To the IARC presentation, yes.

Q. And did any of the information -- with regard to your expert report, you, I believe, testified that you only used the Brazil abstract when you were drafting your expert report; is that correct? 06:54

A. That's correct.

Q. So with regard to all of the other materials related to the NAPP study, all these other slide shows, other abstracts, other posters, did any of them affect or change your opinion as stated in your expert report? 06:55 06:55

A. The only way it changed my opinion is that it solidified the opinion that there is, in fact, carcinogenicity to go after.

Q. In assessing the risk of cancer in glyphosate, is there any potential bias in 06:55

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controlling for concurrent pesticide use?
A. Yes. It's always a problem with concurrent exposures. We haven't really found a mathematical way to get around it. There is probably none to get around it. 06:55
If exposures are highly correlated, you have to sit down and ask the question is it more or less likely that these exposures are independent risk factors or indicators or proxies for the actual exposure under 06:56 investigation?
So when you're putting these in the same statistical model, then something occurs that we call co-linearity, and what that means is that there's some technical 06:56 term. These variables split the variants or the explained variants. And in essence, if you put enough highly correlated variables into the same model, none of them will explain anything anymore. All of them will 06:56 go towards the one.
I've seen that multiple, multiple times in air pollution studies where the air pollutants are highly correlated, and this is what you see. Therefore, you are going 06:56

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one by one by one in order to assess their affect on household counts.
Q. Doctor, you were asked many questions about your criticisms of the draft manuscripts of unpublished AHS data. 06:56
Do you recall those questions?
A. Yes.
Q. You've made several criticisms of the draft manuscripts and the unpublished glyphosate data with regard to the AHS 06:57 study; is that correct?
A. That's correct.
Q. With regard to those criticisms of the AHS study, have you ever publicly made those criticisms prior to being retained in 06:57 this litigation?
A. Yes.
Q. And in what format is that?
A. Well, in my teaching. When I teach my students about the cohort design, I warn 06:57 them against the limitations of cohorts because I think I pointed out that this validity slide in the beginning of one of my slide shows is there to actually cause discussion with my students about these 06:57

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blanket validity statements in terms of studies.
So I'm using the AHS study and the loss to follow up as a good example of what to be careful of when you're conducting a 06:57 cohort study.
Q. And, Doctor, I'd like you to turn to Exhibit 17, please.
A. Yes.
Q. And, Doctor, do you see a date on 06:58 this slide presentation?
A. Yeah. That was on my old slides from fall 2012.
Q. So this was approximately four years before you were retained as an expert 06:58 in this litigation; is that correct?
A. That's correct.
Q. And, Doctor, in Exhibit 17, these slide presentations that you use in your teaching at UCLA, do you have criticisms of 06:58 the AHS study incorporated in there?
A. I believe so.
Q. Can you point those out, please?
A. So what I'm doing here is introducing the AHS cohort to the students 06:58

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talking about retro and prospective data collection and what the problems are, and then I'm showing them the composition of the cohort and data collection progress in different phases and specifically on page 6, 06:59 I show them a slide that was given to me during phase 2 data collection in which I point out how many people are actually not completing phase 2 in different parts of phase 2. 06:59
And I'm then directing them to the issue of exposure assessment being incomplete when you have a time varying exposure that you cannot capture at a second time of follow-up. 06:59
Q. So, Doctor, is it accurate to state that approximately four years before being retained as an expert in this litigation, you were teaching -- you were using the AHS problems, exposure assessment problems you 06:59 described with the AHS cohort study as it relates to glyphosate as a teaching tool to your students as to how not to conduct an epidemiological study?
A. Not as not to conduct but what to 06:59

be careful of when you're conducting studies that otherwise seem so perfect.

Q. Doctor, you were asked a lot of questions today, and you were shown a lot of documents. Do any of the documents or questions that you were asked change your opinion as expressed in your expert report that to a reasonable degree of scientific certainty glyphosate causes non-Hodgkin's lymphoma? 07:00

A. I still stand to my conclusions as cited.

Q. And, Doctor, same question, in other words, you were asked a lot of questions and shown a lot of documents today. Do any of them change your opinion to a reasonable degree of scientific certainty glyphosate-based formulations including Roundup cause non-Hodgkin's lymphoma? 07:00

A. Nothing changes my opinion.

MS. FORGIE: That's it.

MR. LASKER: I have one follow-up question. It's not going to take me five seconds. 07:00

MS. FORGIE: I'm not going to allow any time. No more questions. I'm sorry.

MR. WISNER: Let him have one follow-up. 07:01

MS. FORGIE: You guys are a lot nicer than me.

FURTHER EXAMINATION

BY MR. LASKER: 07:01

Q. Dr. Ritz, you provided your slide deck for teaching students in fall of 2012. Do you have any other slide decks of your teaching of your students that mention the AHS study? 07:01

A. Yes. Many. Every year.

Q. Okay. I will for the record object to the fact --

A. It's the same slide deck. It's updated. 07:01

MR. LASKER: I'll ask those slide decks be produced if they refer to the AHS study. Obviously, we understand all slide decks deal with case control studies or cohort studies is over the 07:01

top, but if she has other slide decks that refer to AHS, that seems pretty squarely in line --

MR. WISNER: To the extent they're different than the one you have. 07:01

MS. FORGIE: He just said it's the same.

MR. LASKER: I don't know.

THE WITNESS: It is the same.

MR. LASKER: I don't understand 07:01 that. I don't know if you've looked at them or not. You can look at them. If they're the exact same slide deck, that's fine. But if they're not the exact same slide deck, we ask they be 07:02 produced. And you don't have to commit to that. You can look at them.

THE WITNESS: Fine.

MS. FORGIE: She said they're the same. I believe her. All right. Done? 07:02

MR. LASKER: I'm sorry. We're off the record.

(Testimony continues on the following page in order to include jurat.) 07:02

THE VIDEOGRAPHER: This concludes today's proceedings in the deposition of Dr. Beate Ritz. The total number of videotapes used today was five, and we're off the record at 7:02 p.m. 07:02

(Time noted: 7:02 p.m.)

_____

Beate Ritz, MD, PhD

Subscribed and sworn to before me this day of , 2017.

_____

(Notary Public)

My Commission expires: _____

C E R T I F I C A T E

STATE OF CALIFORNIA:

I, LISA MOSKOWITZ, CSR, RPR, CRR, CLR, NCRA Realtime Systems Administrator, Certified Shorthand Reporter, do hereby certify:

That the witness whose deposition is hereinbefore set forth was duly sworn, and that such deposition is a true record of the testimony given by such witness.

I further certify that I am not related to any of the parties to this action by blood or marriage, and that I am in no way interested in the outcome of this matter.

IN WITNESS WHEREOF, I have hereunto set my hand this 19th day of September, 2017.

_____

LISA MOSKOWITZ, CSR 10816, RPR, CRR, CLR
NCRA Realtime Systems Administrator

NAME OF CASE: In re: Roundup
DATE OF DEPOSITION: September 18, 2017
DEPONENT: BEATE RITZ, MD, PHD

1. To clarify the record.
2. To conform to the facts.
3. To correct transcription error.

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CURRICULUM VITAE
April 2017

Beate R. Ritz, MD, Ph.D.
Professor
Departments of Epidemiology and Environmental Health
UCLA School of Public Health
Box 951772
Los Angeles, CA 90095-1772

EDUCATION

1995	Ph.D. in Epidemiology, School of Public Health, UCLA
1993	M.P.H. in Epidemiology, School of Public Health, UCLA
1987	Doctoral Degree in Medical Sociology, University of Hamburg.
1983	Medical Examination Certificate, Registration as a Physician (M.D.), Board of Health in Hamburg
1977-1983	Medical School, University of Hamburg, Germany

PROFESSIONAL POSITIONS AND APPOINTMENTS

2012- 2015	Chair, Department of Epidemiology, School of Public Health, University of California Los Angeles (UCLA)
2006-current	Professor, Departments of Epidemiology, Environmental Health, and Center for Occupational and Environmental Health, School of Public Health, and Neurology, School of Medicine, UCLA
2005-2012	Vice Chair, Department of Epidemiology, School of Public Health, University of California Los Angeles (UCLA)
2004-current	Appointment in the Department of Neurology, School of Medicine, UCLA
2002-current	Co-director of the UCLA-CGEP (UCLA center for Parkinson 's Disease Environmental Research (CCPDER- CNS)
2001 -2006	Associate Professor, Department of Epidemiology, Department of Environmental Health, and Center for Occupational and Environmental Health, School of Public Health, UCLA
1995-2001	Assistant Professor, Department of Epidemiology and Center for Occupational and Environmental Health, School of Public Health, UCLA
1993-1995	Assistant Researcher, Department of Epidemiology, School of Public Health, UCLA
1989-1991	Hochschulassistentin (Assistant Professor), Institute of Medical-Sociology, University of Hamburg, Germany.
1987-1988	Research Fellow and Resident, Psychiatric University-Hospital Eppendorf, Hamburg, Germany
1984-1986	Research Fellow, Institute of Medical Sociology, University Hospital Eppendorf, Hamburg, Germany

OTHER HONORARY PROFESSIONAL APPOINTMENTS

2002-2008	Editorial Board: EPIDEMIOLOGY
2004-2009	Editorial Board: Epidemiologic Perspectives & Innovations
2007-2010	Editorial Board: Environmental Health
2001-current	Chair (since 2005) and Member (since 2001) of the external advisory committee for the NCI/NIEHS Agricultural Health Cohort Study
2001-current	Board of Directors for the 'R. Lemelson Foundation for Psychocultural Research.' Annual awards of $800,000 for research and training including a UCLA training grant for cross-disciplinary studies in anthropology, psychology and neuroscience

2001-2002	Member of the external advisory committee for the California Biomonitoring Planning Project conducted by the Environmental Health Laboratory's Biomonitoring Project (CDHS)
2002	Member of the EPA Science Advisory Board for Human Health Research Strategy (HHRS)
2002-2004	Member of the external advisory committee for the California Environmental Health Surveillance System (Governor Davis appointee to expert working group for SB 702)
2003-2006	Member of the Ethic Committee for the International Society for Environmental Epidemiology
2003-2004	Member of NAS, IOM Committee on Gulf War and Health, Phase 3: Literature Review of Selected Environmental Particulates, Pollutants, and Synthetic Chemical Compounds
2002-2004	Member of the external advisory committee for the California Environmental Health Surveillance System (Governor Davis appointee to expert working group for SB 702)
2006	Member of NAS, IOM Committee on Gulf War and Amyotrophic Lateral Sclerosis
2006	Member of the Scientific Steering Committee for Pediatric BioBank in California
2007	Robert M. Zweig M.D. Memorial Award (Clean Air Award) from the California South Coast Air Quality Management District
2007	Appointed as a Collegium Ramazzini Fellow
2007	Scientific Organizing committee for the PPTOX conference in Faroe Island
2008	Scientific Organizing committee for the ISEE conference in Pasadena
2008	Member of the Environmental Exposures Working Group conducted by RTI International for the PhenX project of GWA research at NIH
2009	Member of NAS, IOM Committee on Gulf War and Health, Phase 4
2008-09	Member of the U.S. EPA CO standard setting panel for (CASAC: *Carbon Monoxide National Ambient Air Quality Standards*)
2009-2012	Elected Councilor for the International Society for Environmental Epidemiology (ISEE)
2010-current	Member of the Conference Organizing committee of the ISEE
2009	Award from the American Parkinson's Disease Association (APDA) for outstanding contributions to the medical and scientific communities towards the advancement of Parkinson's disease research
2010-2013	Member of the External Advisory Board for the Superfund site center grant at University of Washington
2010-2013	Member of the External Review Board for the Swiss Tropical and Public Health Institute in Basel
2013	Scientific Organizing committee for the ISEE conference in Basel/Switzerland
2012-current	Member of CA-EPA Scientific Review Panel on Toxic Air Contaminants
2012	Affiliate member of the Institute of the Environment and Sustainability
2014	Scientific Organizing committee for the ISEE conference in Seattle Washington
2014-current	Member of NAS/IOM committee on Incorporating 21st Century Science into Risk-Based Evaluations

FUNDED RESEARCH

NNH12ZDA006O-EVI3
Agency: NASA (PI: Ritz)
Total Direct Costs to UCLA: $1,294,244
Multi-Angle Imager for Aerosols (MAIA) 08/01/16-11/30/25
This project will assess air pollution and adverse birth outcomes using exposure data provided by Dr. Diner's group from the MAIA NASA project. UCLA researchers will be responsible for the modeling the effects of prenatal air pollution exposures on adverse birth outcomes derived from vital statistics records for multiple locations across the world.

1 U01 HD087221 (PI: Devaskar/UCLA Ob-GYN)
Agency: NIH/NICHD Period: 01/01/16-12/30/19
Total Direct Costs: $2,999,640
Imaging Innovations for Placental Assessment in Response to Environmental Pollution
The objective of this proposal is to develop and evaluate a suit of cutting-edge multi-parametric magnetic resonance imaging (mp-MRI) technologies and translate these novel placental imaging modalities to assessing the impact of environmental pollution exposure on prediction of placental insufficiency.

Psychosocial stressors, air pollution and childhood respiratory health in LAFANS
Agency: NIEHS R03ES025908 (PI: Ritz) Period: 07/01/15-06/30/17
Total Direct Costs $100,000
This study will add to the previous literature by constructing a more holistic measure of the stress perceived by the child, and use that measure to determine if a child's perceived stress modifies their risk of asthma or reduced lung function from air pollution.

Pesticide Exposures and Risk of Cerebral Palsy
Agency: NIEHS R03ES025904 (PI: Ritz) Period: 07/01/15-06/30/17
Total Direct Costs $100,000
Using records from the California Department of Developmental Services (DDS), we will identify children born 1995-2007 and diagnosed with CP in California until 2010. For ~10,000 CP cases we will randomly select 1:10 matched controls from the California birth certificates. Ambient pesticide exposure estimates pre-pregnancy, during pregnancy and/or first year of life for each child will be estimated using a Geographic Information System (GIS) model we previously developed based on the California Pesticide Use Reporting (PUR) system. We will examine specific vulnerable periods in pregnancy (trimesters or months of pregnancy) to assess pesticide exposure effects on CP.

Autism, Metabolomics, and Environment (AIME)
Agency: NIEHS R21ES25573 (PI: Ritz) Period: 07/01/15-06/30/17
Total Direct Costs $275,000
We will assess whether autism risk factors can be identified using metabolomic biomarkers of exposure in stored maternal serum samples from mid-pregnancy from 200 case and 200 control pregnancies in Central California and compare biomarker exposure patterns with modelled air pollution and pesticide exposures. Metabolomics analyses will be performed in a targeted as well as untargeted manner with high-resolution metabolomics that uses mass spectrometry and advanced data extraction algorithms to quantify up to 20,000 chemicals in small biologic extracts.

Air Pollution and Childhood Autism
Agency: NIEHS R21ES024006 (PI: Ritz/Ehrenstein – multiple PI) Period: 07/01/15-06/30/17
Total Direct Costs $275,000
We use highly sophisticated modeling and analytical techniques for the detailed spatial and temporal assessment of air pollution to examine their influence on neurodevelopment in a California birth cohort linked to autistic disorder records of the CA Department of Developmental Services.

Environment and cognitive decline in older Hispanics
Multi-PI: Ritz/Haan
Agency: NIEHS Type: R01- RES023451A Period: 04/01/15-03/31/19
Total Direct Costs: $ 2,000,000
The goal of the proposed research is to investigate whether long-term exposure to two ubiquitous environmental exposures, air pollution and pesticides, contribute to cognitive decline and dementia in elderly Mexican Americans (MA) from the "Sacramento Area Latino Study on Aging" (SALSA) cohort. We capitalize upon our expertise in modeling air pollution and pesticide exposure and plan to model 1) long and short term regional, local, and traffic related air pollution using monitored criteria pollutants, CALINE4 - emissions and land use regression (LUR) models; and 2) long-term exposures to pesticides of specific chemical classes with our GIS model; and 3) assess impairment in cognitive domains and the onset of dementia longitudinally based on multiple complex environmental exposure patterns while taking into account vulnerability due to genetic and physiologic risk factors for dementia.

Air Pollution and Autism in Denmark
PI: Ritz
Agency: NIEHS Type: R21 Period: 04/01/15-03/31/17
Total Direct Costs: $ 275,000
The goal of the proposed research is to utilize Danish nationwide population-based registers and sophisticated individual-level air pollution exposure measures to assess whether early life exposure to traffic-related and particulate air pollution during critical periods of fetal development are associated with autism risk. We will use the Danish National Birth Cohort (DNBC) which enrolled pregnant women and collected extensive prospective risk factor data during pregnancy and early life for ~100,000 children

among whom 720 are already diagnosed with ASD to examine potential confounding bias for a large number of risk factors assessed in pregnancy.

Air Pollution and Cardiovascular Diseases: Identification of Novel Biomarkers
Agency: NIEHS R21 ES024560 (PI: Zhu) Period: 05/01/15-04/30/17
Total Direct Costs $275,000
Objectives: The goal of this project is to identify novel and sensitive biomarkers of cardiovascular health effects, in association to air pollution exposures.
Role: Co-I

Environmental exposure, DNA methylation, and Parkinson's disease

Agency: NIEHS 21ES024356 (PI: Ritz/ Horvath) Period: 08/06/14 – 07/31/16

Total Direct Costs: $ 250,000

Environmental exposure, DNA methylation, and Parkinson's disease
Here we use a powerful new tool and systems biology analytic methods to identify signatures for toxic exposures that evoke long-term biologic responses. Using DNA methylation we will investigate specific epigenetic markers (CpGs) correlate with toxic exposures and the role these epigenetic changes play in PD progression using epigenome wide technologies combined with analytic tools to integrate these data. We will investigate epigenetic determinants of Parkinson's disease in over 800 subjects with existing biospecimens.
Role: PI

Maternal comorbidities, prescription drug use in pregnancy, and childhood cancer (COMPAC): a record linkage study in Denmark
PI: Heck
Agency: NIH/NCI Type: R21CA175959 Period: 04/01/14-03/31/16
Total Direct Costs: $ 275,000
This study aims to link several large-scale databases in Denmark to examine maternal health and medication use in pregnancy in relation to childhood cancers. We propose to examine common pregnancy conditions that have been linked to cancers in adults and children in other studies as well as common medications taken in pregnancy which are suspected carcinogens or linked to cancer in other studies.
Role: Co-I

Inflammatory Cytokine Polymorphisms, Air Pollution, and Very Preterm Birth
PI: von Ehrenstein
Agency: NIEHS Type: R21ES022734 Period: 07/01/13 - 06/30/15
Total Direct Costs: $ 275,000
We examine the hypotheses that maternal exposure to air pollutants during pregnancy is associated with an increased risk of very preterm birth (VPTB, <32 weeks gestation), and that polymorphisms in inflammatory genes modify the influence of air pollution on the risk of VPTB. We use data from the CA Very Preterm Birth (CVPTB) Study, a nested case-control study of VPTB from 5 counties in Southern CA known for high particulate matter, ozone, and traffic exposures that has genotyped SNPs related to PTB in 26 inflammatory/immune response pathway genes in mother-infant pairs and will utilize a combination of extensive air monitoring data and air pollution modeling approaches (land use regression (LUR), CALINE4, kriging) to estimate air pollution exposures in pregnancy for CVPTB Study subjects.
Role: CO-I

Pesticide Exposure and Childhood Autism
PI: von Ehrenstein
Agency: NIEHS Type: R21ES022389 Period: 01/01/14 - 12/31/15
Total Direct Costs: $ 275,000
We examine the hypothesis that exposure to specific pesticides during vulnerable periods, particularly during fetal development, determines risks of subsequent development of autistic disorder (AD). We developed a geographic pesticide exposure assessment tool (GRAPES) that utilizes the unique California Pesticide Use Report system, in combination with agricultural land-use maps, to derive record-based estimates of historical residential exposures, and expect to identify >20,000 autism cases with diagnoses up to the age of 72

months from the CA-DDS database born in CA 1997-2009 and >1,700 from agricultural areas as well as 1:10 age-sex match controls from birth records, the largest cohort ever to address hypotheses that exposures to specific chemicals (e.g. neurotoxic or endocrine disrupting agents) contribute to AD during vulnerable periods of development.
Role: CO-I

Parkinson's Susceptibility Genes and Pesticides (PEG-Renewal)
Principal Investigator: Ritz
Agency: NIEHS/NINDS Type:R01ES010544 03/01/11-11/30/15
Total Direct Costs: $ 2,500,000
In this renewal of an epidemiologic population-based case-control study we recruit 500 additional PD patients in three rural California counties and will assessed their exposures to pesticide exposures and the effects of gene-pesticide interactions.
Role: PI

Systems genetic and reverse phenotypic analysis of age and retirement.
PI: Horvath (UCLA)
Agency: NIA Type: R01AG042511-02 07/01/13 - 06/30/17
Total Direct Costs: $ 1,000,000
We will apply/develop state of the art computational, statistical, and bioinformatic approaches with which to investigate the association between genetic data and aging- related phenotypes. Specifically, the study uses data from the Health and Retirement Study (HRS) and a systems biology approach to identifying relevant SNPs and genetic pathways and machine learning techniques and reverse phenotyping methods to better understand the complex relationship between genetics and aging outcomes including cognition and wealth.
Role: CO-I

Exposure to C8-chemicals and autism, ADHD, and cerebral Palsy in the Danish Birth Cohort
PI: Jorn Olsen (UCLA and Aarhus University, Denmark)
Agency: Danish Medical Council
Total Direct Costs (at UCLA): $ 250,000 01/01/11 - 08/31/15
The overall goal of the project is to assess the impact of C8 persistent organic pollutants in maternal serum during pregnancy and childhood outcomes of autism, ADHD and cerebral palsy in the Danish Birth cohort using follow-up data from the National Danish medical registry systems.
Role: CO-I

A Cohort Study on Air Pollution and Breast Cancer in Los Angeles County
IIR13262718 Wu (co-PI) 02/13/14-02/150/17
Susan G Komen $217,728
The overall objective is to examine the role of air pollution and risk of breast cancer among whites and non-whites in Los Angeles using the large Multiethnic Cohort Study
Role: Co-Principal Investigator

Improvements in Air Quality and Health Outcomes among California Medicaid Enrollees Due to Goods Movement Actions — Phase I: Assessing Air Quality Changes
PI: Meng . UCLA
Agency: Health Effects Institute (HEI) #: 4914-RFA11-1/2-6 09/01/12 – 08/31/15
This phase of the project will evaluate the effect of goods movement emission reduction actions on ambient air quality in goods movement corridors, non-goods movement corridors, and areas outside of these two corridors in 10 major California counties between the 2003-2007 pre-policy and 2008-2012 post-policy years.

COMPLETED RESEARCH
Assessing and Reducing Taxi Drivers' Exposure to Ultrafine Particles
PI: Yifang Zhu (UCLA) Type: R21OH10196 09/01/12–08/31/14
Agency: CDC/NIOSH
Total Direct Costs: $ 275,000

Goal: The major goals of this project are to develop ultrafine particle exposure assessment instrument and explore novel low-cost ultrafine particle exposure mitigation strategies for taxi drivers.
Role: Co-I

Air Pollution and PD in Denmark
PI: Ritz Type: R21-ES022391 12/01/12-30/11/14
Agency: NIEHS
Total Direct Costs: $ 275,000
This study will use a sophisticated and validated GIS-based dispersion model, AirGIS, to assess exposure to traffic-related air pollution in PASIDA participants; i.e. NO_2/NO_x. Specific aims are to: (1) assess the influence of long-term traffic-related air pollution exposure on PD risk for 1,867 cases and 1,920 population controls combining existing PASIDA data with new exposure measures from AirGIS; and (2) investigate the combined action of air pollution and genetic variants in inflammatory genes previously linked to PD.
Role: PI

Parental Occupation and Childhood Cancers in Denmark
PI: Heck (UCLA) TYPE: R03 ES021643 4/15/12-3/31/14
Agency: NIEHS
Total Direct Costs: $ 50,000
The specific aims of this study are: 1) Create a linked database of all childhood cancers in Denmark diagnosed 1965-2010 with recorded information on parental employment. 2) Examine the relation between parental employment and childhood cancers focusing on maternal occupational exposures. 3) Examine specific hypotheses in childhood cancer risk (occupational social contact; contact with animals; organic dust; welding fumes; bitumen fumes; outdoor work; and several associations seen in previous literature (solvents, paints and pigments, motor vehicle exhaust related occupations)).
Role: Co-I

Pesticides and Childhood Cancers
Principal Investigator: Ritz (UCLA)
NIEHS R21- ES019986 4/1/11 – 12/31/13
Total Direct Costs: $ 275,000
The specific aims of this study are to examine associations between prenatal exposure to pesticides and specific childhood cancers in California between 1980-2009 using ambient measurement data using our GIS model of pesticide exposures based on land use maps and pesticide use report (PUR) data.

UCLA Center for Centers for Neurodegeneration Science (CNS; former CGEP)
Director: Chesselet, UCLA; Co-director: Ritz
NIEHS P01ES016732 09/15/08-08/31/13
Total Direct Costs: $5,000,000
We have previously shown associations between high levels of exposure to specific environmental pesticides and Parkinson's disease and will build on this knowledge to determine the mechanisms of action that may be causing this association. We will use an integrated, multidisciplinary approach to identify additional agricultural pesticides that are disrupting similar molecular pathways, and determine whether these also increase the risk of Parkinson's. This work is expected to shed light on the pathological processes involved in sporadic Parkinson's disease, the most frequent form of the disorder, and could have public health implications for precautions in the use of some pesticides.
Project 4: Pesticides and Genes in PD: Studies in Humans
Principal Investigator: Ritz
NIEHS 09/15/08-08/31/13
Total Direct Costs: $1,250,000
This project will use the existing PEG data to test biological candidate genes and newly identified putative environmental toxicants for association with PD. We will recruit and collect biological (DNA) samples from and construct exposures estimates for 400 additional population controls. This will enable us to test new hypotheses for rarer exposures to specific toxins and will allow us to investigate gene-gene (GxG) and gene-environment (GxE) interactions with sufficient power. Targeted toxins are either (a) interfering with the ubiquitin proteasomal system (UPS), (b) altering microtubule integrity, and/or (c) inhibiting the aldehyde/alcohol dehydrogenase. Targeted genes include UBE1 and UBE1L2; PSMC2, 3, 4, and 5; HIP2; SKP1A; GSK3B; CDK5; MAPT, Sirt2, and ALDH and ADH gene clusters.

Registry of Parkinson's Disease Study In Denmark (PASIDA)
Principal Investigator: Ritz
NIEHS RO1 - ES013717 09/01/06-08/31/13
Total Direct Costs: $5,600,000
We conduct 1) a case-control study of ~13,000 PD cases and age-gender matched controls from the Danish population via passive record linkage by unique ID between the National Patient Register, Pharmacy Database, and National Pension fund to identify risk factor information contained in these records (e.g. occupations, medication use, diseases prior to PD onset); and 2) recruit actively ~2500 of the most recently registered PD patients and population controls to collect additional risk factor information per interview and biological materials for gene-environment interaction analyses and to characterize PD patients phenotypically.

Air Pollution and Childhood Cancers
Principal Investigator: Heck (UCLA)
NIEHS R21- ES018960 4/1/10 – 12/31/13
Total Direct Costs: $250,000
The specific aims of this study are to examine associations between prenatal exposure to motor vehicle related air pollution toxics and specific childhood cancers in Los Angeles County and all of California between 1980-2009 using ambient measurement data, land use based regression (LUR) and CALINE4 models.

California Parkinson's Disease Registry Pilot Feasibility Study
Principal Investigator: Ritz
DOD 09/01/07-04/30/12
Total Direct Costs: $390,000
The primary goal is to conduct a pilot study for the legally mandated statewide population-based PD registry. We will identify PD cases in Kern, Tulare and Fresno counties from legally mandated sources (pharmacists, health care institutions, physicians and other providers). A secure prototype database will be established, and associations between PD and toxicant chemical exposure will be determined by linking to a database of toxicant chemicals established previously by UCLA based on California state data (e.g. the pesticide use databases).

UCLA UDALL Parkinson's Disease center
Principal Investigator: Chesselet, UCLA
NINDS Type: P50 NS38367 04/01/06-03/31/12
Total Direct Costs: $7,500,000
Project 6 within the center (budget of $ 500,000 annual direct costs): Progression and Health Impacts of PD Motor and Non-Motor Manifestations (C-PI Ritz)
Research goals are to assess whether development and progression of PD motor and non-motor manifestations in 300 PD patients ascertained in the PEG study (PI: Ritz see below) are influenced by environmental, behavioral, and social factors and by genetic variants of ApoE and serotonin transporter alleles, and to determine the relative contributions of progression of motor and non-motor manifestations of PD to changes in HRQOL over time.

Sunlight exposure and variations in vitamin D metabolic genes in Parkinson's disease
Principal Investigator: Ritz
NIEHS R03- ES017139 09/01/09-08/31/11
Total Direct Costs: $100,000
The goal of the proposed research based on the PEG study population is to examine the hypothesis that long-term low levels of vitamin D either through inadequate sunlight exposure or alterations in metabolic genes that influence physiological vitamin D levels increase the risk of PD. We will test associations between long-term UV exposure measures and PD and examine whether genetic alterations presumed to result in different physiological vitamin D activity in genes critical to the vitamin D pathway (VDR, CYP27B1 and CYP24A1) increase the risk of PD.

Traffic-Related Air Pollution and Ultrasound Measures of Fetal Growth
Principal Investigator: Wilhelm Turner (UCLA)

NIEHS R03- ES017314 04/01/09-03/31/11
Total Direct Costs: $100,000
The specific aims of this study are to estimate prenatal exposures to O3 and PM10 and pollutants originating from traffic (NOx) using CALINE4 air dispersion modeling and examine associations with fetal size throughout pregnancy using ultrasound measures to examine associations with weight, length, head circumference, fetal growth ratio, ponderal index, and cephalization index at birth.

Ambient Air Toxics and Adverse Birth Outcomes
Principal Investigator: Wilhelm Turner (UCLA)
NIEHS R03 ES017119-01 12/15/08 – 12/30/10
Total Direct Costs: $100,000
The specific aims of this study are to: (1) examine associations between prenatal exposure to motor vehicle air toxics and low birth weight (LBW) and preterm birth in women residing in Los Angeles County, California between 1994-2006 using both ambient measurement data and land use based regression (LUR) models; and (2) gain information about how LUR models built on NOx measurements reflect exposures to specific toxins thought to have biological relevance for these outcomes.

Exposure to mobile source air pollution and adverse birth outcomes in the Los Angeles Air Basin
Principal Investigator : Jun Wu (UCI)
NIEHS R21 ES016379 9/11/08 -12/31/10
Total Direct Costs: $250,000
The overall goal of the project is to improve exposure assessment of air pollution exposure in pregnant women and investigate the impact of air pollution exposure on adverse reproductive outcomes, such as preterm birth, low birth weight, and intrauterine growth retardation.

Disparity in asthma among Californians from pollutant exposures.
Principal Investigator: Meng, UCLA
California Air Resources Board 04/22/08- 12/31/10
Direct Costs: $270,000
The goal of the research is to conduct a population-based study to examine the effects of long-term air pollution exposure near residence on chronic severe asthma and asthma-like symptoms in vulnerable populations.

Development of Exposure and Health Outcome Indicators for Those with Asthma or Other Respiratory Problems
Principal Investigator: Meng, UCLA
EPA- R833629 09/01/07-12/31/10
Direct Costs: $410,000
The goal of this research is to investigate the feasibility of combining existing environmental monitoring and health survey data to develop indicators that signal trends in exposures and health for those with asthma or other respiratory problems

Neighborhood Effects on Children's Health & Access to Care
Principal Investigator: A. Pebley, UCLA
HRSA 09/01/07- 8/31/10
Total Direct Costs: $500,000
The goal of this study is to significantly advance our knowledge about the relative importance of specific family and neighborhood characteristics in the development of major child health problems. This project is based on the Los Angeles Family and Neighborhood Survey (L.A.FANS), a longitudinal study of neighborhoods, families, adults, and children in Los Angeles County

Traffic-Related Air Pollution and Asthma in Economically Disadvantaged and High Traffic Density Neighborhoods in Los Angeles County, California (with LA F.A.N.S.)
Principal Investigator: Ritz
California Air Resources Board 01/06/05-09/30/09
Total Direct Costs: $420,000
The objectives of this research are: (1) to conduct NO_x and NO_2 monitoring at 200 locations within LA County neighborhoods with varying levels of economic disadvantage and varying exposures to air

pollution originating from vehicular sources; (2) to use these monitoring data to help inform land use-based regression (LUR) models developed to predict traffic pollutant exposures; (3) to use geostatistical models to estimate regional background concentrations of O_3 and $PM_{2.5}$; (4) to evaluate associations between exposure to NO_x, NO and NO_2 and measures of lung function and asthma prevalence, exacerbation and possibly incidence in children ages 0-17 years in conjunction with the Los Angeles Family and Neighborhood Survey (L.A. FANS) study; and (5) to evaluate whether concentrations of the more regionally distributed background pollutants (O_3 and $PM_{2.5}$) confound or modify the effects of exposure to the more heterogeneously distributed traffic-related pollutants (NO_x, NO and NO_2) on lung function and asthma.

Aggregate Exposure Assessment: Longitudinal Surveys of Human Exposure-Related Behavior
Principal Investigator: Irva Hertz-Picciotto, UC Davis
EPA 01/12/04-11/30/09
Direct Direct Costs: $388,111
This project develops data collection platforms for longitudinal assessment of exposure-related behavior. The data characterize short-term, seasonal, and long-term changes in time-activities, food consumption habits, and use of household and personal care products. We assess exposure-related behaviors at multiple collection points over time, and evaluate a number of data collection methods for validity (accuracy), precision, completion rates, cost, feasibility, and user acceptability.

UCLA Center for Gene-Environment Studies in Parkinson's Disease (CGEP-part of the NIEHS CCPDER)
Director: Chesselet, UCLA; Co-director: Ritz
NIEHS 09/01/02-08/31/09
Total Direct Costs: $7,000,000
The overall objective of this Center is to understand how the detrimental effects of pesticides, a suspected environmental risk factor for Parkinson's disease, are modulated by genetic variations that impact dopamine homeostasis in nigrostriatal neurons. The center integrates 3 RO1 research projects that investigate these questions in fly, mouse, cell culture models and applies the results also to human genetics (project 1: PI Ritz)
Research Project I within the CGEP center "Environmental toxins and genes that influence dopamine in Drosophila and humans"
Principal Investigator: Ritz
NIEHS 09/01/02-08/31/09
Total Direct Costs: $1,000,000
This project examines interindividual variability of dopamine vesicular transporter (VMAT) expression due to promoter variants in two human populations in parallel with a reporter gene assay. These populations will be genotyped for functional VMAT2 variants and association analyses of gene-environment interactions and pesticide exposures collected in the parent grant will be conducted. In addition, Drosophila genetics will be used to determine how the expression of VMAT affects dopamine-mediated toxicity and identify genes that modulate VMAT function, which will then be examined in the human population for their relevance to increase risk of PD.

Parkinson's Susceptibility Genes and Pesticides (PEG)
Principal Investigator: Ritz
NIEHS/NINDS 10/01/00-09/30/07
Total Direct Cost: $2,653,852
We are testing the gene-environment interaction hypothesis for Parkinson's disease by conducting an epidemiologic population-based case-control study of 400 newly diagnosed PD patients from three rural California counties matched to population controls; in addition we are collecting data for unaffected sibling controls. Environmental and occupational pesticide exposure estimate are derived from California pesticide-use reporting (PUR) and other data. We are examining the effects of gene-environment interactions by testing for associations of PD using multiallelic repeat markers and genotyping intragenic single nucleotide polymorphisms (SNPs) and/or deletions in 50 candidate genes.

PD Consortium: Genetic and Environmental Factors in Parkinson's Disease
Principal Investigator: L. Nelson, Stanford
MJ Fox Foundation 10/01/04-09/30/07

Total Direct Costs $50,000
We established the Consortium for the Study of Genetic and Environmental Factors in Parkinson's disease, with the goal of organizing the collaborative efforts of five investigative groups that have who have conducted (or are conducting) seven case-control studies of PD. For approximately 1700 PD cases and 2100 gender- and age-matched control subjects, we investigate how the risk of developing PD varies according to tobacco and caffeine intake, as well as variants in ten candidate genes that code for proteins that may be involved in conferring the protective effect of these agents.

Alpha Synuclein and Environmental Exposures: A Study in Humans
Principal Investigator: Langston, The Parkinson's Institute
MJ Fox Foundation 01/01/05-12/31/07
Total Direct Costs $100,000
We are investigating the joint effects of: (1) consequences of alpha-synuclein over-production and enhanced mapping of the SNCA promoter region and (2) the biologic effects specific toxicants (e.g., rotenone, paraquat, organochlorine pesticides). We take advantage of two unique cohorts at high risk for pesticide exposure currently evaluated by members of the NIEHS-funded Collaborative Centers for Parkinson's Disease Environmental Research (CCPDER) at the Parkinson's Institute (PI) and UCLA, the Agricultural Health Study cohort and a population-based study of PD and pesticide exposure in rural Central California (the PEG study).

Prostate Cancer and Pesticide Exposure in Diverse Populations in California's Central Valley
Principal Investigator: Cockburn, USC
DOD 05/01/06-12/31/07
Total Direct Costs: 250,000$
This is a pilot study bringing an innovative collaborative approach to prostate cancer research. Specifically, this study will apply novel methods of pesticide exposure assessment using Geographical Information Systems (GIS), examine whether our proposed method of recruiting and approaching cases and controls for a large population-based case-control study will result in acceptable response rates, or whether our sample will be biased with respect to socioeconomic status, race, and disease characteristics, and whether we will be able to obtain sufficient DNA from mailed (Oragene) spit collection kits to assess effect modification by known relevant genes, and have sufficient stored DNA to assess the impact of genes that may be discovered in future.

Traffic-related Air Pollution and Adverse Birth Outcomes
Principal Investigator: Ritz
NIEHS 07/15/01-06/14/07
Total Direct Costs: $641,612
The objectives of this project are to determine whether exposures to elevated and traffic-related ambient air pollution during pregnancy result in low birth weight, preterm birth, intrauterine and postneonatal mortality, or cardiac defects in infants born to women living in the South Coast Air Basin (SoCAB). We performed a cohort study of all births (between 1995 and 1999), fetal and infant deaths (between 1989 and 1997), and conducted a nested case-control study of 2600 women who delivered children in LA in 2003 to collect additional exposure, confounder, and effects modifier data.

Ergonomic Interventions for Sewing Machine Operators
Principal Investigator: Ritz
CDC/NIOSH 10/01/02-09/31/06
Total Direct Costs: $868,262
We are conducting a randomized trial of a newly developed ergonomic intervention in sewing machine operators working in LA garment shops. The ergonomic intervention package includes changes in work-station design, training of employees, and suggestions of improvement in work procedures. We are examining whether interventions can reduce rates of upper extremity, neck (and lower back) musculoskeletal disorders, severity of pain and impairment, and lost-time compared to 'placebo' (control) interventions. This study will provide employers, employees and public agencies with evidence of the effectiveness of ergonomic interventions in order to guide health and safety policy.

Traffic-Related Air Pollution and Acute Respiratory Diseases and Asthma in Children Ages 0-5 in the SoCAB From 1990-2000

Principal Investigator: Ritz
California Air Resources Board 01/06/04-09/30/05
Total Direct Costs: $55,000
The aims of this study are to estimate the transient effects of traffic related and background air pollution in the South Coast Air Basin (SoCab) on the risk for hospitalization for acute respiratory illness and asthma in children ages 0-5 using a case- crossover study design and a time-series analysis.

Assessment of In-Traffic Exposures and Human Reproductive Health
Pilot project Principal Investigator: Ritz; SCEHSC Center Principal Investigator: Froines, UCLA
EPA 07/01/04-06/30/05
Total Direct Costs Pilot Project within the PM-center: $28,000
The goal of this project is to evaluate whether maternal in-vehicle air pollutant exposures during commutes (either in passenger cases, buses or other means of public transportation) affected the risk of low birth weight (LBW) and preterm birth in infants born to women living in Los Angeles County, California between 2003-2004. Commuting behavior (travel time, mileage and/or modeled routes) will be used to evaluate exposure to motor vehicle exhaust pollutants while in-transit

Molecular Epidemiology and Gene-Environment Interaction
Principal Investigator: Zhang, UCLA
NIH/NIEHS R21 ES 011667 04/01/02-03/31/05
Total Direct Costs: $450,000
This was a planning grant for molecular epidemiology in Environmental genome. The award was to establish a molecular epidemiology research program focusing on environmental genome.

Uncontrolled Asthma and Exposure to Air Pollutants: Linking Chronic Disease and Environmental Data Sources
Principal Investigator: Meng, UCLA
CDC/NIOSH/ 10/01/02-09/01/05
Total Direct Costs: $600,000
Based on the California Health Interview Survey (CHIS 2001) data, an extensive air monitoring network, and detailed information on traffic density we are conducting a population-based epidemiologic case-control study to: (1) ascertain the relationship between control of asthma and exposure to air pollutants in Los Angeles County and San Diego County, California; and (2) build and enhance the partnerships between public health and environmental agencies and local communities.

Center of Excellence for Environmental Public Health Tracking
Principal Investigator: Balmes, UCSF
CDC/ATSDR 10/01/02-09/01/05
Total Direct Costs (UCLA only): $300,000
The UCLA part of this center grant uses the data from 5,200 California Health Interview Survey (CHIS 2001) respondents who reported having been diagnosed with asthma at some point in their lives and live in the Greater Bay Area, San Joaquin Valley, and Los Angeles County. Criteria pollutant averages are employed as measures of background ambient air quality and linked with sociodemographic information and data on asthma management, access to care, and risk behaviors collected through CHIS for each targeted respondent.

Community Response to Maternal/Child Heath Disparities
Principal Investigator: Hobel, Cedars Sinai
NIH 04/1/03-9/30/05
The major goals of this study are to examine the interrelating biological and social-behavioral factors that contribute to health disparities in pregnancy outcomes and infant and early childhood mortality and morbidity. We will participate as one of five selected sites in the nation to plan for a multi-centered, community-based study examining the relationship between environmental factors and child health disparities

Extension of the Rocketdyne/Al Worker Cohort Through 1999
Principal Investigator: Ritz
California Cancer Research Program 07/01/00-06/30/04

CRP award #00-00781V-20218
Total Direct Cost: $324,508
We extended the mortality follow-up of two previously established cohorts of workers employed at Rocketdyne/Atomics International (now Boeing North American) facility for an additional 5 years and added a cancer incidence component for the period 1972-1998. This study allowed evaluating the impact of radiation and some known animal carcinogens on cancer mortality and morbidity.

Assessment Scale for End-of-Life Care in End-Stage Dementia
Principal Investigator: Ackerman, UCLA
Alzheimer's Association 10/01/00-09/30/03
Total Direct Costs: $217,583
This pilot project developed a scale to assess end-of-life care for end-stage dementia patients and evaluated its performance using mortality data.

Pilot grant from Southern California Center for Airborne Particulate Matter (SCCAPM)
Principal Investigator: Froines, UCLA; Pilot grant Principal Investigator: Ritz
U.S.-EPA-Star grant 07/01/01-12/31/02
Total Direct Cost: $12,000
The pilot grant supported exposure assessment for an epidemiologic study of traffic related adverse birth outcomes.

Evaluation and Validation of Pesticide Use Reporting in California
Principal Investigator: Ritz
UC Toxic Substances Research & Teaching Program 07/01/99-06/30/01
Total Direct Costs: $ 50,000
The goal of this pilot grant was to use biomarker data to evaluate the validity of pesticide exposures estimates derived from geographic models of environmental exposure based on pesticide use reports and land use maps in California residents.

Identify and Reduce Work Hazards in Home Health Care Workers
Principal Investigator: Ritz
Institute of Labor and Employment Pilot Study 02/01/01-30/08/01
Total Direct Costs: $ 7,500
This pilot project developed and tested a survey instrument and collected preliminary data for a study of job hazards in 74,000 home health care workers in LA county.

Pilot Study for Gene-Environment Interaction and Parkinson's Disease Study
Principal Investigator: Ritz
APDA Center Pilot Grant 03/01/99-12/31/00
Total Direct Costs: $35,000
This pilot project involved establishing data resources to improve exposure measures for pesticides, and setting up of a county-wide networks to reach incident Parkinson's cases in rural California.

Development of a Temporary Parkinson's Disease Registry for Southern California
Principal Investigator: Ritz
APDA/Pilot Grant from the PD-center at UCLA 03/01/99-12/31/00
Total Direct Costs: $10,000
This pilot project established mechanisms to obtain incident Parkinson's cases in rural California using information provided by local health care providers, Parkinson's disease foundations, clinics, and Medicare, and to determine which data sources exist for the application of capture-recapture methods to validate coverage of a future PD registry.

Modeling Air Pollution and Birth Defects
Principal Investigator: Ritz
CBDMP Grant/SCEHS/NIEHS Pilot Grant 07/01/00-09/30/00
Total Direct Costs: $5,600
The objective of this project was to examine the usefulness of some advanced statistical modeling procedures in order to determine whether exposures to elevated levels of ambient air pollutants (PM10,

CO) at the levels found in the South Coast Air basin (SoCAB) basin caused defects of the cardiac system of fetuses.

Pesticide Exposure Modeling Based on Historical Use Reporting in California to Investigate Long-Term Health Effects
Principal Investigator: Ritz
UCLA-USC NIEHS-Center Pilot Grant 05/01/99-04/30/00
Total Direct Costs: $18,000
The objectives of this pilot grant were to develop a geographic model for pesticide exposure of California residents between 1950 and 1990 using satellite images of crops, aerial photographs, and Pesticide Use Reporting Data from the California Department of Pesticide Regulations.

Epidemiologic Study to Determine Possible Adverse Health Effects on Rockwell/Rocketdyne Workers from Exposure to Radioactive and Hazardous Substances
Principal Investigator: Morgenstern, UCLA
CPHF/DOE/DE-FG-03-91SF18983 01/10/93-03/31/99
Total Direct Costs: $740,000
The major goal of this study was to test the hypothesis whether exposure to toxic chemicals and ionizing radiation among Rockwell/Rocketdyne workers caused an excess of cancer mortality.

Hazard Surveillance in the Defense Nuclear Industry
Principal Investigator: Froines, UCLA
CDC/NIOSH/R01-CCR912034 09/01/95-08/31/99
Total Direct Costs: $1,244,745
The major goals of this project were to develop an integrated theory, approach, and methodology to exposure assessment and hazard surveillance in the U.S. defense nuclear industry.

The Influence of Air Pollution in the Los Angeles Metropolitan Area on the Occurrence of Birth Defects, 1990-1993
Principal Investigator: Ritz
SCEHSC/NIEHS/UCLA-USC NIEHS-Center Pilot Grant 09/01/97-09/30/98
Total Direct Costs: $24,000
The objective of this pilot project were to examine whether the exposure of pregnant women to elevated levels of ambient air pollutants (Ozone, NO2, PM10, CO) at the levels found in the Los Angeles Metropolitan Area or the South Coast Air basin (SoCAB) basin cause low birth weight or preterm birth.

RESEARCH CONDUCTED IN GERMANY (1984-1989)
Health effects of airborne-dioxin exposure in Hamburg nursery schools
Rheumatic disorders, working conditions and coping behaviors in female office workers
Work-related knee-joint and elbow injuries in pipe-fitters and welders
Back and neck pain, psycho-social and ergonomic stresses in nursing professions

HONORS AND AWARDS

1999	UCLA Faculty Career Development Award
1999	'Rothman' award presented at SER by C. Poole
1989-1992	Post-doctoral fellowship received from DAAD ("German Academic Exchange Office of the Ministry of Research and Technology")
2001	Delta-Omega Award
2007	Robert M. Zweig M.D. Memorial Award (Clean Air Award) from the South Coast Air Quality Management District (AQMD)
2009	Award from the American Parkinson's Disease Association for outstanding contributions to the medical and scientific communities and for my work towards the advancement of Parkinson's disease research

TEACHING

UCLA, School of Public Health, graduate courses, 1995-present
Epidemiology Methods (Core methods course (200B) in the UCLA Epidemiology program)
Environmental Epidemiology
Occupational Epidemiology
Advanced Methods in Occupational and Environmental Epidemiology
Seminar: Occupational and Environmental Cancers
Seminar: Policy Issues in Occupational and Environmental Health

University of Hamburg, Medical School, 1984-89
Lectures and seminars in Medical Sociology for medical students
Lectures and seminars in Psychiatry for medical students

ADVISING AND MENTORING OF DOCTORAL STUDENTS (PH.D) AND POSTDOCTORAL FELLOWS (SUBJECT OF DISSERTATION OR FELLOWSHIP)– *note: this list only includes primary advisees (i.e. chair of committee and not member of dissertation committee) and does not include master level students*
At UCLA:

1997 - 2001	Kurt Straif (Cancer mortality in the German rubber industry)
1998 - 2000	Timothy Clary (Pancreatic cancer mortality and pesticide use in California)
1998 - 2004	Michelle Wilhelm (Traffic-related air pollution and pregnancy related health effects)
1998 - 2004	Rudy Rull (GIS modeling of pesticide exposure and neural tube defects)
1998 - 2004	Anusha Krishnadsan (Occupational physical activity and prostate cancer incidence)
2001 - 2004	Yingxu Zhao (Work place exposures to chemicals and cancer incidence)
2003 - 2004	Gail Asleson Kang (*Movement Disorder Fellow*: Clinical characteristics of PD patients)
2002 - 2006	Pin-Chieh Jason Wang (Ergonomic interventions and health effects in LA garment workers)
2003 - 2006	Chad Lewis (TTHM contamination in drinking water and adverse birth outcomes)
2003 - 2005	Kathrine Hoggatt (co-mentored with Dr Greenland: Air pollution and adverse birth outcomes)
2004 - 2008	Angelika Wahner (Doctoral student & postdoctoral fellow: Parkinson's disease, genetic factors and anti-inflammatory drug use)
2004 - 2008	Marie Sharp (The Latina Paradox in Birth Outcomes)
2004 - 2008	Sadie Costello (Parkinson's disease and life style factors)
2005 - 2008	Shannon Rhodes (Doctoral student & postdoctoral fellow: Iron genetics and Parkinson's disease)
2008 - 2010	Nicole Gatto (Postdoctoral fellow: Vitamin D, sunlight and Parkinson's disease)
2004 - 2008	Amanda Colligan (Residential pesticide exposure and Parkinson's disease)
2005 - 2012	Anthony Wang (Occupational pesticide exposures and Parkinson's disease)
2007- 2011	JoKay Ghosh (Air toxics and adverse birth outcomes)
2008- 2013	Tracy Becerra (Autism and race ethnicity in Los Angeles)
2008- 2013	Erin Jacob-Marcotte (Pesticides in pregnancy and childhood cancers)
2011-2012	Anshu Shresta; post-doctoral fellow (Childhood cancers and the environment)
2011-2013	Pei Chen Lee; postdoctoral fellow (Air pollution and pregnancy biomarkers)
2009-2014	Shilpa Narayan (Progression in Parkinson's disease)
2009-2014	Christina Lombardi (Air pollution and childhood cancers)
2011-2014	Zeyan Liew: PFOA exposures in the Danish birth cohort and ADHD and autism)
2012 -present	Gretchen Bandoli (Stress, asthma and birth outcomes in LA)
2012 -present	Kristina Vanderwaal Hool (breast cancer and methylation patterns)
2011- present	Kim Paul (Gene-environment interactions in Parkinson's – PASIDA study)
2011- present	Xin Cui (Bias analysis in the PASIDA study of Parkinsons)
2011- present	Andrew Park (Pesticides and childhood cancers)
2012- present	Vivian Alonso (Nutrition, vitamins use and reproductive health)
2013- present	Yu-Hsuan Chuang (Parkinsons, gene methylation, and gene-environment interactions)
2013- present	Xiaoqing Xu (Pharmaceuticals and childhood cancers in Denmark)
2013- present	Matt Feaster (Occupations risk factors for childhood cancers)
2013- present	I-Fan Shih (Parkinsons and physical activity)
2013- present	Negar Omid (Childhood cancer risk factors)

2013- present Aline Duarte (Parkinson's non-motor symptoms)
2013- present Chenxiao Ling (Bias analysis in environmental epidemiology)
2014- present Cynthia Kuster (Parkinsons' and estrogen receptors)
2014- present Zuelma Esquivel (Childhood cancer risk factors)
At University of Washington:
2004-2006 Kathrine Carr (*Postdoctoral Fellow*: Bronchiolitis and air pollution in LA infants)
At UCI:
2011-2013 Jun Wu (junior faculty mentor for W. Rosenblith award given by HEI)
At the University of Copenhagen, Denmark:
2008-present Line Kenborg (Parkinson's disease and outdoors work and sunlight exposures)
2007-2009 Kathrine Rugbjerg (Parkinson's disease and head trauma and auto-immune diseases)
University of Umea/Sweden
2014 Opponent for doctoral student David Olsson (Air pollution and PTB and preeclampsia in Stockholm)

PARTICIPATION IN GRANT AND CENTER REVIEWS
Reviewer on a NCI Special Emphasis Panel "Improving Exposure Assessment in Environmental and Occupational Epidemiology of Cancer", May 2001
Reviewer of the NIEHS-funded Columbia University Environmental Health Sciences Center, May 2002
Reviewer of the Charles Harkin Award Application for Research in Thyroid Cancer, NIH, April 2003
Reviewer of the Wellcome Trust Application "Pre and post-natal exposure to particulate matter and pregnancy and infant outcomes: an historical cohort study", 2003
Reviewer of the Health Effects Institute's (HEI) Walter Rosenblith New Investigator Award application, April 2003
Reviewer of pilot grants for the Southern California NIEHS center grant (2004 and 2005)
Reviewer of pilot grants for the UCLA-CCPDER center (NIEHS funded) (2003 and 2005 and 2008)
Reviewer for NCI, Epidemiology of Cancer (2004/05 Council EPIC)
Reviewer for several NIH, Department of Health & Human Services meeting applications, 2003-2005
Reviewer (Chair of Review Committee) for a NIEHS-PO1 application (2004)
Appointment to Review Committee of the European Science Foundation (ESF) (2005)
Annual Review of SCEHSC Pilot Project Submission (permanent member 2004-current)
Institutional Patient-Oriented Career Development Programs in the Environmental Health Sciences [K12] (ES06-005), (2007)
Conference grant applications (2004-2007)
NIH reviewer for Outstanding New Environmental Scientist (ONES) award in the Environmental Health Sciences (2006)
Member of the EPA's Clean Air Scientific Advisory Committee (CASAC) Carbon Monoxide (CO) Review Panel (2008-current)
Grant review for an internal NIEHS scientist's application (Dr. Chen) (2007 and 2008)
Grant review for NIEHS special emphasis panels 2009-2010
Grant review for NIH-BCHI 2011
Pilot grant review for the Northern California Center for the National Children's Study –Pilot Projects Program August 2011
External Review of the Neurology Department at Columbia (NY), 2011
Scientific Review of Superfund Site Projects as EAC member for University of Washington, 2012
External Review of the Swiss Tropical and Public Health Institute (TPH), 2012 and 2013
External Review of the Epidemiology Branch at NIEHS, 2013
Review for Harvard NIEHS center pilot grant, 2014
Review of applications for Health Effects Institute (HEI Boston), Rosenblith awardees, 2014
Review for Mount Sinai (NY) NIEHS center pilot grants, 2014
Review for NIEHS USC-UCLAEnvironmental Health Science center pilot grants, 2014
Review of NIEHS conference grants July 2015
Review of Parkinson's disease grant for Parkinson's UK foundation in Great Britain

JOURNAL REVIEWER FOR:
American Journal of Epidemiology
Epidemiology
International Journal of Epidemiology
Annals of Epidemiology

Environmental Health Perspectives
Environmental Health
Occupational and Environmental Medicine
Archives of Neurology
Annals of Neurology
Neurology
Movement Disorders
Pediatrics
JAMA
Lancet
Parkinson's and Related Disorders
Pharmacogenetics and Genomics
Journal of the Air & Waste Management Association
Journal of Exposure Analysis and Environmental Epidemiology
Chemosphere
Zeitschrift Sozial- und Präventivmedizin (SPM)
Human Reproduction
Women & Health
Etc.

INVITED SEMINARS AND LECTURES (SELECTED)

1. The Health Effects of Low-level Ionizing Radiation, USC, Health Sciences 1996
2. Work Environment and Health, UCLA Health Sciences 1996
3. The Effects of Carbon Monoxide Exposure on Low Birth Weight in the LA Metropolitan Area, 1989-1993, USC, Southern California Environmental Health Sciences, 1997
4. Cancer Mortality in Radiation Workers, USC Southern California Environmental Health Sciences, 1997.
5. Basic Principles of Reproductive Epidemiology, European School of Risk Assessment in Reproduction" in Florence/Italy December, 1997.
6. The Rocketdyne/Al Worker Health Study: Results and Lesson's Learned, California Department of Health Services, Occupational Health Branch, 1998
7. Air Pollution and Low Birth Weight in Southern California, GSF Munich Germany, 1998
8. Air Pollution and Adverse Birth Outcomes: Methodological Issues and First Results, Southern California Environmental Health Science Center, USC, 1998.
9. Gene-Environment Interaction and Parkinson's Disease, Neurology Grand Rounds, UCLA 1998
10. Air Pollution and Adverse Birth Outcomes in Southern California, Dept. of Reproductive Epidemiology, University of Michigan, East Lansing, 1999.
11. Methodologic Issues in Studying of Gene-Environment Interaction, GSF Munich Germany, 1999
12. Methodologic Aspects of Studying Cancer Mortality in Radiation Workers, Dept. of Epidemiology, University of Michigan, East Lansing, 2000.
13. Cancer Mortality in Fernald Uranium Workers, NIOSH, Cincinnatti, 2000.
14. GIS Modeling of Pesticide Exposures in California, Dept. Environmental Epidemiology, GSF Munich Germany, 2000
15. Traffic-related Air Pollution and Adverse Birth Outcomes in Southern California, Dept. Environmental Epidemiology, GSF Munich Germany, 2000
16. Studying Parkinson's disease in Populations; American Parkinson's Disease Association conference for patients and care providers at UCLA, 2001
17. From the Epidemiology of Parkinson's Disease to Gene-Environment Interactions, VA-PD conference, Woodland Hills, 2001
18. GIS Modeling of Air Pollution and Pesticide Exposures in California, USC-UCLA NIEHS Town hall meeting, Dec, 2001
19. GIS Modeling in the context of a Gene-Environment Interaction study of Parkinson's disease, Dept. Environmental Epidemiology, GSF Munich Germany, 2001
20. The Epidemiology of Parkinson's Disease, Conference of the Society for Research on Amyotrophic Lateral Sclerosis, Colorado May 2002
21. Traffic-related Air Pollution and Reproductive Health Effects: An Overview; Environmental Health Sciences seminar at UC Riverside, Feb. 2002
22. Reproductive Health Effects due to Carbon Monoxide Air Pollution in Southern California, NRC

Subcommittee on Health Effects from CO pollution meeting at UC Irvine. April 2002
23. Traffic-related Air Pollution and GIS Modeling in Southern California. USC-GIS Workshop Pasadena. May 2002
24. Health Effects Modeling with GIS, USC-GIS Workshop Public Forum at USC, May 2002
25. Dopamine Imbalance and Oxidative Stress in Parkinson's Disease, VA Research Conference on PD and Movement Disorders, Los Angeles 2002
26. The Center for Gene Environment Interaction in Parkinson's disease (CGEP) at UCLA: Dopamine Imbalance in Parkinson's Disease, Inaugural NIEHS Conference at the Parkinson's Institute in Sunnyvale CA, August 2002
27. Air pollution effects on birth outcomes: An overview. Health Effects Institute, Annual conference held at Georgetown University; 2003
28. Linking air pollution effects and adverse birth outcomes in the Los Angeles basin throughout the 1990s. U.S. EPA, Chapel Hill, NC; 2003
29. Air Pollution and Adverse Birth Outcomes in the South Coast Air Basin, 1989-2000; Conference of the Czech NAS meeting on air pollution effects (Dr. Sram), Prague, 2003.
30. Air pollution and adverse birth outcomes, an update on recent developments. Department of Preventive Medicine at the University of Southern California, 2003
31. GIS modeling of environmental exposures: applications to air pollution and pesticide exposures. Department of Environmental Health, Harvard, 2004
32. Air pollution models of adverse birth outcomes. Department of Epidemiology at the University of North Carolina, 2004
33. Parkinson's disease, metals and pesticides. Department of Toxicology, Symposium on Toxics Risks and Aging, Duke 2005
34. Air pollution and adverse birth outcome research in the SoCAB from 1995-2005. California Air Resources Board, Sacramento, Sept 2005
35. Parkinson's disease and pesticide exposure assessment in farming communities in the California Central Valley. Symposium of the Ramazzini Conference, Bologna, Italy Sept. 2005
36. Parkinson's disease and aging. UCLA Center on Aging Research Conference on Aging 2006.
37. Air Pollution and Asthma in Children. AQMD Asthma Impacts of Air Pollution Conference Los Angeles, Feb. 2006
38. Parkinson's disease and pesticides in the Central California Valley. NIEHS center at Columbia University, NY 2007
39. Assessing pesticides exposures for prostate cancers in the Central California Valley IARC. Lyon 2007
40. Air pollution and adverse birth outcomes in LA. INSERM, Paris 2007
41. Gene Environment Interactions in Parkinson's disease. CREAL Institute, Barcelona 2008
42. Latest results on Gene Environment Interactions in Parkinson's disease. INSERM, Paris 2008
43. Re-assessing Gene Environment Interactions in Parkinson's disease. MDS conference symposium, Chicago 2008
44. Methodological Issues in studying risk factor for Parkinson's disease in populations. MDS conference symposium, Chicago 2008.
45. Environmental and occupational health studies in California. University of Dublin 2008
46. Air pollution, pregnancy and child health; Healthy Development and Ageing Workshop. British Foreign & Commonwealth Office, LA 2009
47. Air pollution, pregnancy and child health; Physician's for Social Responsibility Environmental training 2009
48. Air pollution and adverse pregnancy outcomes in LA; Annenberg School of Journalism 2009
49. Parkinson's disease and pesticides. George Washington University Environmental Health Program 2009
50. LUR model for traffic related exposures and adverse birth outcomes in LA. Helmholtz Center Munich 2010
51. Parkinson's disease and gene–pesticide interactions. Symposium on Predictive Health, Human Health: Molecules to Mankind Emory University Atlanta Dec 2010
52. Air Pollution and Adverse Birth Outcomes, invited speaker at HEI annual conference Boston 2011
53. Parkinson's disease in Denmark; the PASIDA study; University of Odense Denmark, May 2011
54. Gene-environment interactions in Parkinson's disease, invited symposium speaker at the International Society for Environmental Epidemiology (ISEE), Barcelona 2011
55. Air Pollution and the Brain; invited plenary speaker at the annual conference of the International Society for Environmental Epidemiology (ISEE), South Carolina 2012

56. Air Pollution and Autism; invited speaker at the University of Aarhus, Denmark 2012
57. Air Pollution, Children and Women's Health in LA; invited speaker at the SCAMQD conference for stakeholders, LA 2013
58. How to be an Epidemiologist, invited speaker at SER, Boston 2013
59. Pesticides and Neurodegeneration; invited speaker at the Conference on safety of fumigated container shipping in Berlin, Germany 2014
60. History of Environmental and Occupational Epidemiology, invited speaker at SER, Seattle 2014
61. History of Air Pollution. Adverse Birth Outcomes and Children's Health in California; Invited Plenary Speaker for the ISEE Young Researcher Conference. Barcelona 2014
62. Environmental Causes of Adverse Neurodevelopment; Invited Speaker at the B-Debate Barcelona (Environment and Child Brain Development: the Challenges in the Global Context) Conference, Barcelona 2014
63. Autism Epidemiology; invited speaker at the annual CART meeting UCLA 2014
64. Epidemiology of Parkinson's disease. invited speaker at annual GEO-PD meeting Vancouver CA. 2014
65. Parkinson's Disease Epidemiology: a Gene-Environment Perspective, invited speaker at the Neurogenetics Institute of Luebeck/Germany, 2015

PUBLICATIONS

PEER REVEIWED JOURNAL ARTICLES (*indicates mentored students/fellows)

1. **Ritz B**. Humeral Epicondylitis Among Gas- And Waterworks Employees. Scandinavian Journal of Work, Environment and Health, 1995 Dec, 21(6). 478-86.
2. **Ritz B**, Heinrich J, Wjst M, Wichmann E, Krause C. Effect Of Cadmium Body Burden On Immune Response Of School Children. Archives of Environmental Health 1998,Jul-Aug; Vol 53: 272-280
3. **Ritz B**, Morgenstern H, Froines J, Young B. Effects Of Exposure To External Ionizing Radiation On Cancer Mortality In Nuclear Workers Monitored For Radiation At Rocketdyne/Atomics International. AJIM 1999, Jan; Vol 35: 21-31.
4. **Ritz B**, Yu F. The Effect Of Ambient Carbon Monoxide On Low Birth Weight Among Children Born In Southern California Between 1989 and 1993. Environmental Health Perspectives 1999 Jan, 107(1):17-25. PMCID: PMC1566307
5. Heinrich J, Hoelscher B, Wjst M, **Ritz B**, Cyrys J, Wichmann HE. Respiratory Diseases And Allergies In Two Polluted Areas In East Germany. Environmental Health Perspectives 1999,Jan; 107(1):53-62. PMCID: PMC1566314
6. **Ritz B**, Morgenstern H, Moncau J. Age At Exposure Modifies The Effects Of Low-Level Ionizing Radiation On Cancer Mortality In An Occupational Cohort. Epidemiology 1999, Mar; 10(2):135-140.
7. **Ritz B**. Radiation Exposure and Cancer Mortality In Uranium Processing Workers. Epidemiology, 1999, Sep; 10:531-538
8. **Ritz B**. Cancer Mortality Among Workers Exposed To Chemicals During Uranium Processing. JOEM 1999, Jul:41(7):556-566.
9. **Ritz B**, Morgenstern H, Froines J., Moncau J. Chemical Exposures Of Rocket Engine Test Stands Personnel And Cancer Mortality In A Cohort Of Aerospace Workers. JOEM, 1999 Oct; 41(10): 903-910.
10. Jacob B, **Ritz B**, Heinrich J, Hoelscher B, Wichmann HE. The Effect Of Low-Level Blood Lead On hematologic parameters In Children. Environmental Research, 2000 Feb, 82 (2): 150-159.
11. **Ritz B**, Yu F. Parkinson's Disease Mortality And Pesticide Exposure In California 1984-1994. International Journal of Epidemiology, 2000 Apr, Vol. 29:323-329.
12. Hoelscher B, Heinrich J, Jacob B, **Ritz B**, Wichmann HE. Gas Cooking, Respiratory Health And White Blood Cell Counts In Children. Int. J. Hygiene and Environ Health, 2000 Mar; 203 (1): 29-37.
13. **Ritz B**, Morgenstern H, Crawford-Brown D,Young B.The Effects Of Internal Radiation Exposure On Cancer Mortality In Nuclear Workers At Rocketdyne/Atomics International. Environ Health Perspect, 2000 Aug; 108(8):743-751. PMCID: PMC1638302
14. **Ritz B**, Yu F, Chapa G, Fruin S. Effect Of Air Pollution On Preterm Birth Among Children Born In Southern California Between 1989 And 1993. Epidemiology, 2000 Sep; 11(5):502-511.
15. Morgenstern H, **Ritz B**. Effects of Radiation And Chemical Exposures On Cancer Mortality Among Rocketdyne Workers: A Review of Three Cohort Studies. Occup. Med. 2001 Apr-Jun;16(2): 219-237.
16. **Ritz B**, Yu F, Chapa G, Fruin S, Shaw G, Harris J. Ambient Air Pollution And Risk of Birth Defects in Southern California. Am J Epidemiol 2002 Jan 1;155:17–25.

17. **Ritz B**, Hoelscher B, Frye C, Meyer I, Heinrich J. Allergic sensitization owing to 'second-hand' cat exposure in schools. Allergy 2002 Apr;57(4):357-61
18. Jacob B, **Ritz B,** Gehring U, Koch A, Bischof W ,Wichmann HE, Heinrich J for the INGA-Study group. Indoor Exposure To Molds And Allergic Sensitization. Environ Health Perspect. 2002 Jul;110(7):647-53. PMCID: PMC1240910
19. Clary T, **Ritz B**. Pancreatic Cancer Mortality And Organochlorine Pesticide Exposure In California, 1989-1996. Am J Ind Med. 2003 Mar;43(3):306-13.
20. Wilhelm M, **Ritz B.** Residential Proximity To Traffic And Adverse Birth Outcomes In Los Angeles County, California, 1994-1996. Environ Health Perspect. 2003 Feb; 111(2):207-16. PMCID: PMC1241352
21. Rull R, **Ritz B**. Historical Pesticide Exposure In California Using Pesticide Use Reports And Land-Use Surveys: An Assessment Of Misclassification Error And Bias. Environ Health Perspect. 2003 Oct; 111(13):1582-9. PMCID: PMC1241678.
22. Hashibe M, **Ritz B**, Le AD, Li G, Sankaranarayanan R, Zhang ZF. Radiotherapy For Oral Cancer As A Risk Factor For Second Primary Cancers. Cancer Letters 2005 Apr 8; 220(2):185–195.
23. **Ritz,B**, Tager I, Balmes J. Can Lessons From Public Health Disease Surveillance Be Applied To Environmental Public Health Tracking? Environ Health Perspect. 2005 Mar; 113(3):243-9. PMCID: PMC1253746
24. Kang G, Bronstein JM, Masterman DL, Redelings M, Crum JA, **Ritz B**. Clinical Characteristics In Early Parkinson's Disease In A Central Californian Population-Based Study. Mov Disord. 2005 Sep; 20(9):1133-42. PMCID: PMC3643967
25. Ponce NA, Hoggatt KJ, Wilhelm M, **Ritz B**. Preterm Birth: The Interaction Of Traffic-Related Air Pollution With Economic Hardship In Los Angeles Neighborhoods. Am J Epidemiol. 2005 Jul 15;162(2):140-8.
PMCID: PMC3636775
26. Wilhelm M, **Ritz, B**. Local Variations In CO And Particulate Air Pollution And Adverse Birth Outcomes In Los Angeles County, California, USA. Environ Health Perspect; 2005 Sep;113(9):1212-21. PMCID: PMC1280404
27. Rull RP, **Ritz B**, Shaw GM. Validation Of Self-Reported Proximity To Agricultural Crops In A Case-Control Study Of Neural Tube Defects. Journal of Exposure Analysis and Environmental Epidemiology; J Expo Sci Environ Epidemiol. 2006 Mar;16(2):147-55.
28. Zhao Y, Krishnadasan A, Kennedy N, Morgenstern H, **Ritz B**. Estimated effects of solvents and mineral oils on cancer incidence and mortality in a cohort of aerospace workers. Am J Ind Med. 2005 Oct;48(4):249-58.
29. Lewis C, Suffet I, **Ritz B**. Estimated Effects Of Disinfection By-Products On Birth Weight In A Population Served By A Single Water Utility. Am J Epidemiol. 2006 Jan 1;163(1):38-47.
30. Karr C, Lumley T, Shepherd K, Davis R, Larson T, **Ritz B**, Kaufman J. A Case Crossover Study Of Wintertime Ambient Air Pollution And Infant Bronchiolitis. Environ Health Perspect. 2006 Feb;114(2):277-81. PMCID: PMC1367844
31. **Ritz B,** Zhao Y, Krishnadasan A, Kennedy N, Morgenstern H. Estimated Effects of Hydrazine Exposure on Cancer Incidence and Mortality in Aerospace Workers. Epidemiology. 2006 Mar;17(2):154-61.
32. Rull RP, **Ritz B**, Shaw GM. Neural Tube Defects And Maternal Residential Proximity To Agricultural Pesticide Applications. Am J Epidemiol. 2006 Apr 15;163(8):743-53.
33. Glatt CE, Wahner AD, White DJ, Ruiz-Linares A, **Ritz B**. Gain Of Function Haplotypes In The Vesicular Monoamine Transporter Promoter Are Protective For Parkinson Disease In Women. Hum Mol Genet. 2006 Jan 15;15(2):299-305. PMCID:PMC3643966
34. Marusek JC, Cockburn MG, Mills PK, **Ritz B**. Control Selection And Pesticide Exposure Assessment Via GIS In Prostate Cancer Studies. Am J Prev Med. 2006 Feb;30(2 Suppl):S109-16.
35. **Ritz B**, Wilhelm M, Zhao Y. Air pollution and infant death in southern California, 1989-2000. Pediatrics 2006 Aug;118(2);493-502. PMCID: PMC3636770
36. Schernhammer E, Chen H, **Ritz B**. Circulating Melatonin Levels: Possible Link Between Parkinson's Disease And Cancer Risk? 2006 May;17(4):577-82.
37. Karr C, Lumley T, Schreuder A, Davis R, Larson T, **Ritz B**, Kaufman J. Effect of Subchronic and Chronic Exposure to Ambient Air Pollutants on Infant Bronchiolitis. Am J Epidemiol. 2007 Mar 1;165(5):553-60.
38. **Ritz B**, Ascherio A, Checkoway H, Marder KS, Nelson LM, Rocca WA, Ross GW, Strickland D, Van Den Eeden SK, Gorell J. Pooled Analysis Of Tobacco Use And Risk Of Parkinson Disease. Arch Neurol. 2007 Jul;64(7):990-7.

39. **Ritz B,** Costello S. Geographic model and biomarker-derived measures of pesticide exposure and Parkinson's disease. Ann N Y Acad Sci. 2006 Sept;1076:378-87. PMCID: PMC3656600
40. Elbaz A, Nelson LM, Payami H, Ioannidis JPA, Fiske BK, Annesi G, Belin AC, Factor SA, Ferrarese C, Hadjigeorgiou GM, Higgins DS, Kawakami H, Krüger R, Marder KS, Mayeux RP, Mellick GD, Nutt JG, **Ritz B**, Samii A, Tanner CM, Van Broeckhoven C, Van Den Eeden SK, Wirdefeldt K, Zabetian CP, Dehem M, Montimurro JS, Myers RM, Southwick A, Trikalinos TA. Lack Of Replication Of Thirteen Single-Nucleotide Polymorphisms Implicated In Parkinson's Disease: A Large-Scale International Study. Lancet Neurol. 2006 Nov; 5(11):917-23. PMCID: PMC3636768
41. Rempel DM, Wang PC, Janowitz I, Harrison RJ, Yu F, **Ritz B**. A Randomized Controlled Trial Evaluating the Effects of New Task Chairs on Shoulder and Neck Pain among Sewing Machine Operators: The Los Angeles Garment Study. 2007 Apr 20. Spine; 32(9): 931–938
42. Wahner AD, Sinsheimer JS, Bronstein JF, **Ritz B**. Inflammatory Cytokine Gene Polymorphisms And Increased Risk of Parkinson disease. Arch Neurol. 2007 Jun;64(6):836-40
43. Wahner AD, Glatt CE, Bronstein JM, **Ritz B**. Glutathione S-Transferase Mu, Omega, Pi, And Theta Class Variants And Smoking In Parkinson's Disease. Neurosci Lett. 2007 Feb 21;413(3):274-8. PMCID: PMC1864949
44. Lewis C, Suffet HI, Hoggatt KJ, **Ritz B**. Estimated Effects of Disinfection By-products On Preterm Birth in a Population Served by a Single Water Utility. Environ Health Perspect. 2007 Feb;115(2):290-5. PMCID: PMC1831522
45. Krishnadasan A, Kennedy N, Zhao Y, Morgenstern H, **Ritz B**. Nested Case-Control Study of Occupational Chemical Exposures and Prostate Cancer in Aerospace and Radiation Workers. Am J Ind Med. 2007 May; 50(5):383-90.
46. Meng YY, Wilhelm M, Rull R, English P, **Ritz B**. Traffic And Outdoor Air Pollution Levels Near Residences And Poorly-Controlled Asthma In Adults. Ann Asthma, Allergy, Immunol; 2007 May, 98(5), 455-63.
47. Wang PC, Rempel DM, Harrison RJ, Chan J, **Ritz B**. Work-Organizational And Personal Factors Associated With Upper Body Musculoskeletal Disorders Among Sewing Machine Operators. Occup Environ Med. 2007 Dec;64(12):806-13. Epub 2007 May 23. PMCID: PMC2095384
48. **Ritz B**, Wilhelm M, Hoggatt KJ, Ghosh JKC. Ambient Air Pollution And Preterm Birth In the Environment And Pregnancy Outcomes Study at the University of California, Los Angeles. Am J Epidemiol. 2007 Nov 1;166(9):1045-52.
49. Wahner AD, Bronstein JM, Bordelon YM, **Ritz B**. Nonsteroidal Anti-Inflammatory Drugs May Protect Against Parkinson Disease. Neurology. 2007 Nov 6;69(19):1836-42.
50. Wahner AD, Bronstein JM, Bordelon YM, **Ritz B**. Statin Use and the Risk of Parkinson's Disease. Neurology. 2008 Apr 15;70(16 Pt 2):1418-22. PMCID: PMC3690297
51. Krishnadasan A, Kennedy N, Zhao Y, Morgenstern H, **Ritz B**. Nested Case-control Study of Occupational Physical Activity and Prostate Cancer Among Workers Using a Job Exposure Matrix. Cancer Causes Control. 2008 Feb;19(1):107-14.
52. **Ritz B**, Wilhelm M. Ambient Air Pollution And Adverse Birth Outcomes: Methodologic Issues In An Emerging Field. Basic Clin Pharmacol Toxicol. 2008 Feb;102(2):182-90. PMCID: PMC3656653
53. Meng YY, Wilhelm M, Rull RP, English P, Nathan S, **Ritz B**. Are frequent asthma symptoms among low-income individuals related to heavy traffic near homes, vulnerabilities, or both? Ann Epidemiol. 2008 May;18(5):343-50
54. Wilhelm M, Qian L, **Ritz B**. Outdoor air pollution, family and neighborhood environment, and asthma in LA FANS children. Health Place. 2009 Mar;15(1):25-36. PMCID: PMC2658528
55. Heck JE, **Ritz B**, Hung R, Hashibe M, Boffetta P. The Epidemiology of Neuroblastoma: A Review. Paediatr Perinat Epidemiol. 2009 Mar;23(2):125-43.
56. Wilhelm M, Meng YY, Rull RP, English P, Balmes J, **Ritz B.** Environmental public health tracking of childhood asthma using California health interview survey, traffic, and outdoor air pollution data. Environ Health Perspect 2008 Sep;116(9):1254-60. PMCID: PMC2535631
57. Wang PC, **Ritz, B**, Janowitz I, Harrison RJ, Yu F, Chan J, Rempel DM. A Randomized Controlled Trial of Chair Interventions on Back and Hip Pain Among Sewing Machine Operators: The Los Angeles Garment Study. J Occup Environ Med. 2008 Mar;50:255–262.
58. Wang PC, Rempel DM, Hurwitz EL, Harrison RJ, Janowitz I, **Ritz B**. Self-Reported Pain And Physical Signs For Musculoskeletal Disorders In The Upper Body Region Among Los Angeles Garment Workers. Work. 2009;34(1):79-87.
59. Rhodes SL, **Ritz, B**. Genetics of Iron Regulation and the Possible Role of Iron in Parkinson's Disease. In Neurobiol Dis. 2008 Nov;32(2):183-95. PMCID: PMC3643980

60. Goldberg DW, Wilson JP, Knoblock CA, **Ritz B**, Cockburn MG. An effective and efficient approach for manually improving geocoded data. International Journal of Health Geographics 2008 Nov 26, 7:60. PMCID: PMC2612650.
61. **Ritz B**, Rull R. Assessment of Environmental Exposures from Agricultural Pesticides in Childhood Leukemia Studies: Challenges and Opportunities. Radiat Prot Dosimetry. 2008;132(2):148-55.
62. Rugbjerg K, **Ritz B**, Korbo L, Martinussen N, Olsen JH. Risk for Parkinson's disease after hospital contact for head injury: a population-based case–control study. BMJ. 2008 Dec 15;337. PMCID: PMC2603581
63. Costello S*, Cockburn M., Bronstein J, Zhang X, **Ritz B.** Parkinson's disease and residential exposure to Maneb and Paraquat from agricultural applications in the central valley of California. Am J Epidemiol. 2009 Apr 15;169(8):919-26. PMCID: PMC2727231.
64. Hoggatt KJ, Greenland S, **Ritz B**. Adjustment for response bias via two-phase analysis: an application. Epidemiology. 2009 Nov;20(6):872-9. PMCID: PMC3656648
65. Wang PC, Harrison RJ, Yu F, Rempel DM, **Ritz B**. Follow-up Of Neck And Shoulder Pain Among Sewing Machine Operators: the Los Angeles Garment Study. Am J Ind Med. 2010 Apr;53(4):352-60.
66. **Ritz B**, Manthripragada A, Costello S, Lincoln SJ, , Farrer M, Cockburn M, Bronstein J. Dopamine transporter genetic variants and pesticides in Parkinson's disease. Environ Health Perspect 2009 Jun;117(6):964-9 PMCID: PMC2702414.
67. Meng YY, Rull RP, Wilhelm M ,Lombardi C,Balmes J, **Ritz B**. Outdoor air pollution and uncontrolled asthma in the San Joaquin Valley, California. J Epidemiol Community Health. 2010 Feb;64(2):142-7.
68. Manthripragada A, Cockburn M, Costello S, Bronstein J, **Ritz B**. Paraoxonase 1, agricultural organophosphate exposure, and Parkinson disease. Epidemiology. 2010 Jan;21(1):87-94. PMCID: PMC3117899
69. Su JS, Jerrett M, Beckerman B, Wilhelm M, Ghosh JK, **Ritz B**. Predicting traffic-related air pollution in Los Angeles using a distance decay regression selection strategy. Environ Res. 2009 Aug; 109(6):657-70. PMCID: PMC 3656661
70. Wu J, Ren C , Delfino R, Chung J, Wilhelm M, **Ritz B**. Association between local traffic-generated air pollution and preeclampsia and preterm delivery in the South Coast Air Basin of California. Environ Health Perspect. 2009 Nov;117(11):1773-9. PMCID: PMC2801174.
71. Gatto N, Cockburn M, Bronstein J, Manthripragada A, **Ritz B**. Well Water Consumption and Parkinson's Disease in Rural California. Environ Health Perspect 2009 Dec; 117: 1912–1918 PMCID: PMC2799466.
72. Rugbjerg K. Friis S. **Ritz B**. Schernhammer ES. Korbo L. Olsen JH. Autoimmune disease and risk for Parkinson's disease: a population based case–control study. Neurology. 2009 Nov 3;73(18):1462-8. PMCID: PMC2779008
73. Rod-Nielsen N, Schernhammer E, Hansen J, **Ritz B**. Major life events and risk of Parkinson's disease. Mov Disord. 2010 Aug 15;25(11):1639-45. PMCID: PMC2928859
74. Plaitakis A, Latsoudis H, Kanavouras K, **Ritz B**, Bronstein JM, Skoula I, Mastorodemos V, Papapetropoulos S, Borompokas N, Zaganas I, Xiromerisiou G, Hadjigeorgiou GM, Spanaki C._Gain-of-function variant in GLUD2 glutamate dehydrogenase modifies Parkinson's disease onset. Eur J Hum Genet. 2010 Mar;18(3):336-41. PMCID: PMC2987208
75. **Ritz B,** Rhodes SL, Qian L, Schernhammer E, Olsen J, Friis, S. L-type Calcium Channel blockers and Parkinson disease in Denmark. Ann Neurol. 2010 May;67(5):600-6. PMCID: PMC2917467
76. Gosh JKC, Wilhelm M, Dunkel-Shetter C, Lombardi C*, **Ritz B**. Paternal support and preterm birth, and the moderation of effects of chronic stress: a study in Los Angeles county mothers. Arch Womens Ment Health. 2010 Aug;13(4):327-38.PMCID: PMC2896639
77. Costello S, Bordelon Y, Bronstein J, **Ritz B.** Familial Associations of Alzheimer Disease and Essential Tremor with Parkinson Disease. Eur J Neurol. 2010 Jun 1;17(6):871-8. PMCID: PMC2895681
78. Wu J, Hou H, **Ritz B**, Chen Y Exposure to Polycyclic Aromatic Hydrocarbons and Missed Abortion in Early Pregnancy in a Chinese Population. Science of the Total Environment 2010 May 1;408(11):2312-8.
79. **Ritz B,** Mandripragada A, Qian L, Schernhammer E, Olsen J, Wermuth L, Friis S. Statin use and Parkinson's Disease in Denmark. Mov Disord. 2010 Jul 15;25(9):1210-6. PMCID: PMC2910157
80. Rugbjerg K, Friis S, Jorgensen T, **Ritz B**, Korbo L, Olsen JH. Risk of Parkinson disease among patients with osteoarthritis: a Danish cohort study. Mov Disord. 2010 Oct 30;25(14):2355-60. PMCID:PMC2992436

81. Gatto NM, Rhodes SL, Manthripragada AD, Bronstein J, Cockburn M, Farrer M, **Ritz B**. a-Synuclein Gene May Interact with Environmental Factors in Increasing Risk of Parkinson's Disease. Neuroepidemiology. 2010;35(3):191-5. PMCID: PMC2945263
82. Wu X, Bennett DH, **Ritz B**, Frost J, Cassady D, Lee K, Hertz-Picciotto I. Residential Insecticide Usage in Northern California Homes with Young Children. J Expo Sci Environ Epidemiol. 2011 Jul-Aug;21(4):427-36.
83. Jacob EL, Gatto NM, Thompson A, Bordelon Y, **Ritz B.** Occurrence of Depression and Anxiety prior to Parkinson's Disease. Parkinsonism Relat Disord. 2010 Nov;16(9):576-81. PMCID: PMC2963655
84. Wu X, Bennett DH, **Ritz B**, Cassady DL, Lee K, Hertz-Picciotto I. Usage Pattern of Personal Care Products in California Households. Food Chem Toxicol. 2010 Nov;48(11):3109-19.
85. Rhodes SL, Sinsheimer JS, Bordelon Y, Bronstein JM, **Ritz B**. Replication of GWAS associations for GAK and MAPT in Parkinson's disease. Annals of Human Genetics. Ann Hum Genet. 2011 Mar;75(2):195-200.
PMCID: PMC3074465
86. Kenborg L, Funch C, **Ritz B**, Schernhammer E, Hansen J, Gatto N, Olsen JH. Outdoor work and risk for Parkinson disease: a population-based case–control study. Occup Environ Med. 2011 Apr;68(4):273-8. PMCID: PMC3667158
87. Hertz-Picciotto I, Cassady D, Lee K, Bennett DH, **Ritz B**, Vogt R. Study of Use of Products and Exposure-Related Behaviors (SUPERB): study design, methods, and demographic characteristics of cohorts. Environ Health. 2010 Aug 29;9:54. PMCID: PMC2940867
88. Sapkota A, Chelikowski A, Nachman K, Cohen A, **Ritz B**. Exposure to Particulate Matter and Adverse Birth Outcomes: A Comprehensive Review and Meta Analysis. Air Quality, Atmosphere and Health; 2012, Vol 5, Issue 4; 369-381
89. Cockburn M, Mills P, Zhang X, Zadnick j, Goldberg D, **Ritz B**. Prostate cancer and ambient pesticide exposure in agriculturally intensive areas in California. Am J Epidemiol. 2011 Jun 1;173(11):1280-8 PMCID: PMC3121318
90. Popat R, Van Den Eeden SK, Tanner CM, Kamel F, Umbach D, Marder K, Mayeux R, **Ritz B**, Ross GW, Petrovitch H, Topol B, McGuire V, Costello S, Manthripragada AD, Southwick A, Myers RM, Nelson LM. Coffee, ADORA2A, and CYP1A2: the caffeine connection in Parkinson's disease. Eur J Neurol. 2011 May;18(5):756-65. PMCID: PMC3556904
91. Lewis C, Hoggatt KJ, **Ritz B**. The Impact of Different Causal Models on Estimated Effects of Disinfection By-Products on Preterm Birth. Environ Res. 2011 Apr;111(3):371-6.
92. Lee PC, Talbott EO, Roberts JM, Catov JM, Sharma RK, **Ritz B.** Particulate Air Pollution Exposure and C-Reactive Protein during Early Pregnancy. Epidemiology. 2011 Jul;22(4):524-31
93. Schernhammer E, Hansen J, Rugbjerg K, Wermuth L, **Ritz B**. Diabetes and the risk of developing Parkinson's disease in Denmark. Diabetes care. 2011 May;34(5):1102-8. PMCID:PMC3114482
94. Wang A, Costello S, Cockburn M, Zhang X, Bronstein J, **Ritz B**. Parkinson's Disease risk from ambient exposure to pesticides. Eur J Epidemiol. 2011 Jul;26(7):547-55. Epub 2011 Apr 20. PMCID: PMC3643971
95. Manthripragada A, Schernhammer ES, Qiu J, Friis S, Wermuth L, Olsen J, **Ritz B**. Non-steroidal anti-inflammatory drug use and the risk of Parkinson's Disease. Neuroepidemiology. 2011;36(3):155-61. PMCID:PMC3095838
96. Wu X, Bennett DH, Lee K, Cassady DL, **Ritz B**, Hertz-Picciotto I. Feasibility of Using Web Surveys to Collect Time-Activity Data. Journal Of Exposure Science And Environmental Epidemiology. J Expo Sci Environ Epidemiol. 2012 Mar-Apr;22(2):116-25.
97. Gatto NM, Bordelon Y, Gatz M, **Ritz B**. Personality Characteristics and Motor Skills Attributed to Occupations in Parkinson Disease. Cognitive and Behavioral Neurology. Cogn Behav Neurol. 2011 Mar; 24(1):18-25.PMCID: PMC3656654
98. Wu J, Wilhelm M, Chung J, **Ritz B**. Comparing exposure assessment methods for traffic-related air pollution in an adverse pregnancy outcome study. Environ Res. 2011 Jul;111(5):685-92. PMCID: PMC3114297
99. McGuire V, Van Den Eeden SK, Tanner CM, Kamel F, Umbach D, Marder K, Mayeux R, **Ritz B**, Ross GW, Petrovitch H, Topol B, Popat RA, Costello S, Manthripragada AD, Southwick A, Myers RM, Nelson LM. Association of DRD2 and DRD3 Polymorphisms with Parkinson's Disease in a Multiethnic Consortium. J Neurol Sci. 2011 Aug 15;307(1-2):22-9. PMCID: PMC3155471
100. Wilhelm M, Ghosh JK, Su J, Cockburn M, Jerrett M, **Ritz B**. Traffic-related air toxics and preterm birth: a population-based case-control study in Los Angeles County, California. Environmental Health. Environ Health. 2011 Oct 7;10:89. PMCID:PMC3204282

101. Hamza TH, Chen H, Hill-Burns EM, Rhodes SL, Montimurro J, Kay DM, Tenesa A, Kusel VI, Sheehan P, Eaaswarkhanth M, Yearout D, Samii A, Roberts JW, Agarwal P, Bordelon Y, Park Y, Wang L, Gao J, Vance JM, Kendler KS, Bacanu SA, Scott WK, Ritz B, Nutt J, Factor SA, Zabetian CP, Payami HGenome-Wide Gene-Environment Study Identifies Glutamate Receptor Gene GRIN2A as a Parkinson's Disease Modifier Gene via Interaction with Coffee. PLoS Genet. 2011 Aug;7(8):e1002237. PMCID: PMC3158052
102. Armes MN, Liew Z, Wang A, Wu X, Bennett DH, Hertz-Picciotto I, **Ritz B.** Residential Pesticide Usage in Older Adults Residing in Central California. International Journal of Environmental Research and Public Health. Int J Environ Res Public Health. 2011 Aug;8(8):3114-33. PMCID:PMC3166730.
103. Wilhelm M, Gosh J, Su J, Cockburn M, Jerret M, **Ritz B**. Traffic-Related Air Toxics and Term Low Birth Weight in Los Angeles County, California. Environ Health Perspect. 2012 Jan;120(1):132-8. PMCID:PMC3261935
104. Wu X, Bennett DH, Lee K, Cassady DL, **Ritz B**, Hertz-Picciotto I. Longitudinal variability of time-location/activity patterns of population at different ages: a longitudinal study in California. Environmental Health 2011 Sep 20;10:80 PMCID: PMC3184256
105. Hoggatt KJ, Sharp M, Wilhelm M, Solorio R, **Ritz B**. The Latina Epidemiologic Paradox revisited: the role of birthplace and acculturation in predicting infant low birth weight for Latinas in Los Angeles, CA. Journal of Immigrant and Minority Health (JOIH). J Immigr Minor Health. 2012 Oct;14(5):875-84. PMCID: PMC3643973
106. Gosh JK, Wilhelm M, Su J, Goldberg D, Cockburn M, Jerrett J, **Ritz B**. Assessing the influence of traffic-related air pollution on risk of term low birth weight on the basis of land-use-based regression models and measures of air toxics. Am J Epidemiol. 2012 Jun 15;175(12):1262-74. PMCID: PMC3372317
107. Nielsen HH, Qiu J, Friis S, Wermuth L, **Ritz B**. Treatment of Helicobacter Pylori infection and risk of Parkinson's disease in Denmark. Eur J Neurol. 2012 Jun;19(6):864-9. PMCID: PMC3330170
108. Wermuth L, Lassen CF, Himmerslev L, Olsen J, **Ritz B.** Validation of hospital register-based diagnosis of Parkinson's disease. Dan Med J. 2012 Mar;59(3):A4391. PMCID: PMC3643969
109. Rugbjerg K, Friis S, Lassen CF, **Ritz B**, Olsen J. Malignant melanoma, breast cancer and other cancers in patients with Parkinson's disease. 2012 Oct 15;131(8):1904-11. PMCID: PMC3636769
110. Heck JE, Lombardi CA, Cockburn M, Meyers TJ, Wilhelm M, **Ritz B**. Epidemiology of rhabdoid tumors of early childhood. Pediatr Blood Cancer. 2013 Jan;60(1):77-81. PMCID: PMC3399923
111. Li L, Wu J, Wilhelm M, **Ritz B**. Use of Generalized Additive Models and Cokriging of Spatial Residuals to Improve Land-Use Regression Estimates of Nitrogen Oxides in Southern California. Atmos Environ 2012 Aug 1;55:220-228. PMCID: PMC3579670
112. Lee PC, Roberts JM, Catov JM, Talbott EO, **Ritz B**. First trimester exposure to ambient air pollution, pregnancy complications and adverse birth outcomes in Allegheny County, PA. Matern Child Health J. 2013 Apr;17(3):545-55. PMCID: PMC3636771
113. Bennett DH, Wu X, Teague C, Lee K, Cassady DL, **Ritz B**, Hertz-Picciotto I. Passive Sampling Methods to Determine Household and Personal Care Product Use. J Expo Sci Environ Epidemiol. 2012 Mar-Apr;22(2):148-60.
114. **Ritz B.** Rhodes SL, Bordelon Y, Bronstein J. α-Synuclein genetic variants predict faster motor symptom progression in idiopathic Parkinson disease. PLoS One. 2012;7(5):e36199. PMCID: PMC3352914
115. Lee PC, Talbott EO; Roberts JM; Catov JM Bilonick RA; Stone RA; Sharma RK; **Ritz B**. Ambient Air Pollution Exposure and Blood Pressure Changes during Pregnancy. Environ Res. 2012 Aug;117:46-53. PMCID: PMC3656658
116. Gosh JK, Wilhelm M, **Ritz B**. Effects of residential indoor air quality and household ventilation on preterm birth and term low birth weight in Los Angeles County, California. Am J Public Health. 2013 Apr;103(4):686-94. PMCID: PMC3643965
117. Heck JE, Lombardi CA, Meyers TJ, Cockburn M, Wilhelm M, **Ritz B**. Perinatal characteristics and retinoblastoma. 2012 Sep;23(9):1567-75. PMCID: PMC 3429932
118. Lee PC, Bordelon Y, Bronstein J, **Ritz B**. Traumatic Brain Injury, Paraquat Exposure, and their Relationship to Parkinson Disease. Neurology. 2012 Nov 13;79(20):2061-6. PMCID: PMC3511918
119. Mata IF, Checkoway H, Hutter CM, Samii A, Roberts JW, Kim HM, Agarwal P, Alvarez V, Ribacoba R, Pastor P, Lorenzo-Betancor O, Infante J, Sierra M, Gómez-Garre P, Mir P, **Ritz B**, Rhodes SL, Colcher A, Van Deerlin V, Chung KA, Quinn JF, Yearout D, Martinez E, Farin FM, Wan JY, Edwards KL, Zabetian CP.Common Variation in the LRRK2 Gene is a Risk Factor for Parkinson's Disease. Mov Disord. 2012 Dec;27(14):1822-5. PMCID: PMC3536918

120. Block ML, Elder A, Auten RL, Bilbo SD, Chen H, Chen JC, Cory-Slechta DA, Costa D, Diaz-Sanchez D, Dorman DC, Gold DR, Gray K, Jeng HA, Kaufman JD, Kleinman MT, Kirshner A, Lawler C, Miller DS, Nadadur SS, **Ritz B**, Semmens EO, Tonelli LH, Veronesi B, Wright RO, Wright RJ. The outdoor air pollution and brain health workshop. Neurotoxicology. 2012 Oct;33(5):972-84. PMCID: PMC3726250
121. Rod-Nielsen N, Bordelon Y, Thompson A, Marcotte E, **Ritz B**. Major life events and development of major depression in Parkinson's disease patients. Eur J Neurol. 2013;20(4):663-70. PMCID: PMC3566278
122. Vogt R, Bennett D, Cassady D, Frost J, **Ritz B**, Hertz-Picciotto I. Cancer and non-cancer health effects from food contaminant exposures for children and adults in California: a risk assessment. Environ Health 2012 Nov 9 ;11:83. PMCID: PMC3551655
123. Becerra T, Wilhelm W, Olsen J, Cockburn **M**, **Ritz B**. Ambient Air Pollution and Autism in Los Angeles County, California. Environ Health Perspect. 2013 Mar;121(3):380-6. PMCID: PMC3621187
124. Fitzmaurice AG, Rhodes SL, Lulla A, Murphy NP, Lam HA, O'Donnell KC, Barnhill L, Casida JE, Cockburn M, Sagasti A, Stahl MC, Maidment NT, **Ritz B**, Bronstein JM. Aldehyde dehydrogenase inhibition as a pathogenic mechanism in Parkinson disease. Proc Natl Acad Sci U S A. 2013 Jan 8;110(2):636-41. PMCID: PMC3545765
125. Lim SS, et al. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012 Dec 15;380(9859):2224-60. PMCID: PMC4156511
126. Clark AJ, **Ritz BR**, Prescott E, Rod NH. Psychosocial risk factors, pre-motor symptoms, and first-time hospitalization with Parkinson's Disease: a prospective cohort study. Eur J Neurol 2013 Aug;20(8):1113-20. PMCID: PMC3664243
127. Shrestha A, **Ritz B,** Ognjanovic S. Lombardi CA, Wilhelm M, Heck JE. Early life factors and risk of childhood rhabdomyosarcoma. Front Public Health. 2013 May 31;1:17. PMCID: PMC3854857
128. Li L, Wu J, Ghosh JK, **Ritz B**.Estimating Spatiotemporal Variability of Ambient Air Pollutant Concentrations with A Hierarchical Model. Atmospheric Environment 2013 Jun 1;71:54-63. PMCID: PMC3627373
129. Liew Z, Wang A, Bronstein B, **Ritz B**. Job Exposure Matrix (JEM) derived estimates of life-time occupational pesticide exposure and the risk of Parkinson's Disease. Arch Environ Occup Health. 2014;69(4):241-51. PMCID: PMC3916959
130. Lee PC, Rhodes SL, Sinsheimer JS, Bronstein J, **Ritz B**. Functional Paraoxonase 1 Variants Modify the Risk of Parkinson's Disease due to Organophosphate Exposure. Environ Int. 2013 Jun;56:42-7 PMCID: PMC3690300
131. Schernhammer E, Qiu J, Wermuth L, Funch Lassen C, Friis S, **Ritz B**. Gout and the risk of Parkinson's disease in Denmark. European Journal of Epidemiology. 2013 Apr;28(4):359-60. PMCID:PMC3655156
132. Lombardi C, Heck JE, Cockburn M, **Ritz B**. Solar UV radiation and cancer in young children. Cancer Epidemiol Biomarkers Prev. 2013 Jun;22(6):1118-28 PMCID:PMC369030
133. von Ehrenstein OS, Wilhelm M, **Ritz B.** Maternal Occupation and Term Low Birth Weight in a Predominantly Latina Population in Los Angeles, California. J Occup Environ Med. 2013 Sep;55(9):1046-51.
134. Gosh JK, Heck J, Cockburn M, Su J, Jerrett M, **Ritz B**. Prenatal exposure to traffic-related air pollution and risk of early childhood cancers. Am J Epidemiol. 2013 Oct 15;178(8):1233-9. PMCID:PMC3792733
135. von Ehrenstein OS, Wilhelm **M**, **Ritz B**. Preterm Birth and Prenatal Maternal Occupation: Preterm Birth and Prenatal Maternal Occupation: The Role of Hispanic Ethnicity and Nativity in a Population Based Sample in Los Angeles, California. Am J Public Health. 2014 Feb;104 Suppl 1:S65-72. PMCID: PMC4011103
136. Chen H, Burton EA, Ross GW, Huang X, Savica R, Abbott RD, Ascherio A, Caviness JN, Gao X, Gray KA, Hong JS, Kamel F, Jennings D, Kirshner A, Lawler C, Liu R, Miller GW, Nussbaum R, Peddada S, Rick AC, **Ritz B**, Siderowf AD, Tanner CM, Tröster AI, Zhang J. Research on the pre-motor symptoms of Parkinson's disease Clinical and etiological implications. Environ Health Perspect. 2013 Nov-Dec;121(11-12):1245-52. PMCID: PMC3855519
137. Rhodes SL, Fitzmaurice AG, Cockburn M, Bronstein JM, Sinsheimer JS, **Ritz B**. Pesticides that Inhibit the Ubiquitin-Proteasome System: Effect Measure Modification by Genetic Variation in SKP1 in Parkinson's Disease. Environ Res. 2013 Oct; 126:1-8. PMCID: PMC3832349

138. Narayan S, Liew Z, Paul K, Lee PC, Sinsheimer JS, Bronstein JM, **Ritz B.** Household Organophosphorus Pesticide Use and Parkinson's Disease. Int J Epidemiol. 2013 Oct;42(5):1476-85. PMCID:PMC3807617
139. Murray CJ et al. (125 US Burden of Disease Collaborators). The state of US health, 1990-2010: burden of diseases, injuries, and risk factors. JAMA. 2013 Aug 14;310(6):591-608.
140. Roede JR, Uppal K, Park YH, Lee K, Tran V, Strobel FH, Rhodes SL, **Ritz B,** Jones DP. Serum Metabolomics of Slow vs. Rapid Motor Progression Parkinson's Disease: a Pilot Study. PLoS One. 2013 Oct 22;8(10):e77629. PMCID:PMC3805572
141. Nielsen M, Hansen J, **Ritz B**, Nordahl H, Schernhammer E, Wermuth L, Rod NH. Cause-specific mortality among spouses of Parkinson disease patients. Epidemiology. 2014 Mar;25(2):225-32.
142. Heck JE, Wu J, Lombardi CA, Meyers TJ, Wilhelm M, Cockburn M, **Ritz B.** Childhood cancer and traffic-related air pollution exposure in pregnancy and early life. Environ Health Perspect. 2013 11-12;121(11-12):1385-1391. PMCID: PMC3855517
143. Heck JE, Park AS, Qiu J, Cockburn M, **Ritz B**. An exploratory study of ambient air toxics exposure in pregnancy and the risk of neuroblastoma in offspring. Environ Res. 2013 Nov;127:1-6. PMCID: PMC3960946
144. Rhodes SL, Buchanan D, Ahmed I, Taylor KD, Loriot MA, Sinsheimer JS, Bronstein J, Elbaz A, Mellick G, Rotter JI, **Ritz B**. Pooled Analysis of Iron-related Genes in Parkinson's Disease: Association with Transferrin. Neurobiol Dis. 2014 Feb;62:172-8. PMCID: PMC3968945
145. Wu XM, Bennett DH, **Ritz B**, Tancredi DJ, Hertz-Picciotto I. Temporal variation of residential pesticide use and comparison of two survey platforms: a longitudinal study among households with young children in Northern California. Environ Health. 2013 Aug 20;12(1):65. PMCID: PMC3765515
146. Heck JE, Cockburn M, **Ritz B**. Case-Control Study of Birth Characteristics and the Risk of Hepatoblastoma. Cancer Epidemiol. 2013 Aug;37(4):390-5. PMCID: PMC3679264
147. Heck JE, Park AS, Qiu J, Cockburn M, **Ritz B.** Retinoblastoma and ambient exposure to air toxics in the perinatal period. J Expo Sci Environ Epidemiol. 2013 Nov 27 PMCID: PMC4059784
148. Fitzmaurice AG, Rhodes SL, Cockburn M, **Ritz B**, Bronstein JM. Aldehyde dehydrogenase variation enhances effect of pesticides associated with Parkinson disease. Neurology. 2014 Feb 4;82(5):419-26. PMCID: PMC3917685
149. Liew Z, **Ritz B**, Rebordosa C, Lee PC, Olsen J. Acetaminophen use during pregnancy, behavioral problems and Hyperkinetic disorders. JAMA Pediatr. 2014 Apr;168(4):313-20.
150. Marcotte E, **Ritz B.** Cockburn M, Clarke CA , Heck JE. Birth Characteristics and Risk of Lymphoma in Young Children. Cancer Epidemiology PMCID: PMC4100477
151. Wang A, Cockburn M, Ly TT, Bronstein J, **Ritz B.** The Association Between Ambient Exposure to Organophosphates and Parkinson's Disease Risk. Occup Environ Med. 2014 Apr;71(4):275-81. PMCID:PMC4351788
152. Heck JE, Park AS, Qiu J, Cockburn M, **Ritz B**. Risk of leukemia in relation to exposure to ambient air toxics in pregnancy and early childhood. Int J Hyg Environ Health. 2014 Jul;217(6):662-8. PMCID: PMC4071125
153. Shresta A, **Ritz B**, Wilhelm M, Qiu J, Cockburn M, Heck JE. Prenatal exposure to air toxics and risk of Wilms' tumor in 0-5 year old children. J Occup Environ Med. 2014 Jun;56(6):573-8. PMCID: PMC4204106
154. **Ritz B**, Qiu J, Lee PC, Lurmann F, Penfold B, Weiss RE, McConnell R, Arora C, Hobel C, Wilhelm M. Prenatal Air Pollution Exposure and Ultrasound Measures of Fetal Growth in Los Angeles, California. Environ Research. 2014 Apr;130:7-13. PMCID: PMC4016959
155. Greene N, Lassen C, Rugbjerg K, **Ritz B**. Reproductive factors and Parkinson's disease risk in Danish women. Eur J Neurol. 2014 Sep;21(9):1168-77, e68.
156. Liew Z, **Ritz B**, Bonefeld EC, Henriksen TB, Nohr EA, Bech BH, Fei C, Bossi R, von Ehrenstein O, Streja E, Uldall P, Olsen J. Prenatal Exposure to Perfluoroalkyl Substances and Risk of Congenital Cerebral Palsy in Children. Am J Epidemiol. 2014 Sep 15;180(6):574-81.
157. Becerra T, von Ehrenstein O, Heck JE, Olsen J, Arah O, Jeste S, Rodriguez M, **Ritz B**. Autism and Maternal Race/Ethnicity and Nativity in Los Angeles. Pediatrics. 2014 Jul;134(1):e63-71.PMCID: PMC4067639
158. Marcotte E, Heck J, Cockburn M, Yu F, **Ritz B**. Exposure to Infections and Risk of Leukemia in Young Children. Cancer Epidemiol Biomarkers Prev. 2014 Jul;23(7):1195-203. PMCID: PMC4100471
159. Burdick DJ, Watson GS, Siderowf A, Trojanowski JQ, Weintraub D, **Ritz B**, Rhodes S, Rausch HR, Factor SA, Wood-Siverio C, Quinn JF, Chung K, Cholerton B, Srivatsal S, Edwards KL, Montine TJ, Zabetian CP, Leverenz JB. People with Parkinson's disease and normal MMSE score have a broad range of cognitive performance. Mov Disord. 2014 Sep;29(10):1258-64. PMCID: PMC4162839

160. Mata IF, Leverenz JB, Weintraub D, Trojanowski JQ, Hurtig HI, Van Deerlin V, **Ritz B**, Rausch R, Rhodes SL, Factor SA, Wood-Siverio C, Quinn JF, Chung KA, Peterson AL, Espay AJ, Revilla FJ, Devoto J, Hu SC, Cholerton BA, Montine TJ, Edwards KL, Zabetian CP. APOE, MAPT, and SNCA Genes and Cognitive Performance in Parkinson Disease. JAMA Neurology. 2014 Nov;71(11):1405-12. PMCID: PMC4227942
161. Krøigård T, Christensen J, Wermuth L, **Ritz B**, Lassen CF. The use of antidepressant medication in Parkinson's disease patients is not affected by the type of anti-parkinson medication. J Parkinsons Dis. 2014;4(3):327-30.
162. **Ritz B**, Lee PC, Lassen FC, Arah O. Ease of quitting is an early sign of Parkinson's Disease: Parkinson's and smoking revisited. Neurology. 2014 Oct 14;83(16):1396-402. PMCID: PMC4206154
163. Shelton JF, Geraghty EM, Tancredi DJ, Delwiche LD, Schmidt RJ, Hansen R, **Ritz B,** Hertz-Picciotto I. Neurodevelopmental Disorders and Prenatal Residential Proximity to Agricultural Pesticides: The CHARGE Study. Environ Health Perspect. 2014 Oct;122(10):1103-9. PMCID:PMC4181917
164. von Ehrenstein O, Aralis H, Cockburn M, **B Ritz**. In Utero Exposure to Toxic Air Pollutants and Risk of Childhood Autism. Epidemiology. 2014 Nov;25(6):851-8.PMCID: PMC4698150
165. Gatto N, Deapen D, Stoyonoff S; Pinder R, Narayan S, Bordelon Y, **Ritz B**. Lifetime Exposure to Estrogens and Parkinson's Disease in California Teachers. Parkinsonism Relat Disord. 2014 Nov;20(11):1149-56.
166. Ahmed I, Lee PC, Lill CN, Nielsen SS, Artaud F, Gallagher LG, Loriot MA, Mulot C, Nacfer M, Liu T, Biernacka JM, Armasu S, Anderson K, Farin FM, Lassen CF, Hansen J, Olsen JH, Bertram L, Maraganore DM, Checkoway H, **Ritz B**, Elbaz A. Lack of replication of the GRIN2A-by-coffee interaction in Parkinson's disease. PLoS Genet. 2014 Nov 20;10(11):e1004788. PMCID: PMC4238979
167. Lee PC, Bordelon Y, Bronstein J, Sinsheimer JS, Farrer M; **Ritz B**. Head injury, alpha-synuclein genetic variability and Parkinson's disease. Eur J Neurol. 2015 May;22(5):874-8. PMCID: PMC4390403
168. Kenborg L, Rugbjerg K; Lee PC; Ravnskjær L; Christensen J; **Ritz B**; Lassen CF. Head injury and risk for Parkinson disease: results from a Danish case- control study. Neurology. 2015 Mar 17;84(11):1098-103 PMCID:PMC4371406
169. Kenborg L, Lassen CF, **Ritz B**, Andersen KK, Christensen J, Schernhammer ES, Hansen J, Wermuth L, Rod NH, Olsen JH. Lifestyle, Family History, and Risk for Idiopathic Parkinson Disease: a Large Danish Case-Control Study. Am J Epidemiol. 2015 May 15;181(10):808-16 PMCID:PMC4423523
170. Liew Z, **Ritz B**, von Ehrenstein OS, Bech BH, Nohr E, Fei C, Bossi R, Henriksen TB, Bonefeld-Jørgensen EC, Olsen J. Attention Deficit/Hyperactivity Disorder and Childhood Autism in Association with Prenatal Exposure to Perfluoroalkyl Substances: A Nested Case–Control Study in the Danish National Birth Cohort. Environ Health Perspect. 2015 Apr;123(4):367-73.
171. Liew Z, Olsen J, Cui X**, Ritz B**, Arah OA. Bias from conditioning on live birth in pregnancy cohorts: an illustration based on neurodevelopment in children after prenatal exposure to organic pollutants. Int J Epidemiol. 2015 Feb;44(1):345-54.
172. Bandoli G, von Ehrenstein OS, Flores M, **Ritz B**. Breastfeeding and Asthmatic Symptoms in the offspring of Latinas - the role of maternal nativity. J Immigr Minor Health. 2015 Dec;17(6):1739-45. PMCID:PMC4499015
173. Lill CM, Rengmark A, Pihlstrøm L, Fogh I, Shatunov A, Sleiman PM, Wang LS, Liu T, Lassen CF, Meissner E, Alexopoulos P, Calvo A, Chio A, Dizdar N, Faltraco F, Forsgren L, Kirchheiner L, Kurz A, Larsen JP, Liebsch M, Linder J, Morrison KE, Nissbrandt H, Otto M, Pahnke J, Partch A, Restagno G, Rujescu D, Schnack C, Shaw CE, Shaw PJ, Tumani H, Tysnes OB, Valladares O, Silani V, van den Berg LH, van Rheenen W, Veldink JH, Lindenberger U, Steinhagen-Thiessen E, SLAGEN Consortium, Teipel S, Perneczky R, Hakonarson H, Hampel H, von Arnim CAF, Olsen JH, Van Deerlin VM, Al-Chalabi A, Toft M, **Ritz B**, Bertram L. The role of TREM2 R47H as a risk factor for Alzheimer's disease, frontotemporal lobar degeneration, amyotrophic lateral sclerosis, and Parkinson's disease. Alzheimers Dement. 2015 Apr 29. pii: S1552-5260(15)00122-3.
174. Lombardi C, Ganguly A, Bunin GR, Azary S, Alfonso V, **Ritz B**, Heck JE. Maternal Diet during Pregnancy and Unilateral Retinoblastoma: A Report from the Children's Oncology Group. Cancer Causes Control. 2015 Mar;26(3):387-97. PMCID: PMC4334703
175. Bronstein JM, Paul K, Yang L, Hass RH, Shults CW, **Ritz B.** Platelet Mitochondrial Activity and Pesticide Exposure in Early Parkinson's Disease. Mov Disord. 2015 May;30(6):862-6. PMCID: PMC4439327
176. Srivatsal S, Cholerton B, Leverenz JB, Wszolek ZK, Uitti RJ, Weintraub D, Trojanowski JQ, Van Deerlin VM, Quinn JF, Chung KA, Peterson AL, Factor SA,Wood-Siverio C, Goldman JG, Stebbins

GT, Bernard B, **Ritz B**, Rausch R, Espay AJ, Revilla FJ, Devoto J, Rosenthal LS, Dawson TM, Albert MS, Mata IF, Hu SC, Montine KS, Johnson C, Montine TJ, Edwards KL, Zabetian CP. Cognitive Profile of LRRK2-related Parkinson's Disease. Mov Disord. 2015 Apr 15;30(5):728-33. PMCID: PMC4397146

177. Su JG, Jerrett M, Meng YY, Pickett M, **Ritz B**. Integrating smart-phone based momentary location tracking with fixed site air quality monitoring for personal exposure assessment. Sci Total Environ. 2015 Feb 15; 506-507:518-26.
178. **Ritz B,** Lee PC, Hansen J, Lassen CF, Ketzel M, Sørensen M, Raaschou-Nielsen O. Traffic-Related Air Pollution is a Risk Factor for Parkinson's Disease in Denmark. Environ Health Perspect. 2016 Mar;124(3):351-6.
179. Paul KC, Sinsheimer JS, Rhodes SL, Cockburn M, Bronstein JM**, Ritz B.** Organophosphate Pesticide Exposures, Nitric Oxide Synthase Gene Variants, and Gene-Pesticide Interactions in a Case-Control Study of Parkinson's Disease, California (USA). Environ Health Perspect. 2015 Sep 18. [Epub ahead of print]
180. Lill CM, Hansen J, Olsen JO, Binder H**, Ritz B**, Bertram L. Impact of Parkinson's disease risk loci on age at onset. Mov Disord. 2015 May;30(6):847-50.
181. Gatto NM, Sinsheimer JS, Cockburn M, Escobedo LA, Bordelon Y, **Ritz B**. Vitamin D receptor gene polymorphisms and Parkinson's disease in a Population with High Ultraviolet Radiation Exposure. J Neurol Sci. 2015 May 15;352(1-2):88-93.
182. Kannarkat GT, Cook DA, Lee JK, Chang J, Chung V, Sandy E , Paul KC, **Ritz B**, Bronstein J, Factor SA, Boss JM, Tansey MG. Common Genetic Variant Association with Altered HLA Expression, Synergy with Pyrethroid Exposure, and Risk for Parkinson's Disease: An Observational and Case-Control Study. npj Parkinson's Disease (2015) 1, 15002; doi:10.1038/npjparkd.2015.2; published online 22 April 2015
183. Heck JE, Park AS, Cockburn M, **Ritz B**. Can the "Hispanic paradox" shed light on childhood cancer risk? Cancer Epidemiol Biomarkers Prev. 2015 Apr;24(4):764-5.
184. Pearce NE, Blair A, Vineis P, Ahrens W, Andersen A, Anto JM, Armstrong BK, Baccarelli AA, Beland FA, Berrington A, Bertazzi PA, Birnbaum LS, Brownson RC, Bucher JR, Cantor KP, Cardis E, Cherrie JW, Christiani DC, Cocco P, Coggon D, Comba P, Demers PA, Dement JM, Douwes J, Eisen EA, Engel LS, Fenske RA, Fleming LE, Fletcher T, Fontham E, Forastiere F, Frentzel-Beyme R, Fritschi L, Gerin M, Goldberg M, Grandjean P, Grimsrud TK, Gustavsson P, Haines A, Hartge P, Hansen J, Hauptmann M, Heederik D, Hemminki K, Hemon D, Hertz-Picciotto I, Hoppin JA, Huff J, Jarvholm B, Kang D, Karagas MR, Kjaerheim K, Kjuus H, Kogevinas M, Kriebel D, Kristensen P, Kromhout H, Laden F, Lebailly P, LeMasters G, Lubin JH, Lynch CF, Lynge E, 't Mannetje A, McMichael AJ, McLaughlin JR, Marrett L, Martuzzi M, Merchant JA, Merler E, Merletti F, Miller A, Mirer FE, Monson R, Nordby KK, Olshan AF, Parent ME, Perera FP, Perry MJ, Pesatori AC, Pirastu R, Porta M, Pukkala E, Rice C, Richardson DB, Ritter L, **Ritz B**, Ronckers CM, Rushton L, Rusiecki JA, Rusyn I, Samet JM, Sandler DP, de Sanjose S, Schernhammer E, Seniori Constantini A, Seixas N, Shy C, Siemiatycki J, Silvermann DT, Simonato L, Smith AH, Smith MT, Spinelli JJ, Spitz MR, Stallones L, Stayner LT, Steenland K, Stenzel M, Stewart BW, Stewart PA, Symanski E, Terracini B, Tolbert PE, Vainio H, Vena J, Vermeulen R, Victora CG, Ward EM, Weinberg CR, Weisenburger D, Wesseling C, Weiderpass E, Zahm SH. IARC Monographs: 40 Years of Evaluating Carcinogenic Hazards to Humans. Environ Health Perspect. 2015 Feb 24. [Epub ahead of print]
185. Schernhammer ES, Lassen CF, Kenborg L, **Ritz B**, Olsen JH, Hansen J. Night shift work and Parkinson's disease in Denmark. Scand J Work Environ Health. 2015 Jul 1;41(4):377-83.
186. Walker RF, Liu JS, Peters BA, **Ritz BR**, Ophoff R, Horvath S. Epigenetic age analysis of blood from "Peter Pan" children". Aging (Albany NY). 2015 May;7(5):334-9.
187. von Ehrenstein, Aralis H, Flores MS, **Ritz B**. Fast Food Consumption in Pregnancy and Subsequent Asthma Symptoms in Young Children. Pediatr Allergy Immunol. 2015 Sep;26(6):571-7.
188. Coker ES, Beckerman B, Ghosh JC, Gomez-Rubio V, Jerrett M, Li A, Liverani S, **Ritz B**, Su J, Molitor J. Modeling spatial effects of PM2.5 on term low birth weight in Los Angeles County. Environ Res. 2015 Jul 17;142:354-364.
189. Narayan S, Sinsheimer JS, Paul KC, Liew Z, Cockburn M, Bronstein JM, **Ritz B**. Genetic Variability in ABCB1, Occupational Pesticide Exposure, and Parkinson's Disease. Environ Res. 2015 Nov;143 (Pt A):98-106.
190. Mata IF, Leverenz JB, Weintraub D, Trojanowski JQ, Chen-Plotkin A, Van Deerlin VM, **Ritz B**, Rausch R, Factor SA, Wood-Siverio C, Quinn JF,Chung KA, Peterson-Hiller AL, Goldman JG, Stebbins GT, Bernard B, Espay AJ, Revilla FJ, Devoto J, Rosenthal LS, Dawson TM, Albert MS, Tsuang D, Huston H, Yearout D, Hu SC, Cholerton BA, Montine TJ, Edwards KL, Zabetian CP. GBA

variants are associated with a distinct pattern of cognitive deficits in Parkinson disease. Mov Disord 2016 Jan;31(1):95-102.
191. von Ehrenstein OS, Heck JE, Park A, Cockburn M, Escobedo L, **Ritz B**. In Utero and Early-Life Exposure to Ambient Air Toxics and Childhood Brain Tumors: A Population-Based Case-Control Study in California, USA. Environ Health Perspect. 2016 Jul;124(7):1093-9. PMCID: PMC4937846
192. Virk J, Liew Z, Olsen J, Nohr E, Catov JM, **Ritz B**. Preconceptional and Prenatal Supplementary Folic Acid and Multivitamin Intake and Autism Spectrum Disorders. Autism. 2016 Aug;20(6):710-8.
193. Bandoli G, von Ehrenstein OS, Gosh JKC, Flores M, Dunkel-Schetter C, **Ritz B**. Prenatal maternal stress and the risk of lifetime wheeze in young offspring: An examination by stressor and maternal race/ethnicity. J Immigr Minor Health. 2016 Oct;18(5):987-95.
194. Heck JE, Azary S, **Ritz B**, Bunin GR, Ganguly A. A case-control study of sporadic retinoblastoma in relation to maternal health conditions and reproductive factors. BMC Cancer. 2015 Oct 19;15:735. PMCID: PMC4615328
195. Virk J, **Ritz B,** Li J, Obel C, Olsen J. Childhood Bereavement and Type 1 Diabetes: A Danish National Register Study. Paediatr Perinat Epidemiol. 2016 Jan;30(1):86-92.
196. Julvez J, Paus T, Bellinger D, Eskenazi B, Tiemeier H, Pearce N, **Ritz B**, White T, Ramchandani P, Gispert JD, Desrivières S, Brouwer R, Boucher O, Alemany S, López-Vicente M, Suades-González E, Forns J, Grandjean P, Sunyer J. Environment and Brain Development: Challenges in the Global Context. Neuroepidemiology. 2015 Dec 19;46(2):79-82.
197. Wermuth L, Cui X, Greene NH, Schernhammer ES, **Ritz BR**. Medical Record Review to Differentiate between Idiopathic Parkinson's Disease (IPD) and Parkinsonism: A Danish Record Linkage Study with 10 Years of Follow-up. Parkinsons Dis. 2015;2015:781479.
198. Liew Z, **Ritz B**, Virk J, Olsen J. Maternal Use of Acetaminophen During Pregnancy and Risk of Autism Spectrum Disorders in Childhood: a Danish National Birth Cohort Study. Autism Res. 2016 Sep;9(9):951-8.
199. Horvath S, **Ritz BR.** Increased epigenetic age and granulocyte counts in the blood of Parkinson's disease patients. Aging (Albany NY). 2015 Dec;7(12):1130-42.
200. Liew Z, **Ritz B**, Virk J, Arah O, Olsen J Prenatal Use of Acetaminophen and Child IQ: a Danish Cohort Study. Epidemiology. 2016 Nov;27(6):912-8.
201. Heck JE, Park AS, Contreras ZA, Davidson TB, Hoggatt KJ, Cockburn M, **Ritz B**. Cancer in the Children of US and Foreign-born Hispanics: a test of the "Hispanic paradox" JAMA Pediatr. 2016 Jun 1;170(6):585-92.
202. Paul KC, Rausch R, Creek MM, Sinsheimer JS, Bronstein JM, Bordelon Y, **Ritz B.** APOE, MAPT, and COMT genetic variants and cognitive symptom progression in a Parkinson's disease patient cohort. J Parkinsons Dis. 2016 Apr 2;6(2):349-59.
203 **Ritz B**, Paul KC, Bronstein JM. Of Pesticides and Men: A California Story of Genes and Environment in Parkinson's Disease. Curr Environ Health Rep. 2016 Mar;3(1):40-52.
204. Coker E, Liverani S, Ghosh J, Jerrett M, Beckerman B, Su J, Li A, **Ritz B,** Molitor J. A. Multi-Pollutant Exposure Profiles Associated with Term Low Birth Weight in Los Angeles County. Environ Int. 2016 May;91:1-13.
205. Heck JE, Contreras ZE, Park AS, Cockburn M, **Ritz B**. Smoking in pregnancy and risk of cancer among young children: a population-based study. Int J Cancer. 2016 Aug 1;139(3):613-6.
206. Azary S, Ganguly A, Bunin GR, Lombardi C, Park AS, **Ritz B**, Heck JE. Sporadic Retinoblastoma and Parental Smoking and Alcohol Consumption before and after Conception: A Report from the Children's Oncology Group. PLoS One. 2016 Mar 18;11(3):e0151728
207. Alfonso VH, Bandoli G, von Ehrenstein O, **Ritz B**. The influence of pre-natal supplement initiation on preterm birth among majority Hispanic women in Los Angeles County: the role of nativity. Matern Child Health J. 2016 Sep;20(9):1861-8.
208. Bandoli G, Ghosh J, von Ehrenstein O, **Ritz B**. Psychosocial stressors and lung function in youth ages 10-17: an examination by stressor, age and gender. J Public Health (Oxf). 2016 May 8. pii: fdw035. [Epub ahead of print]
209. Bandoli G, Ghosh J, von Ehrenstein O, **Ritz B.** Synergistic effects of air pollution and psychosocial stressors on adolescent lung function. J Allergy Clin Immunol. 2016 Apr 30. pii: S0091-6749(16)30196-8. [Epub ahead of print]
210. Shih IF, Liew Z, Krause N, **Ritz B**. Lifetime Occupational and Leisure Time Physical Activity and Risk of Parkinson's Disease Parkinsonism & Related Disorders. Parkinsonism Relat Disord. 2016 Jul;28:112-7.

211. Contreras ZA, **Ritz B**, Virk J, Cockburn M, Heck JE. Maternal diabetes, obesity, weight gain in pregnancy, and risk of childhood cancer in offspring: a population-based study in California. Cancer Causes Control. 2016 Oct;27(10):1273-85.
212. Levine ME, Lu AT, Chen BH, Hernandez DG, Singleton AB, Ferrucci L, Bandinelli S, Salfati E, Manson JE, Quach A, Kusters CDJ, Kuh D, Wong A, Teschendorff AE, Widschwendter M, **Ritz BR**, Absher D, Assimes T, Horvath S.. Menopause accelerates biological aging. Proc Natl Acad Sci U S A. 2016 Aug 16;113(33):9327-32.
213. Kettner LO, Kesmodel US, Ramlau-Hansen CH, Bay B, **Ritz B**, Matthiesen NB, Brink Henriksen T. Fertility Treatment and Childhood Epilepsy: a Nationwide Cohort Study of 565,166 Live Births. Paediatr Perinat Epidemiol. 2016 Sep;30(5):488-95.
214. Hill-Burns EM, Ross OA, Wissemann WT, Ortolaza AI, Mellick GD, Scherzer CR, **Ritz B**, Marthi V, Zareparsi S, Zabetian CP, Factor SA, Payami H. Identification of genetic modifiers of age-at-onset for familial Parkinson's disease. Hum Mol Genet. 2016 Jul 11. pii: ddw206.
215. Su J, Meng YY, Pickett M, Seto E**, Ritz B,** Jerrett M. Identification of the effects of regulatory actions on improvements in air quality in the goods movement corridors. Environ Sci Technol. 2016 Aug 16;50(16):8687-96.
216. Horvath S, Gurven M, Levine ME, Trumble BC, Kaplan B, Allayee H, **Ritz BR**, Chen B, Lu AT, Rickabaugh TM, Jamieson BD, Sun D, Li S, Chen W, Quintana-Murci L, Fagny M, Kobor MS, Tsao PS, Reiner AP, Edlefsen KL, Absher D, Assimes TL. An epigenetic clock analysis of race/ethnicity, sex, and coronary heart disease. Genome Biol. 2016 Aug 11;17(1):171.
217. Lee PC, Raaschou-Nielsen O, Lill CM, Bertram L, Sinsheimer JS, Hansen J, **Ritz B**. Gene-environment interactions linking air pollution and inflammation in Parkinson's disease. Environ Res. 2016 Nov;151:713-720.
218. Contreras ZA, **Ritz B**, Virk J, Cockburn M, Heck JE. Maternal pre-pregnancy and gestational diabetes, obesity, gestational weight gain, and risk of cancer in young children: a population-based study in California. Cancer Causes Control. 2016 Oct;27(10):1273-85
219. A European Respiratory Society & American Thoracic Society Policy Statement: What Constitutes an Adverse Health Effect of Air Pollution? An analytical framework Joint ERS/ATS statement'
220. Gatto NM, Paul K, Sinsheimer JS, Bronstein JM, Bordelon Y, Rausch R, Ritz B., **Ritz B**. Vitamin D receptor gene polymorphisms and cognitive decline in Parkinson's disease. J Neurol Sci. 2016 Nov 15;370:100-106.
221. Liew Z, Bach CC, Asarnow RF, **Ritz B**, Olsen J. Paracetamol use during pregnancy and attention and executive function in offspring at age 5. International Journal of Epidemiology 2016.
222. Chuang YH, Lill CM, Lee PC, Hansen J, Lassen CF, Bertram L, Greene N, Sinsheimer JS, **Ritz B.** Gene-environment interaction in Parkinson's disease: coffee, ADORA2A, and CYP1A2. Accepted in Neuroepidemiology.
223. Malmqvist E, Liew Z, Källén K, Rignell-Hydbom A, Rittner R, Rylander L, **Ritz B.** Fetal growth and air pollution -A study on ultrasound and birth measures. Environ Res. 2016 Oct 11;152:73-80.
224. Hall C, **Ritz B**, Cockburn M, Davidson TB, Heck JE. Risk of malignant childhood germ cell tumors in relation to demographic, gestational, and perinatal characteristics. Accepted for publication in Cancer Epidemiology
225. Lee PC, Liu LL, Sun Y, Chen YA, Liu CC, Li CY, Yu HL, **Ritz B.** Traffic-related air pollution increased the risk of Parkinson's disease in Taiwan: A nationwide study. Environ Int. 2016 Nov;96:75-81.
226. Chuang YH, Austin Quach A, Absher D, Assimes T, Horvath S, **Ritz B**. Coffee consumption is associated with DNA methylation levels of human blood. Accepted: European Journal of Human Genetics
227. Virk J, Liew Z, Olsen J, Nohr EA, **Ritz B**. Pre-conceptual and Prenatal Supplementary Folic Acid and Multivitamin Intake, Behavioral Problems and Hyperkinetic Disorders. A Study Based on the Danish National Birth Cohort (DNBC). Accepted in Nutritional Neuroscience
228. Xu X, **Ritz B**, Cockburn M, Lombardi C, Heck J. Maternal Preeclampsia and Odds of Childhood Cancers in Offspring — A California Statewide Case-Control Study. Paediatric and Perinatal Epidemiology
229. Omidakhsh N, Ganguly A, Bunin GR, **Ritz B,** Ehrenstein O, Heck JE.. Residential pesticide exposures in pregnancy and the risk of sporadic retinoblastoma: a report from the Children's Oncology Group. Journal of Ophthalmology
230. Quach A, Levine M, Tanaka T, Lu A, Chen B, Ferrucci L, **Ritz B**, Neuhouser M, Beasly J, Snetselaar L, Wallace R, Tsao P, Absher D, Assimes T, Stewart J, Li Y, Hou L, Baccarelli A, Whitsel E, Horvath S. Epigenetic clock analysis of diet, exercise, education, and lifestyle factors. Aging.

231. Shih I, Starhof C, Lassen CF, Hansen J, Liew Z, **Ritz, B**.Occupational and Recreational Physical Activity and Parkinson's Disease in Denmark. In Press: Scand J Work Environ Health
232. McAllister K, Mechanic LE, Amos C, Aschard H, Blair I, Chatterjee N, Conti D, Gauderman WG, Hsu L, Hutter CM, Jankowska M, Kerr J, Kraft P, Montgomery SB, Mukherjee B, Papanicolaou GJ, Patel CJ, Ritchie MD, **Ritz BR**, Thomas DC, Wei P, Witte JS on behalf of GxE meeting participants. Current Challenges and New Opportunities for Gene-Environment Interaction Studies of Complex Diseases. Accepted: AJE
233. **Ritz BR**, Chatterjee N, Garcia-Closas M, Gauderman JW, Pierce BL, Kraft P, Tanner CM, Mechanic LE, McAllister K. Lessons Learned from Past Gene-Environment (GxE) Interaction Successes. Accepted: AJE
234. Narayan S, Sinsheimer JS, Paul KC, Liew Z, Cockburn M, Bronstein JM, **Ritz B**. Occupational Pesticide Use and Parkinson's Disease in the Parkinson Environment Gene (PEG) Study. Accepted in: Environment International
235. Mata, Johnson, Leverenz, Weintraub, Trojanowski, Van Deerlin, **Ritz**, Rausch, Factor, Wood-Siverio, Quinn, Chung, Peterson-Hiller, Espay, Revilla, Devoto, Yearout, Hu, Cholerton, Montine, Edwards, Zabetian. Large-scale Exploratory Genetic Analysis of Cognitive Impairment in Parkinson's Disease. Accepted: Neurobiology of Aging
236. Sanders LH, Paul KC, Howlett EH, Lawal H, Boppana S, Bronstein J, **Ritz B**, Greenamyre TJ. Base excision repair variants and pesticide exposure increase Parkinson's disease risk. Accepted: Toxicological Sciences

MANUSCRIPTS CURRENTLY UNDER REVIEW

1. Chuang YH, Paul K, Bronstein J, Horvath S, Ritz B. EWAS in Parkinson's disease. Movement Disorders.
2. Paul KC, Ling C, Haan M, Ritz B. Organophosphate pesticides exposure and cognitive decline in SALSA. EHP
3. Paul KC, Sinsheimer JS, Cockburn M, Bronstein JM, Bordelon Y,Ritz BR. Organophosphate pesticide exposure and PON1 L55M in Parkinson's disease progression. Environment International
4. Paul KC, Sinsheimer JS, Cockburn M, Bronstein JM, Bordelon Y, Ritz B. NFE2L2, PPARGC1α, and Oxidative Stress in Parkinson's disease susceptibility and progression. Environ Health
5. Reading SR, Arun S Karlamangla,; Tara L Gruenewald,; Natalie Slopen, David R Williams, Dallas T Swendeman; Beate R Ritz, Brandon Koretz; Teresa E Seeman. Relationship between Psychosocial Stressors and Allostatic Load: Findings from the MIDUS Study. Annals of Behavioral Medicine.
6. Alfonso,VH, Bandoli G, von Ehrenstein O, Ritz B. Early folic acid supplement initiation and risk of adverse early childhood respiratory health: A Los Angeles population-based study. Maternal and Child Health Journal
7. Contreras ZA, Hansen J, Ritz B, Olsen B, Yu F, Heck JE. Parental age and childhood cancer risk: A Danish population-based registry study. Cancer Causes Controls
8. Alfonso,VH, Wang MC, von Ehrenstein O, Bandoli G, Ritz B. Enrollment in the Special. Supplemental Program for Women, Infants and Children reduces risk of recurrent preterm birth among eligible California siblings. IJE
9. Lee PC, Nielsen S, Loriot MA, Hansen J, Lill C, Checkoway H, Elbaz A, Ritz B. Meta-analysis of head injuries and *SNCA* interactions in Parkinson Disease. Neurology
10. Lee PC, Ahmed I, Loriot MA, Mulot C, Lambert JC, Ritz B, Elbaz A. Smoking and Parkinson's disease: evidence for gene-by-smoking interactions. Neurology
11. Patel CJ, Kerr J, Thomas DC, Mukherjee B, Ritz BR, Chatterjee N, Jankowska M, Madan J, Karagas MR, McAllister K, Leah E. Mechanic10, M. Daniele Fallin11, Chris Ladd-Acosta11, Ian Blair12, Susan Teitelbaum13, Amos CI. Opportunities and Challenges for Environmental Exposure Assessment in Population-Based Studies. AJE
12. Wojcik KY, Escobedo LA, Wysong A, Heck JE, Ritz B, Cockburn M. High Birth Weight, Early UV exposure, and Melanoma Risk in Children, Adolescents and Young Adults. Pediatrics.
13. Park AS, B Ritz, C Ling, M Cockburn, JE Heck. Exposure to Ambient Dichloromethane in Pregnancy and Infancy from Industrial Sources and Childhood Cancers in California
14. Omidakhsh N, Heck JE, **Ritz B**, Kennedy N, Ehrenstein OS, Krause N, Ganguly A, Bunin GR.. Parental occupational exposures and the risk of childhood sporadic retinoblastoma: a report from the Children's Oncology Group. Occupational and Environmental Medicine
15. Li L, Lurmann F, Habre R, Urman R, Rappaport E, **Ritz B**, Chen JC, Gilliland FD, Wu J. Constrained Mixed-Effect Models with Ensemble Learning for Prediction of Nitrogen Oxide Concentrations at a High

Spatiotemporal Resolution. Environmental Science & Technology.

INVITED COMMENTARIES AND EDITORIAL (peer reviewed)

1. **Ritz B.** Environmental Toxins and Neurodegenerative Diseases: A Challenge for Epidemiologists. Epidemiology. 2006 Jan;17(1):2-3.
2. Kheifets, L, **Ritz B.** Electromagnetic Fields, Science and Public Concern. Soz Praeventive Med 51 (2006): 1-2.
3. **Ritz, B**. Wahner A*, Bordelon Y, Bronstein J. Can Anti-Inflammatory Agents Protect Against Parkinson's Disease? Future Neurology 2008
4. Chesselet M-F, **Ritz B**. Transcriptional regulation of α-synuclein: insights from blood? Commentary on: GATA transcription factors directly regulate the Parkinson's disease-linked gene alpha-synuclein; Scherzer et al. Future Neurology, March 2009, Vol. 4, No. 2, Pages 145-147
5. **Ritz, B.** Birth defects and ambient air pollution, opportunities and challenges. Editorial; Occup Environ Med. 2010 Apr;67(4):221-2.
6. **Ritz B**, Rhodes SL. After half a century of research on smoking and PD, where do we go now? Neurology. 2010 Mar 16;74(11):870-1.
7. Bower J, **Ritz B**. Is the answer for Parkinson disease already in the medicine cabinet? Unfortunately not. Neurology. 2011 Mar 8;76(10):854-5.
8. Blair A, **Ritz B**, Wesseling C, Beane Freeman L. Pesticides and human health. Occup Environ Med. 2015 Feb;72(2):81-2.

BOOKS AND MONOGRAPHS

1. Karmaus W, Glaser-Möller N, Hullmann B, **Ritz B**, Schäfer K-H, Sonn E: Arbeitsbedingte rheumatische Erkrankungen, Büroarbeit und Bewältigung. Ergebnisse einer Längsschnittstudie von weiblichen Angestellten. (*"Working Conditions, Health Behaviour and Rheumatic Disorders II; Results of a Longitudinal Study on Female Office Workers"*) Forschungsbericht des BMFT, HDA 01 HA 033/4, 1987.
2. Hullmann B, Karmaus W, Osterholz U, **Ritz B**: Work-Related Musculo-Skeletal Disorders. Proceedings of an International Symposium. HDA, Tagungsbericht TB 48, Wirtschaftsverlag NW, Bremerhaven, 1987.
3. Osterholz U, Patjens S, **Ritz B**: Forschungsdokumentation "Rheuma und Arbeit" *"Research Documenation on Working Conditions and Musculo-Skeletal Disorders"*). Arbeitspapier Nr 10, Projektgruppe HdA des WSI, Eds.: Geschäftsfuhrung des WSI, Düsseldorf, 1987.

PEER REVIEWED REPORTS

1. Morgenstern H, Froines J., **Ritz B**, Young B. Epidemiologic Study to Determine Possible Adverse Effects to Rocketdyne/Al Workers from Exposure to Selected Chemicals. July 1998
2. Morgenstern H, Froines J., **Ritz B**, Young B. Epidemiologic Study to Determine Possible Adverse Effects to Rocketdyne/Al Workers from Exposure to Ionizing Radiation. June 1997.
3. Sloss E, Geschwind SA, McCaffrey DF, **Ritz B**. Groundwater Recharge with Reclaimed Water - An Epidemiologic Assessment in Los Angeles County, 1987-1991. Rand Technical Report DRR-1192-WRDSC, 1995
4. Karmaus W, Glaser-Moeller N, Hullmann B, **Ritz B**, Schäfer K-H, Sonn E: Final Report of the project "Arbeitsbedingte rheumatische Erkrankungen in der Verwaltung" (*"Work Related Rheumatic Disorders in Administrative Jobs"*) Schriftenreihe der Bundesanstalt fuer Arbeitsschutz, Forschung Fb 608, Bonn, 1990.
5. Sloss E, McCaffrey DF, Fricker RD, Geschwind, SA, **Ritz B**. Groundwater Recharge with Reclaimed Water - Birth Outcomes in Los Angeles County, 1982-1993. Rand Technical Report, 1999.
6. **Ritz, B.** X- & Gamma Radiation and Neutrons. In: Report on Carcinogens, 11th edition. Carcinogen Profiles. U.S. Department of Health and Human Services, Public Health Service, National Toxicology Program. 2004.
7. Meng YY, Rull RP, Wilhelm M, **Ritz B**, English P, Yu H, Nathan S, Kuruvilla M, Brown ER. Living near heavy traffic increases asthma severity. Policy Brief UCLA Cent Health Policy Res. 2006 Aug:1-5.

8. Molitor J, Coker E, Jerrett M, **Ritz B**, Li A; Health Review Committee. Part 3. Modeling of Multipollutant Profiles and Spatially Varying Health Effects with Applications to Indicators of Adverse Birth Outcomes.Res Rep Health Eff Inst. 2016 Apr;(183 Pt 3):3-47.

CHAPTERS OR SECTIONS IN BOOKS

1. Appelt H, **Ritz B**: Medikamentengebrauch und -abhängigkeit bei Frauen ("FemaleDrug Abuse and Dependency"). In: Medikamente und Sucht, Berichtsheft zur Arbeitstagung der Hamburgischen Landesstelle gegen die Suchtgefahren e.V.(Eds.) Hamburg 1984.
2. **Ritz B**, Karmaus W, Ellinger S: Schmerz-,Beruhigungs-und Schlafmittel - die verordnete Normalität ("Pain Killers, Sleeping Pills and Tranquilizers - Prescribed Norms"). In: Jahresheft 1984 Hamburgische Landesstelle gegen die Suchtgefahren e.V.(Eds.) Hamburg 1984.
3. Glaser N, **Ritz B**: Lungenkrebs, Rauchen und Schadstoffbelastung bei Hamburger Gaswerkern; Risikoabschätzung anhand der logistischen Regression ("Lung Cancer, Smoking and Air Pollutants of Workers Employed at the Hamburg Gas Company "). In: Muß Arbeit krank machen? Eds: G.Elsner, W.Karmaus, L.Lißner, VSA-Verlag,Hamburg 1986.
4. **Ritz B:** Zur Epidemiologie degenerativer rheumatischer Erkrankungen im Zusammenhang mit Arbeitsbedingungen: Halswirbelsäulenveränderungen bei weiblichen Verwaltungsangestellten ("The Epidemiology of Musculo-Skeletal Disorders and Working Conditions of Female Office Workers: Work-Related Neck Disorders"). In: Rheuma und Krebs; Beiträge zur wissenschaftlichen Jahrestagung der Deutschen Gesellschaft für Sozialmedizin Eds: E.O. Krasemann, U.Laaser, E.Schach, Springer Verlag, Heidelberg, München 1987.
5. **Ritz B**: Methodological Aspects in Studying Musculo- Skeletal Disorders and Working Conditions in Office Work Places. In: Work-related musculo-skeletal disorders. Proceedings of an International Symposium. HDA, Tagungsbericht TB 48, Wirtschaftsverlag NW, Bremerhaven, 1987.
6. **Ritz B**, Hullmann B: How Women Office Workers Deal with Stress In: Health Promotion in the Working World. Springer-Verlag Berlin Heidelberg 1989.
7. **Ritz B**: Chapter 3 - Health and Regulatory Considerations In: Using Reclaimed Water to Augment Potable Water Resources. Water Environment Federation, Virginia 1998.
8. **Ritz B**, Karmaus W: Die Nutzung von Surveillance-programmen und Registern fuer umweltbezogene Fragestellungen (The use of surveillance programs and registries for environmental health research; a historical perspective). In Press: Buch zur Verabschiedung von Heidrun Kaupen-Haas, Mabuse Verlag 2002
9. Van Den Eeden S, **Ritz B**, Cobb K. Measurement and Analysis. In: Neuroepidemiology; From Principles to Practice. Eds: Nelson L, Tanner C, Van Den Eeden S, McGuire V. Oxford University Press 2004.
10. **Ritz B**, and other Committee Members: Chapter 4 Cancer: Gulf War and Health volume 3, Fuels, Combustion products, and Propellants, The National Academies Press Washington, D.C., 2005
11. **Ritz B**, and other Committee Members: Amyotrophic Lateral Sclerosis in Veterans. Review of the scientific literature. IOM, NAS National Academy Press, Washington DC, 2006

LETTERS AND OTHER PUBLICATIONS

1. Morgenstern H, **Ritz B.** Workplace Radiation is Indeed Harmful (letter). Los Angeles Times, March 2, 1998, p S6.
2. Morgenstern H, **Ritz B**. Alarming But Neither Absurd nor Amusing (letter). Washington Post, Febuary 11, 1998, p S6.
3. **Ritz B**: Der Einfluß sozialer und struktureller Bedingungen an Büroarbeitsplätzen auf den Gebrauch psychotroper Medikamente; Ergebnisse einer epidemiologischen Untersuchung *("The Influence of Psycho-Social Factors and Job Latitudes on the Use of Psychotropic Medication")*. Ph.D.Dissertation, Hamburg 1986.
4. Meng YY, Rull RP*, Wilhelm M, **Ritz B**, English P, Yu H, Nathan S, Kuruvilla M, Brown ER. Living near heavy traffic increases asthma severity. Policy Brief UCLA Cent Health Policy Res. 2006 Aug;1-5

5. Grandjean B, Bellinger D, Bergman A, Cordier S, Davey-Smith G, Eskenazi B, Gee D, Gray K, Hanson M, Van den Hazel P, Heindel JJ, Heinzow P, Hertz-Picciotto I, Hu H, Huang TK, Kold Jensen T, Landrigan PJ, McMillen IC, Murata K, **Ritz B**, Schoeters G, Skakkebæk NE, Skerfving S, Weihe P. The Faroes Statement: Human Health Effects of Developmental Exposure to Chemicals in Our Environment. Basic & Clinical Pharmacology & Toxicology, 2007
6. Slama R, Darrow L, Parker J, Woodruff TJ, Strickland M, Nieuwenhuijsen M, Glinianaia S, Hoggatt KJ*, Kannan S, Hurley F, Kalinka J, Srám R, Brauer M, Wilhelm M, Heinrich J, **Ritz B**. Meeting report: atmospheric pollution and human reproduction. Environ Health Perspect. 2008 Jun;116(6):791-8
7. Popat RA, Van Den Eeden SK, Tanner CM, Kamel F, Umbach DM, Marder K, **Ritz B**, Webster Ross G, Petrovitch H, Topol B, McGuire V, Nelson LM. Response to Hill-Burns et al. letter: An attempt to replicate interaction between coffee and CYP1A2 gene in connection to Parkinson's disease. Eur J Neurol. 2011 Sep;18(9):e109.
8. Liew Z, **Ritz B**, Olsen J. Characteristics of acetaminophen users compared with nonusers during pregnancy, behavioral problems, and hyperkinetic disorders--reply. JAMA Pediatr. 2014 Sep;168(9):865-6.
9. Liew Z, Olsen J, Cui X, **Ritz B**, Arah OA. Response to Werler and Parker letter: Comment on live-birth bias in pregnancy cohorts. Int J Epidemiol. 2015 Jun;44(3):1080-1
10. Bennett D, Bellinger DC, Birnbaum LS, Bradman A, Chen A, Cory-Slechta DA, Engel SM, Fallin MD, Halladay A, Hauser R, Hertz-Picciotto I, Kwiatkowski CF, Lanphear BP, Marquez E, Marty M, McPartland J, Newschaffer CJ, Payne-Sturges D, Patisaul HB, Perera FP, **Ritz B**, Sass J, Schantz SL, Webster TF, Whyatt RM, Woodruff TJ, Zoeller RT, Anderko L, Campbell C, Conry JA, DeNicola N, Gould RM, Hirtz D, Huffling K, Landrigan PJ, Lavin A, Miller M, Mitchell MA, Rubin L, Schettler T, Tran HL, Acosta A, Brody C, Miller E, Miller P, Swanson M, Witherspoon NO. 2016. Project TENDR: Targeting Environmental Neuro-Developmental Risks. Project TENDR: Targeting Environmental Neuro-Developmental Risks The TENDR Consensus Statement. Environ Health Perspect. 2016 Jul 1;124(7):A118-22.
11. Thurston GD, Kipen H, Annesi-Maesano I, Balmes J, Brook RD, Cromar K, De Matteis S, Forastiere F, Forsberg B, Frampton MW, Grigg J, Heederik D, Kelly FJ, Kuenzli N, Laumbach R, Peters A, Rajagopalan ST, Rich D, **Ritz B,** Samet JM, Sandstrom T, Sigsgaard T, Sunyer J, Brunekreef B. A joint ERS/ATS policy statement: what constitutes an adverse health effect of air pollution? An analytical framework. Eur Respir J 2017; 49:1600419.

UNITED STATES DISTRICT COURT

NORTHERN DISTRICT OF CALIFORNIA

IN RE: ROUNDUP PRODUCTS LIABILITY LITIGATION	MDL No. 2741 Case No. 16-md-02741-VC
This document relates to: ALL ACTIONS	

EXPERT REPORT OF DR. BEATE RITZ, M.D., Ph.D.

IN SUPPORT OF GENERAL CAUSATION

ON BEHALF OF PLAINTIFFS

1. Beate Ritz, MD, PhD, Background and Qualifications

I, Beate Ritz, MD, Ph.D., am Professor of Epidemiology at the UCLA Fielding School of Public Health, former Chair of the Epidemiology Department, and I hold co-appointments in Environmental Health Sciences and Neurology at the UCLA, School of Medicine. I was trained in Medicine at the University of Hamburg/Germany and received a doctoral degree from the University of Hamburg in Medical Sociology in 1986. I furthermore received another doctoral degree in Epidemiology from UCLA in 1995, and subsequently was hired as a faculty at UCLA. My faculty appointment at UCLA is one of several positions specifically assigned to the Center of Occupational and Environmental Health (COEH) mandated by the State of California to conduct research, teaching, and service to communities in California on occupational and environmental health issues. Hence, my primary research interests are health effects from occupational and environmental exposures with a focus on pesticides and air pollution and chronic diseases including cancers, reproductive outcomes, neurodevelopmental disorders and neurodegenerative diseases. I served for more than a decade as the co-director of the NIEHS-

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RITZ
Date: 9/18/2017
Reporter: Lisa Moskowitz
CSR 10816, RPR, CRR, CLR

funded UCLA Center for Gene-Environment Studies in Parkinson's disease (PD) and am currently the Director of the American Parkinson's Disease Association Center for Excellence in PD Research. In the past two decades, I was the principal investigator of numerous Parkinson's disease, pesticides and gene-environment epidemiology studies in California and also conducted research based on large databases (such as cancer registries) assembled in California and Denmark. As part of my research, I developed geographic information system (GIS) based exposure assessment tools to assess chronic health effects of long-term pesticide exposures and of air pollution in California. In the early 2000s, I served as a member of the external advisory committee for the NCI/NIEHS Agricultural Health Cohort Study and for one year chaired this committee. I also was a visiting scientist at IARC/Lyon in 2006-07. In 2007, I received the Robert M. Zweig M.D. Memorial Award (Clean Air Award) from the California South Coast Air Quality Management District and in 2008 I was awarded the "Excellence in Research" award from the American Parkinson's Disease Association. I served on multiple National Academy of Sciences/Institute of Medicine (NAS/IOM) committees evaluating Gulf War Illness – including IOM reviews of cancer and of amyotrophic lateral sclerosis (ALS). Recently, I served on the NAS/IOM committee on "Incorporating 21st Century Science into Risk-Based Evaluations" and I just newly began serving on the committee to assess "Health Effects in Vietnam Veterans from Agent Orange (herbicides)". I am a CA Governor appointed member of the scientific review board for the California Air Resources Board (CARB) panel on Air Toxics. I served on the editorial Board of the Journal *Epidemiology* as well as other journals (currently I am editing a section of the journal *Current Environmental Health Reports*) and I am the newly elected President Elect of the International Society for Environmental Epidemiology (ISEE). My Curriculum Vitae is attached as Exhibit A. A list of the materials I have reviewed, in addition to those set forth in my CV, are attached as Exhibit B. Exhibit C contains my billing rate and prior testimony.

2. Methodology

2.0 Definitions of statistical and methodological terms.

(Population-based) Case-control study. A case-control study is a study where the subjects are selected for inclusion based on their disease status. In other words, study subjects referred to as

cases are enrolled because they have the disease (in this case, NHL) and controls are subjects who at the time the cases are diagnosed are not afflicted by the disease of interest; additionally, a study is considered population-based if the controls are selected without bias from the same population from which all cases arose. After study enrollment, everyone is either asked to report their past exposures (in this case, glyphosate or Roundup) or – if possible – exposures are reconstructed from a record system (e.g. sales records or application records) or by experts who evaluate job tasks and titles among all study participants (generally referred to as a job exposure matrix).

Cohort study. In a cohort study, subjects are enrolled in the study based on their exposures (in this case, to glyphosate or Roundup), and followed over time to determine who develops the disease(s) of interest. At enrollment, all participants are asked to report their past exposures or exposure is reconstructed from records, basically similar as in the case-control study, except that at enrollment no study participant is allowed to suffer from the disease of interest yet i.e. at the time of exposure assessment. In some cohorts, exposure is only assessed at enrollment (baseline) while in others exposures continue to be assessed throughout follow-up until disease occurs.

Odds Ratio (OR). An odds ratio, or OR, is a measure of association between an exposure and a disease. It represents the odds that the disease will occur in a group of people given a particular exposure, in comparison to the odds of the disease in a group of people without the exposure. An OR of 1.00 is the null, meaning no effect. Thus, an OR of 1.40 as reported in one of the studies below, for example, represents a 40% increase in NHL from exposure to glyphosate. An OR of 3.10 in one of the studies below represents a 210% increase in the odds of NHL from exposure to glyphosate. An odds ratio is a "point estimate" or the 'central' estimate of the relationship between exposure and disease, in a given study (note: the OR is in the center of the upper and lower confidence limit boundaries, see below). Odds Ratios are the statistics that are used most often to analyze case-control studies, and they are often calculated using a statistical technique called logistic regression but can also be derived by simple calculations based on a 2x2 table of data.

Rate Ratio (RR). A rate ratio is the measure of association between exposure and disease that can be calculated from cohort study data. It compares the incidence rates of disease given an exposure, to the incidence rate of disease among people without the exposure. The incidence rate allows us to take time into account and may depend on how much time has passed from the start of the study until the point in time when disease is diagnosed (or until the end of the study), thus it not only uses information based on persons but based on person times time under observation (also known as 'persontime'). Therefore, a RR different from an OR inherently relies on measures that included time under observation (i.e. rates). However, the results are interpreted in the same way: a RR of 1.00 is the null (no effect); a RR of 1.40 is a 40% increase in the rate of disease, etc.

Risk Ratio (or Relative Risk) is a ratio of the risk in the exposed divided by the risk in the unexposed in a cohort - where risks are defined as the number of (un)exposed cases divided by the total number of (un)exposed. Thus, different from rate ratios, this measure uses the number of subjects rather than the number of person-years a subject contributes during follow-up as the denominator. This method is used for well-defined (similar length) follow-up periods in the exposed and the unexposed such that the time under observation will not contribute additional information and we can substitute persons for person-time.
NOTE: under certain circumstances often met especially for rare diseases, the odds ratio (OR), risk ratio (RR) and rate ratio (RR) are the same (albeit calculated as the ratio of odds, risks, or rates) and the interpretation of the estimates is also the same.

P-value. The p-value is the probability of obtaining an estimate at least as far from a pre-specified value (in case of the null hypothesis the 'null' value) as the estimate we have obtained, if the specified value were the true value (note: no p-value, for the null hypothesis or any other hypothesis, is the probability that the specified hypothesis is true). For example, a p-value of 0.04 means that, given the null hypothesis is true, if you repeatedly conducted 100 tests of samples drawn from the same population (people), then in 4% of your tests, you would obtain the results you got solely due to random error (chance). It is a metric intended to show the likelihood of random error. It *should not* be interpreted as the probability that an agent causes an outcome.

Confidence interval (CI). A confidence interval, or CI, is given around an OR or a RR to give the likely interval which potentially includes the unobservable true measure of effect. In other words, it is an interval estimate (as compared to a point estimate) of the true underlying relationship between exposure and disease, in a given study. In practice, most published estimates are 95% confidence intervals, which means that in 95 out of 100 times when sampling your study subjects, you will find the true result (effect estimate) within the given confidence interval.

Hierarchical regression is a type of statistical analysis that was used in the 2003 De Roos study.[1] It is used when there are many correlated exposures and as a means to adjust for multiple comparisons. In De Roos, there were many different pesticides used by farmers and pesticide applicators, and therefore use of one pesticide can be strongly correlated with the use of another pesticide. For example, imagine glyphosate is often used together with another pesticide, dicamba. If the Odds Ratio that is reported between glyphosate and cancer is 2.0, then dicamba –assuming it is mostly used together with glyphosate – would be a proxy for glyphosate exposure and its OR would also be close to 2.0, just because these pesticides tend to be used together even if dicamba is not a carcinogen. However, if both pesticides truly increase risk (both are carcinogens) and we put them into the same (regression) model, we would not be able to estimate their effects properly, since they would now both have an attenuated effect estimate (this is also referred to as correlated variables 'stealing variance from each other'). De Roos used hierarchical regression to tease apart such correlations in order to determine which pesticides are the ones that are driving increases in NHL and narrow down the long list of pesticides to find the "bad actors" which were increasing risk of NHL. But, this approach makes a number of assumptions, for example that either all pesticides considered or pesticides within certain groups have similar effects on the outcome which might be incorrect.

N (number). The number of people in a study.

Statistical power is the ability of a study to estimate an effect. In essence, it is a reflection of the sample size (number of subjects in a study – in cohorts also the number of cases), the prevalence

of exposure, and the expected effect size. Large sample sizes give us generally higher statistical power, which means they have narrower and more stable confidence intervals around point estimates. Smaller sample sizes have wider confidence intervals. Thus, larger studies are much more able to find statistically significant results especially when exposures or outcomes are rare and the expected size of the effect moderate or small in size.

Data pooling or pooled analysis. To pool data is to use the raw (un-analyzed or non-summarized) data from several studies and merge them together to conduct analyses. Data pooling is often done when there have been multiple small studies on a topic, because the pooling allows for larger sample sizes and a uniform approach to the analysis of the pooled data. In order to conduct data pooling, scientists need to have permission to access the data from the investigators of multiple studies. Pooled studies have greater statistical power than the original studies from which they draw.

Meta-analysis. In some instances, scientists are interested in pooling data but do not easily have access to the raw data from each study. This is, typically, because the studies were conducted many years earlier, or perhaps because the investigators do not know/trust each other or human subject restrictions do not allow for the sharing of raw data; it is quicker and more efficient to conduct a meta-analysis based on summary estimates from published reports. A meta-analysis uses the Odds Ratios or Rate Ratios and confidence intervals which were published in the original studies, and comes up with a summary estimate of the relationship between exposure and disease. Similar to pooled analyses, meta-analyses also have much greater statistical power than each study does on its own, but the authors do not have the option of re-analyzing the original data as could be done if raw data were available (such as lagging exposures or generating different exposure categories etc.).

Null hypothesis means no effect. In the studies described below, their null hypothesis was that NHL is not related to glyphosate/Roundup exposure. The statistical tests done in the studies described below aim to test the null hypothesis: they want to determine if there the null hypothesis can be rejected with adequate statistical certainty and whether they can determine

whether there any relationship between exposure to glyphosate/Roundup and the development of NHL is suggested by a study.

A Forest Plot is a visual representation of the main results of all studies on a topic. The purpose of grouping them all together visually is that it can give the reader a sense of overall size of the effect estimates and the direction of the associations in the existing literature. See pg. 14.

Dose-response. A dose-response association represents an increasing risk with an increasing dose, such as a larger number of days per year, or a longer number of years, being related to higher Odds Ratios. For example, the overall study Odds Ratio might be 1.40, but for people who used glyphosate more often, the Odds Ratio was 2.5 while for those using it less often it might have been 1.5. This is a sign of a dose-response effect.

Incident/incidence refers to newly diagnosed cases; while prevalent cases are any existing cases at any point in time or over a certain period in time.

Confounding is a bias that occurs because a risk factor for the outcome is also a cause or precursor of the exposure of interest such that the outcome is caused by this confounder and not by the exposure one is trying to assess. For example, if sex is a risk factor for NHL and sex is also associated with occupational exposure to pesticides, we would want to adjust all effect estimates for pesticides by sex to remove potential confounding bias.

Recall bias is one type of exposure misclassification that is considered 'differential' by epidemiologists. This means that cases and controls remember or report past exposures differently because they have or do not have the disease. Generally, it has been suggested that cases may put more effort into recalling exposures since they have a need to explain their disease or are more motivated to do so to help researchers while controls are less motivated to recall past exposures. However, this is most likely a problem if the diseased subject knows or suspects an agent to cause their disease. If the subject has no way to know which pesticide might have caused a cancer for example and is asked to report all chemicals they have ever used occupationally, it is unlikely that they would only recall one and not another chemical

differentially. Thus, if recall bias existed, we would expect all pesticides they reported to the researchers to show an association with the outcome and not just one amongst many, since the tendency to recall better or more exposures than controls would not be expected to be specific to one chemical. In fact, when recall has been compared with record based evaluations, differential recall that causes recall bias has generally not been shown to be a problem. *Note:* non-differential recall error such that both cases and controls misreport their exposures is known to cause mainly bias towards the null i.e. masking any true effect rather that enhancing them. These recall biases are one type of information bias (see below).

Other biases include information bias which is characterized as mismeasurement of exposures or outcomes which can severely distort results in both case-control and cohort studies. As long as mismeasurement is non-differential (see above) i.e. the same for cases and controls or for exposed and unexposed, such biases most often cause underestimation of true effect sizes i.e. bias results towards the null that can be severe. Finally, there is selection-bias if controls are not representative of the exposures in the population that gave rise to the cases in case-control studies, or when there is a large and differential (with regard to case status) loss to follow-up in cohort studies.

2.1 Literature search

To obtain all published studies on the relationship between non-Hodgkin's Lymphoma (NHL) and glyphosate (the active ingredient in Roundup), I undertook a literature search using the same method to search for articles that I normally use in my research. This is the same method that I teach my UCLA students to use. As such, I relied upon two search engines, PubMed (https://www.ncbi.nlm.nih.gov/pubmed) and Google Scholar (https://scholar.google.com/). PubMed is an excellent resource for finding papers on the exact topic one is interested in, but it does not do as well in finding papers which were largely about a different topic but may have also briefly reported on the topic of interest. Google Scholar does well in capturing every possible paper of interest, but will often provide many articles not relevant to the subject matter at hand. I use both search engines to be as thorough as possible, but also to identify the most relevant articles. These searches initially yielded 290 articles in PubMed and 9000+ articles in Google Scholar for epidemiological studies; and over 550 articles for

animal and mechanistic literature; and over 600 citations for cancer. [Most citations were not immediately relevant to the present question, due to their focus on topics such as effects in fish resulting from runoff; effects on pregnancy and child development; or effects on other cancer types.]

As is typical in most published meta-analyses and reviews, I took additional steps to ensure I did not miss any relevant articles by also reviewing other published papers to check their citations. For these, I relied on the IARC Glyphosate Monograph as well as the two meta-analyses on glyphosate and NHL, as well as other articles on the topic that were published more recently.[2-4]

Furthermore, I read the US EPA's Cancer Assessment Review Committee (CARC) report, however I disagreed with their results because they relied heavily on statistical significance in studies that were not sufficiently statistically powered to answer the question (more on this below).

2.2 Reliance on peer-reviewed literature

As I teach my students, the most relevant articles, and indeed the only articles I nearly ever review and cite in my own research, are those that have gone through peer review at a reputable journal. Each field has its own journals considered reputable; but in general, a reputable journal is a journal that is listed in the most well-known and respected indexing sources such as PubMed.[i] Typically, these journals have been published for many years and many are backed by well-recognized and respected medical or research non-profit organizations, such as the American Medical Association, the British Medical Association, the American Association for Cancer Research (AACR), the Union for International Cancer Control (UICC), or the American Cancer Society.

Peer review, as defined by Danzik, is "a system by which manuscripts submitted for publication are evaluated, using outside referees (peers), who comment on the manuscripts' merit, originality, significance, and appropriateness to the journal. The intent is to identify flaws

[i] PubMed is a service of the US National Institutes of Health (NIH). On their website (https://www.nlm.nih.gov/pubs/factsheets/j_sel_faq.html) they explain that NIH uses a committee, the Literature Selection Technical Review Committee, to review and recommend which biomedical and health- related life science journals are included. Criteria include relevant subject matter as well as journals that meet PubMed Central's scientific quality standard, described as "scientific and editorial character and quality of a journal."

in design and analysis or interpretation, to suggest improvements, to direct manuscripts to the most appropriate outlets, to discourage repetition in publishing, and to weed out poor science or scholarship."[5]

Independent peer review is the cornerstone of science in the United States and internationally, and has formed the basis for what is considered acceptable and reliable medical and scientific research. The peer review process, which is almost always done anonymously (the reviewer is nearly always anonymous, although the authors are usually not) provides the intellectual rigor required to ensure that manuscripts adhere to what is acceptable in the field with regards to reviewing the relevant literature, and examining the statistics, and determining whether research protocols apply widely accepted methods, report valid results and avoid or account for biases, and draw conclusions appropriate to the study's findings. Peer reviewers are responsible for deciding whether an article is acceptable for publication. Because of this, authors typically will first, only submit their best work; and secondly, authors have to respond to reviewer critiques and be willing to make changes as requested or argue against suggested changes if there is a compelling reason to not do so which must be explained and justified to and accepted by the journal editors. I have personally peer reviewed on hundreds of occasions and for more than 20 different journals. I have also served on the editorial boards of three journals: Epidemiology, Epidemiologic Perspectives and Innovations, and Environmental Health.

The system of peer review has been in practice for decades. Although it is not without imperfections, the revisions that are suggested improve the quality of published manuscripts, it heads off potential fraud, and its existence encourages honest and state-of-the-sciences work.[5]

It is usual that peer reviewers will assemble comments for the editors who will communicate these and the editor's own comments to the authors as requests for clarification and additional information with the intention to not only improve the manuscript but most importantly to allow them to assess research validity. When any validity issues spotted during the review process cannot be addressed sufficiently by the authors in their responses and/or a revised manuscript, the editor may decide that the manuscript is not ready for publication.

2.3 Conflicts of interest.

There have been several systematic reviews published on the role of conflicts of interest in medical research. In 2003, a review of 1140 original studies reported a strong relationship

between industry sponsorship and pro-industry conclusions, with industry-sponsored studies more than 3 times as likely to find conclusions sympathetic to industry [pooled Odds Ratio (OR): 3.60, 95% Confidence Interval (CI), 2.63-4.91].[6]

Similarly, a 2016 article in the British Medical Journal (BMJ), which analyzed the results of 190 clinical trials published in 2013, reported that the presence of a financial tie between study investigators and industry resulted in a threefold increase in a positive study result (OR=3.23, 95% CI 1.7-6.1).[7]

As these reviews show, and as is widely recognized across the medical and research communities, industry sponsorship and financial incentives are unequivocally related to study findings. For this reason, journals have increasingly required that investigators report conflicts of interest when they submit articles, and these conflicts are published for the reader to see and to take into account when drawing conclusions as to the verity of the findings or the interpretation of the presented data. This information is also made available to journal reviewers, because it may influence the choice to recommend a manuscript for publication i.e. it may contribute to assessing scientific validity of the reported research. Furthermore, this is what I as a professor teach my students, and UCLA teaches to students in bioethics courses and lectures.

I performed an analysis of the data contained in the literature review of Williams, et al. (2016) and provide my opinions on that and other data throughout this report. There is a clear conflict of interest with several of the authors, and my review of the Dr. William Heydens and Dr. John Acquavella transcripts shows that some of the authors failed to properly disclose these conflicts. Therefore, I put less weight on this group's conclusions since it suggests they lack an ability to be impartial.

2.4 Statistical significance.

If we start off a study assuming that there is no association between glyphosate/Roundup and NHL (the "null hypothesis"), then, after we do our statistical analysis, we can determine the p-value for the null hypothesis of our findings, which is the probability of obtaining an estimate at least as far from a pre-specified value (the null value in case of the null hypothesis) as the estimate we have obtained, if that specified value were the true value (note: no p-value, for the null hypothesis or any other, is the probability that the specified hypothesis is true). There is a convention to consider a $p<0.05$ as "statistically significant" however, this is simply a

convention which is sometimes replaced by other p-values such as $p<0.01$ or $p<10^{-7}$ (in genomic studies). What a p-value of 0.04 actually means is that, given the null hypothesis is true, if you repeatedly conducted 100 tests of samples drawn from the same population (people), then in 4% of your tests, you would obtain the results solely due to random error (chance). It is a metric intended to show the likelihood of random error. It *should not* be interpreted as the probability that glyphosate/Roundup causes NHL. Moreover, if $p>0.05$, this doesn't "prove" the null hypothesis; absence of proof is not proof of absence.

Similarly, when a (95%) confidence interval excludes 1.0 (such as OR=2.0, 95% CI=1.2-2.8) – because 1.0 (the null value) is outside of the confidence interval-- it would be considered "statistically significant". As with p-values, confidence intervals can be defined as 95% intervals or 90% or 80% etc. intervals. However, confidence intervals provide additional information that p-values do not provide, and this information is related to the precision of the estimates or what is also called the informativeness of the data. In practice, p-values and confidence intervals close to the null (for example, if one side of the confidence interval is between 0.9 to 1.1) are considered marginal in terms of significance. Importantly, however, the estimates least influenced by chance are not those with low p-values, but those with narrow confidence intervals.

Statistical significance testing has been widely used and often misused in the medical literature, and is use has thus been widely criticized. One journal now bans the use of all statistical tests and even confidence intervals.[8] In the last decade, there has been considerable debate on the merits and problems of significance testing,[9-29] and in many Schools of Medicine and Public Health such as UCLA, students have been taught for decades to not rely upon statistical significance to draw their conclusions in accordance with the writings of the faculty member Dr. Sander Greenland, an author of the most widely used textbook in Epidemiology Methods entitled "Modern Epidemiology."[30] At UCLA, we teach students to focus on the point estimate (e.g. the Odds Ratio or Rate Ratio) as a measure of the size of the association between exposure and disease and the confidence interval to gage the precision of this estimate and the informativeness of the data/study.

Also important to consider is the rarity of the disease, because the rarer a disease, the harder it is for a scientist to create a large enough study with enough cancer cases enrolled to have adequate statistical power. Cancer is by its nature a rare disease. The annual incidence rate

(number of new cases) of NHL is 19.7 cases per 100,000 people. This is why it is so hard to study NHL with a cohort study design, because you would have to follow hundreds of thousands of people for many years in order to find any result that would give us a $p<0.05$ if we assume that the effect estimate size is moderate (less 2). This is the main reason why most cancer studies are employing a case-control design which is much more efficient in terms of the necessary sample size for sufficient statistical power and in terms of costs in general.

Many of the case-control studies cited below in this review, particularly those that tried to recruit cases in rural areas, had a limited sample size simply because there are a finite number of cases of NHL in rural areas (with low population density). For example, the Nebraska study (which contributed to De Roos' pooled analysis) included 220 cases;[31] the Kansas study[32] included 200 cases. These are not large numbers, and the result is that we get wide confidence intervals, particularly when exposures are also rare (as they were in these two studies, with 6% of cases and 3% of controls reporting ever use of glyphosate).

As recognized by the US National Cancer Institute, wide confidence intervals are often seen in epidemiologic studies of rare diseases like NHL, but scientists are nonetheless encouraged to move forward and publish their results anyway. This is because smaller studies can later be used in pooled or meta-analyses, and those will have much improved statistical power to estimate precise effect estimates.

In addition, as we teach at UCLA, one study alone is never definitive. It is important for a reviewer to look at the information in the literature as a whole to understand relationships between exposure and disease. We teach students to consider point estimates (Odds Ratios) as indicators of associations and effect sizes, and to not dismiss or mis-interpret studies that have wide confidence intervals that may or may not include the null.

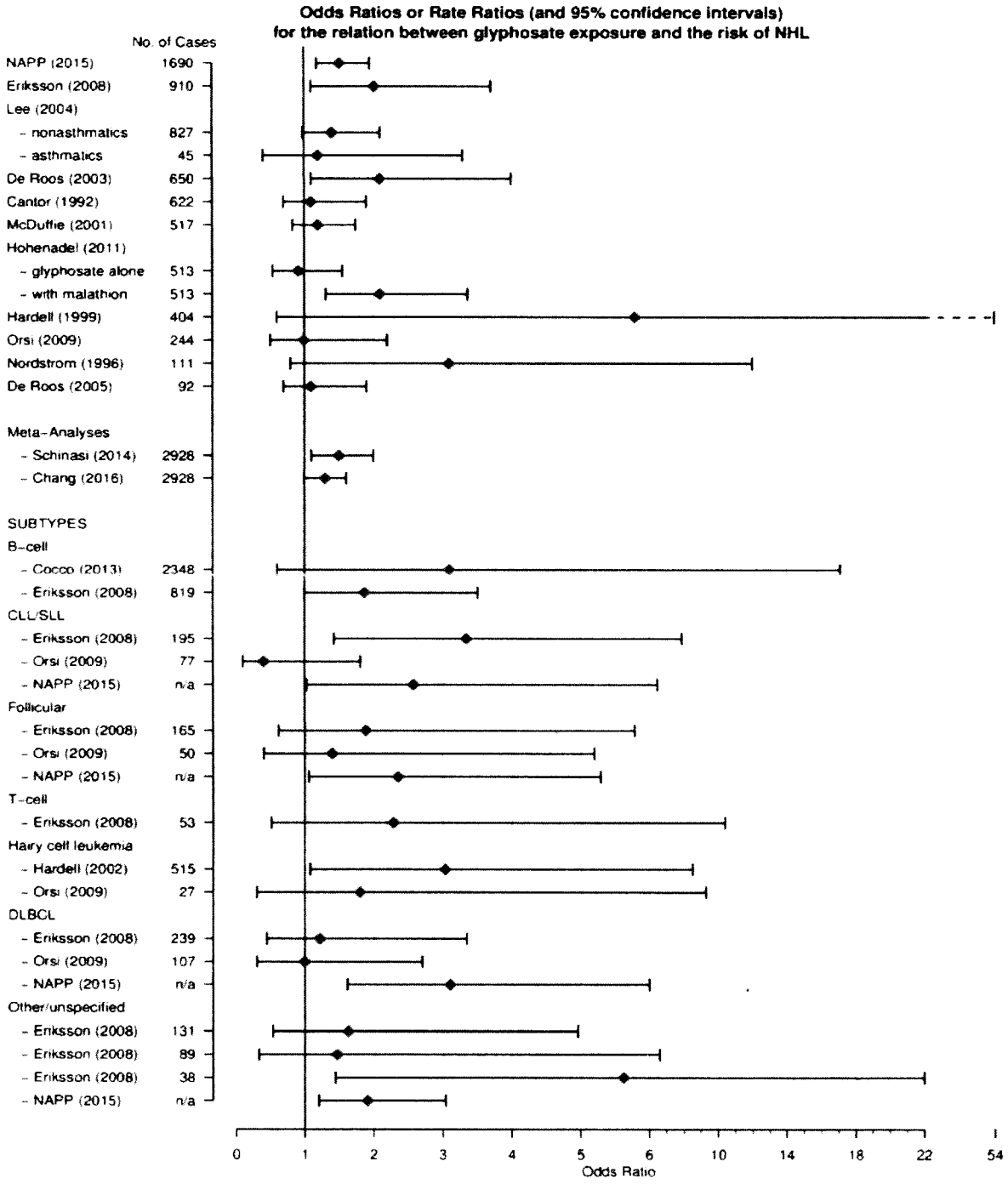
s2.5 Abstracts vs. full articles.

2.5 Abstracts vs. full articles.

Whenever possible it is preferable to examine and cite a full article over an abstract of the same study, because full articles have the space to provide a detailed overview of study methods and findings. If the full article is not yet published, however, it is common practice to cite abstracts.

3. Literature Review.

Here I summarize the findings of the epidemiologic studies on glyphosate and NHL in a forest plot, a graphical representation of all study results.



In reviewing the literature, the sample sizes and especially the number of cases should be noted, because of their bearing on 'statistical significance' and the width of confidence intervals. Because many of the smaller studies had suggestive findings but wide confidence intervals, it is particularly important to instead consider pooled and meta-analyses that summarize across these smaller studies and not only provide a much larger sample size but may allow us to assess NHL subtypes with sufficient precision. Here I show the sample sizes of each human study of glyphosate and NHL.

First author, date	Number of cases in the study (all NHL cases combined)	Number of controls in the study
Cocco, 2013	1869	2462
Pahwa, 2015 (commonly known as the NAPP study)	1690	5131
Eriksson, 2008	910	1016
Lee, 2004	872	2336
De Roos 2003	650	1933
Cantor, 1992	622	1245
McDuffie, 2001	517	1506
Hardell, 2002	515	1141
Hohenadel, 2011	513	1506
Hardell, 1999	404	781
Orsi, 2009	244	426
Nordstrom, 1996	111	400
De Roos, 2005 (commonly known as the AHS study)	92	(54223)*

* these are the N of unaffected cohort members, however we calculate person time and generally do not use person N in analyses.

Because sample size is so relevant in considering exposure-disease associations, an informative study to consider is Pahwa's pooled analysis of the North American and Canadian studies, the North American Pooled Project (NAPP).[33] This abstract was presented at the International Society for Environmental Epidemiology's annual conference, and hence was peer-

reviewed, as are all abstracts presented at this meeting. In this analysis of 1690 cases and 5131 controls, NAPP reported an elevated risk of all NHL with any glyphosate use (OR=1.51, 95% CI 1.18-1.95) and a dose-response effect was seen with greater use (>2 days/year, OR=2.66, 1.61-4.40). An OR of 2.66 means that glyphosate exposure increases the risk of developing NHL by more than 160%. With regards to NHL subtypes, increases were observed for small lymphocytic lymphoma (SLL; 2.58, 95% CI 1.03-6.48, among those using for more than 5 years), and for follicular lymphoma (OR=2.36, 95% CI 1.06-5.29), diffuse large B-cell lymphoma (DLBCL; OR=3.11, 95% CI 1.61-6.00), and other subtypes (OR=2.99, 95% CI 1.10-8.09) for use more than 2 days per year. These study results were published in 2014, and as such were not included in any of the meta-analyses.

There were three meta-analyses conducted on glyphosate and NHL. The first, by Schinasi and colleagues,[34] included 2928 cases from 6 studies[1,2,35-38] and reported increases in NHL risk with any glyphosate exposure (meta-RR: 1.5, 95% CI 1.1–2.0), similar to the results of the NAPP study. Particularly stronger increases were reported for B-cell lymphoma (meta-RR = 2.0, 95% CI 1.1-3.6). Notably, heterogeneity of study results was low, which means that the results across studies were highly consistent. This is important because it suggests that the increases in NHL risk were unlikely to be the result of random fluctuations of estimates across populations: when you see the same results in multiple studies across different settings, it improves confidence in the findings.

The IARC Working Group's Monograph on glyphosate[4] noted that the above meta-analysis did not always use the most "highly adjusted estimates" from each study. The most highly adjusted estimates (also known as "fully adjusted" models) are the estimates that adjust for as many confounding variables as possible, such as adjusting for age, sex, race, and also sometimes other pesticide exposures. This is relevant because it gives the reader confidence that the findings are most likely due to glyphosate/Roundup exposure, instead of another potential cause that acts as a confounder. As such IARC's Working Group conducted their own meta-analysis using solely the most highly adjusted estimates from the same studies,[1,2,35-38] and reported a meta risk-ratio of 1.3 (95% CI, 1.03–1.65), with consistent findings across studies (low heterogeneity). I concur with the IARC conclusions after conducting my own independent analysis of the studies included in the IARC review.

Also helpful to consider is the Swedish study by Eriksson,[2] which was large (N=910 cases) and in addition, this study examined cases diagnosed 1999-2002 and thus allowed for a longer time period to have elapsed between exposure and disease development (glyphosate first came on the market in 1974); this is known as the latency period between exposure and disease occurrence. Although a short latency period does not completely exclude the possibility of exposure-disease relationships in cancer, a longer latency period increases confidence in results due to increased biological plausibility i.e. typically we would generally expect a 5-10 year minimum latency between exposure and disease onset for blood system related cancers. (However, in an individual case the latency period could be as short as 1 year, and as long as 50+ years.) Eriksson reported a twofold increase in NHL risk with glyphosate exposure (OR=2.02, 95% CI 1.10-3.71). Notably, there was also evidence of a dose-response effect: with >10 days use, the risk was higher (OR=2.36, 95% CI 1.04-5.37) compared to less than 10 days of use (OR=1.69, 95% CI 0.70-4.07). This was the only study reviewed which conducted analyses and also accounted for latency (>10 years after use, OR=2.26, 95% CI 1.16-4.40) and these results are more convincing due to biologic plausibility; in the group in which less than 10 years had elapsed since exposure, the effect estimate was much lower, as would be expected since these exposures are less likely to contribute to disease onset (OR=1.10, 0.24-5.08).

Eriksson also stratified by NHL subtype; effect estimates were increased for every NHL subtype and confidence intervals overlapped, meaning that there was evidence for increased risk for all NHL types: B-cell lymphomas (OR=1.87, 95% CI 0.998-3.51); SLL/CLL (OR=3.35, 95% CI 1.42-7.89); follicular (OR=1.89, 95% CI 0.62-5.79); Diffuse large B-cell (OR=1.22, 95% CI 0.44-3.35); other specified B-cell lymphomas (OR=1.63, 95% CI 0.53-4.96); unspecified B-cell (OR=1.47, 95% CI 0.33-6.61); T-cell lymphomas (OR=2.29, 95% CI 0.51-10.4); unspecified NHL (OR=5.63, 95% CI 1.44-22.0).

An earlier Swedish study by the same research group[39] ascertained cases diagnosed 1987-1990; thus this population was distinct from those in Eriksson's analysis. This study was smaller (N=404 cases) and had few participants ever exposed to glyphosate, leading to wide confidence intervals (4 cases and 3 controls ever exposed; OR=2.3, 95% CI 0.4–13). The small sample size limits our ability to draw definitive conclusions, but it is interesting that the estimate effect size is quite similar to the one reported by the larger later study. Likely because of this limitation, authors later conducted a pooled analysis which grouped these cases with cases of hairy-cell

leukemia (a subtype of NHL), reporting a threefold increased risk of any NHL (OR=3.04, 95% CI 1.08-8.52).[36] An earlier report of only the hairy-cell leukemia cases also reported increases in risk with glyphosate exposure (OR=3.1, 95% CI 0.8-1.2), but relied on a quite small sample size (N=121 cases).[40]

The Canadian studies (McDuffie[35] and Hohenadel[41]) ascertained cases diagnosed 1991-1994 hence allowing for a latency period between first possible use of glyphosate and disease occurrence, however the sample size (N=517 cases) was smaller than that of the pooled US studies. McDuffie reported a weak increased risk of NHL with glyphosate exposure which was similar in size in minimally adjusted and fully adjusted models (OR=1.26, 0.95-1.90; OR=1.20, 0.83-1.74). This study had a variety of sources for controls and a control participation rate of 48%, which is of concern if this caused selection of controls that does not reflect the population exposure to glyphosate. To examine the accuracy of self-reported pesticide use, McDuffie conducted a validation study comparing questionnaire data from farmers to records from a local chemical supplier on pesticide purchases. They stated that concordance between self-reported and sales record based exposures was excellent, although more specific information was not provided.

Pesticides sometimes exert stronger health effects when mixed (co-exposure) with other pesticides than when used alone. McDuffie reported that when glyphosate exposure was mixed with dicamba, the risk was increased (OR=1.92, 95% CI 1.39-2.66, minimally adjusted model; OR=1.88, 95% CI 1.32-2.68; fully adjusted model) compared to dicamba exposure alone (OR=1.59 and 1.68, respectively).[35] Similarly, when glyphosate exposure was mixed with malathion (OR=2.10, 95% CI 1.31-3.37) it was stronger than when farmers only reported using glyphosate alone (OR=0.92, 95% CI 0.54-1.55).[41]

The study by Cocco was limited in how much we can glean from its results, as only 4 cases and 2 controls had ever used glyphosate. The prevalence may have been low in this study because the Cocco study included people with a range of occupations, unlike many of the other studies which focused on agricultural populations. Cocco reported increases in B-cell lymphoma with glyphosate use (OR= 3.1, 9% CI 0.6 to 17.1).[42]

Less informative for the current evaluation is the Cantor study[43] because, although it was carefully conducted, cases (in Iowa and Minnesota) were included that were diagnosed 1980-1983. Hence, only 6-10 years could have elapsed between a potential first glyphosate exposure

and NHL diagnosis, which for cancer epidemiologic studies is considered an inadequate latency period (see above) and one would want to see an at least the median latency period of 10 years. Again, for an individual the latency period may vary (1 year to many decades), but on average for a study one would prefer a minimum latency period of on average 10 years.

The Lee study[44] utilized Cantor's cohort to build upon by including subjects from Nebraska who were diagnosed July 1983 to June 1986, thus this study includes cases with a longer latency period, which improves confidence in results. Lee reported increases in NHL among non-asthmatics (OR=1.4, 95% CI 0.98-2.1, N cases=827) and a smaller elevated effect estimate in asthmatics with wide confidence intervals (OR=1.2, 95% CI 0.4-3.3) due to the small number of asthmatic cases (N=45).

De Roos 2003 reanalyzed the US studies[1] and used hierarchical regression in addition to conventional logistic regression models, a statistical technique (described above) which can account for co-exposures and correlations between pesticides but makes some strong assumptions about all pesticides or groups of pesticides having similar effects on the outcomes. Using regular logistic regression, De Roos reported an increased risk with glyphosate use (OR =2.1, 95% CI 1.1 to 4.0) and in the hierarchical regression analysis the effect estimate was smaller 1.6 and the 95% CI included the null value of 1 (95% CI =0.9-2.8). Notably, the OR for glyphosate was among the highest of 47 pesticides tested, which suggests that glyphosate may indeed be the pesticide most strongly related to NHL in these farmers among all pesticides they used. The selection of pesticides for this paper was based upon a "carcinogenic probability factor" developed for all cancers, not specific to NHL, so it is not clear whether the hierarchical regression represented the best analytic strategy for NHL since – as stated above – the model assumes that all pesticides included have a similarly strong effect on the outcome; thus we would expect the largest effect estimate to be pulled towards the null of 1 which is what happened. Also, in terms of possible exposure mismeasurement, a validation of questionnaire responses had previously been conducted which reported strong agreement between self-reported pesticide use in comparison to pesticide supplier records, and recall was similar between cases and controls.[45]

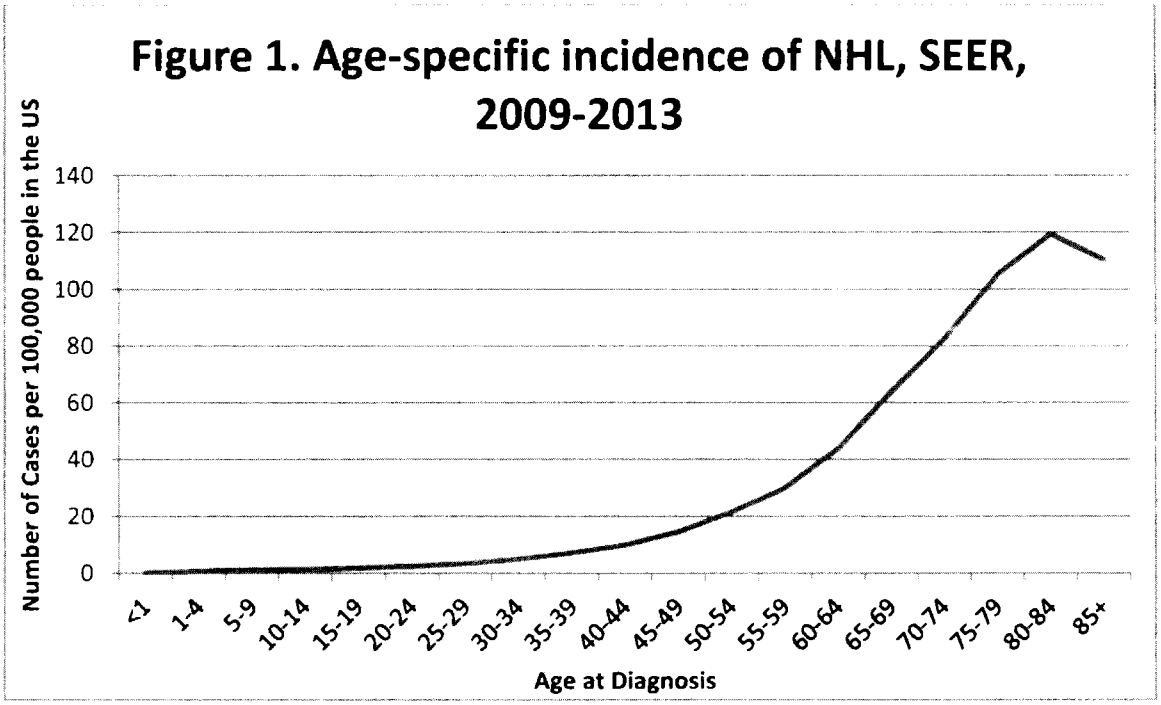
The French study by Orsi and colleagues[38] utilized a hospital-based study design, i.e. in this design cases and controls are recruited from among hospital patients. This is in contrast to nearly all of the other studies described above which used a population-based study design (with the exception of some countries within the Cocco study). Population-based studies are

considered superior to hospital based designs, because epidemiologic studies aim to select controls from the same population that gave rise to the cases, because it improves study validity. The patients who go to a hospital for NHL treatment may not live in the same area as the control patients selected; this can occur if the study hospitals are regional cancer centers which draw cases from a large geographic area. Orsi's study recruited controls who had been admitted largely from orthopedic and rheumatological admissions (mostly fractures, injuries and back pain). This may be problematic because orthopedic and musculoskeletal illnesses and injuries are conditions that typically do not require travel to a distant center for treatment, suggesting there was possible non-overlap between the case and control populations. In addition, hospital patients are an unusual group: they tend to be older, sicker, and have higher tobacco and alcohol use (and other behavioral/lifestyle differences) than the general population.[46-49] Consequently, the use of hospital controls can create unexpected and surprising findings (such as studies of cancer where the controls smoke more than the cases[48]). Further, biases can occur when the reasons for hospitalization are related to exposure. For example, if people exposed to glyphosate are more likely to be hospitalized (due to, perhaps, higher rates of time spent outdoors leading to greater injuries and back pain in farmers/gardeners) then this would bias the results. This may indeed be the case because there are known higher rates of musculoskeletal injuries among gardeners, and these people may also have higher glyphosate use.[50-52] Orsi and colleagues were unable to observe any association between glyphosate and NHL (OR=1.0, 95% CI 0.5 to 2.2; all NHL types combined). When authors examined risk by subtype, elevated risk with wide confidence intervals was reported for follicular lymphoma (OR=1.4, 95% CI 0.4-5.2) but not large diffuse large cell lymphoma (OR=1.0, 0.3-2.7). However, with 244 cases this study has only limited statistical power to conduct any subtype specific analyses.

De Roos 2005 is an analysis of the Agricultural Health Study (AHS).[37] Pesticide applicators were recruited for this study between 1993-1997 and followed for incidence of cancers up until December 2001, therefore active follow-up ranged from 4-8 years with a median follow-up period[ii] of 6.7 years, which is considered a short latency period in cancer epidemiology. Only 92 NHL cases had developed in the cohort by end of this follow-up period,

[ii] The follow-up period is the time that elapses between the start and the end of a study. Typically, participants are followed from the start date until 1) cancer diagnosis; 2) death; 3) study end; or 4) loss to follow-up (e.g. the study investigators cannot locate them or they drop out of the study), whichever comes first.

making this the smallest case sample size of any study reviewed; this is not surprising because the mean age at AHS study enrollment was 45.3 years.[53] NHL, like most other cancers, is a disease of aging, with dramatically higher incidence as people age. Figure 1 shows the incidence of NHL among Americans, with data taken from the US National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program.[54] It is not informative to follow a group of workers that young for only 4-8 years and draw meaningful conclusions about their cancer risk, especially for a rare cancer and an expected risk of moderate size (OR or RR of 1.5 to 2.5). The estimated RR was low and the confidence intervals were wide: the risk for any NHL was 1.2 (95% CI 0.7-1.9, adjusted for age; RR=1.1, 0.7-1.9, adjusted for age, demographic and lifestyle factors, and other pesticides).



AHS investigators collected information on 50 pesticides at enrollment (in 1993-1997); as the study description states, participants were asked about ever/never pesticide exposures and years of use and frequency of use (# of days per year) for 22 pesticides at enrollment and for another 28 pesticides in a take-home questionnaire that only 44% of applicators returned. The median time of employment involving mixing and applying any pesticide was 15 years at enrollment, and therefore the pesticide exposures occurring during the most relevant time period

for cancer development may not be known.[53] Among all pesticide applicators included in the analysis, 76% had ever used glyphosate, which made it among the most common pesticide used among applicators in this study. This is in line with other research on glyphosate, which reports that as of 1999, glyphosate was the highest selling crop-protection product on the market.[55] However, it is important to note that the first year genetically engineered, glyphosate-tolerant crops were planted commercially in the U.S. is 1996, and that prior to this date glyphosate accounted for just 3.8% of the total volume of herbicide active ingredients applied in agriculture[56] while glyphosate accounted for half of the total agricultural herbicide use in 2009 [see Coupe]. Also, in a 20-year timespan covered by EPA sales and usage reports (1987–2007), glyphosate use rose faster and more substantially than any other pesticide (in 2007, usage was in the range of 81.6–83.9 million kilograms, more than double the next most heavily sprayed pesticide (atrazine: ~33.1–35.4 million kilograms) making it the most heavily applied pesticide in the U.S. with 2/3 of the share of the total volume having been applied in just the last decade.[57-59]

Given the persistence of glyphosate in soil (with a half-life of 29-60 days[60,61]), the possibility of exposure to glyphosate due to drift from fields[iii] ,[62-64] and a possibility of contaminated water supplies,[65] it is plausible that passive exposure may have ultimately been much higher among agricultural communities and pesticide applicators than the 76% who reported ever use; more importantly, the baseline exposure assessment in the AHS only covered the first two years of very intensive use of glyphosate i.e. those who were enrolled in 1996/97. When exposure to an agent is extremely high—and potentially even ubiquitous as in a cohort of pesticide applicators, who spend their days in agricultural fields—it eventually becomes impossible to study its health effects since there are little or no exposure contrast to measure at

[iii] Studies of pesticide drift suggest the distance that pesticides travel depends upon several factors: first, the method of application, with air spraying by plane or helicopter (common due to its ease of use) leading to further drift than ground spraying, because the spraying occurs higher above crops; secondly, wind speed; and thirdly, pesticide droplet size, with smaller droplets travelling further. Estimates of pesticide drift vary from 74 meters in an area with low wind, up through >2400 meters under windy conditions. Studies of glyphosate pesticide drift suggest droplets can travel upwards of 800-1000 meters. According to the US EPA, spray drift has been reported to be a problem with glyphosate, as there have been multiple reports of damage from glyphosate to non-target crops.

least at the ever/never or cruder types of classification that do not rely on biomarker assays of dose.[iv],[66]

De Roos (2005) also conducted dose-response analyses by examining intensity-weighted exposure (years of use X days per year X intensity level), grouped into 3 levels (0.1-79.5; 79.6-337.1; and 337.2-18,241); and by cumulative exposure days (years of use X days per year), categorized into 3 groups (1-20, 21-56, 57-2,678). Authors decided to compare the cancer risk in these exposed groups not to that among the never exposed, but instead compared high exposure to low exposure. While this type of comparison attempts to control for and eliminate other risk factors that may distinguish non-exposed from exposed (hence reduce potential confounding bias) this type of approach also reduces any remaining exposure contrasts even further and thus reduces the ability to estimate risk increases with exposure and make the effect estimates also less comparable to those form other studies.

Industry-sponsored studies

A meta-analysis by Chang and Delzell was sponsored by Monsanto.[67] This meta-analysis found similar results to the above meta-analyses for any increases in NHL (meta-OR: 1.3, 95% CI 1.0-1.6) and particularly elevated risks for B-cell lymphoma (meta-OR: 2.0, 95% CI 1.1-3.6). This study also found extremely low heterogeneity across studies— unusual in most meta-analyses— supporting the consistency of findings across different settings.

Bradford-Hill criteria evaluation

The strength (effect size) criterion is partially met since the overall meta-analytical (point) effect estimates reported for ever never glyphosate use are between 1.3 and 1.5 reflecting a weak to moderate size association. However, the effect estimates for longer or more extensive use in several studies were larger i.e. between 2 and 3 and this can be considered a stronger endorsement of a causal relation; it is further supported by the observed dose response (biological gradient such that risk increases with dose - another Bradford Hill criterion) that these studies found (also note: a small association does not mean that there is not a causal effect,

[iv] Rose argues that when a risk factor is ubiquitous in a population, it may strongly influence the population incidence of a disease, but may not identify high-risk individuals within a population. For example, in a society where everyone smokes, smoking will not identify high-risk individuals for lung cancer.

though the larger the association, the more likely that it is unbiased and thus causal). In terms of consistency, this criterion is met since positive associations have been reported for different populations and in different places and different time periods which strengthens the likelihood of a true effect. Temporality i.e. that the cancer occurred after exposure and that there is an expected delay between the cause and effect has been shown i.e. all exposures were assessed and recorded for the periods prior to NHL occurrence. Unfortunately, only one study examined the influence of exposure lagging i.e. considered the latency period: that study found a strong association with a 10-year lag, which further corroborates causality in terms of cancer etiology. The specificity criterion (i.e. that one specific exposure causes one specific outcome) is hard to apply in the case of herbicide or pesticide exposure since almost none of the farmers/pesticide applicators is expected to solely be exposed to glyphosate, since most farming operations require the use of multiple pesticides over time. Also in the case of blood system cancers, one could argue that different pesticides have possible carcinogenic effects on different cell types. Nevertheless, it is of interest that NHL is one cancer reported consistently among farmers for the past 2 to 3 decades, and glyphosate is consistently the most widely used herbicide in farming especially after 1995 with the advent of genetically modified crops. Finally, some studies suggested that types of NHL that are showing T14/18 translocations in lymphocytes are the ones most likely caused by external agents including some pesticides and smoking and this increases also biologic plausibility for the action of genotoxic or oxidative stress pathways (see below) with certain pesticides such as glyphosate.

Biological plausibility.

Biomonitoring studies affirm that some (not all) persons who apply glyphosate occupationally have measurable glyphosate excreted in urine, and measurable glyphosate is also seen in farming household members who reside close to treated fields.[68-70] Research on exposed agricultural workers suggests increases in genomic instability (binucleated cells, micronuclei).[71] Rodent studies report increases in DNA oxidative damage (increases in 8-OHdG in either kidney or liver; lipid peroxidation) as well as cytogenetic damage (sister-chromatid exchanges, increases in micronuclei), and DNA single-strand breaks.[72-74] Cytotoxicity and genotoxicity are also reported in studies of human cells.[75]

Roundup vs. glyphosate. One study compared the effects in rodents of glyphosate to those of Roundup, and results were similar with regards to cytotoxic and genotoxic effects.[73] While a *plausible mechanism* between cause and effect is helpful, Bradford Hill noted that knowledge of the mechanism is often limited by current knowledge; nevertheless for glyphosate two mechanisms have recently been proposed, oxidative stress and genotoxicity, and been confirmed by the laboratory experiments listed above. Finally, while *coherence* between epidemiological and laboratory findings increases the likelihood of a true effect, Bradford Hill noted that "... lack of such [laboratory] evidence cannot nullify the epidemiological effect on associations". Due to ethical concerns, there will never be any human experimental evidence for glyphosate toxicity or carcinogenicity, but human cell based studies and animal experiments can substituted as model systems and have increasingly been used in the recent past.

4. Conclusions

The epidemiologic studies as a whole support an increased risk of NHL with exposure to glyphosate or glyphosate based formulations, including Roundup. Due to the rarity of this disease, many of the earlier studies were small in size, leading to wide confidence intervals; yet findings were consistent with nearly all studies having point estimates above 1.0. In the pooled and meta-analyses, results are consistent and unequivocal. Studies that assessed dose also generally found that higher levels of exposure were associated with increased risk and importantly in the one study that did assess the importance of having been exposed more than 10 years prior to a diagnosis of cancer, the results clearly pointed to those exposures as the relevant one as compared to the more recent exposures (within 10 years) increasing plausibility of associations greatly.

In my opinion, to a reasonable degree of scientific certainty, glyphosate causes NHL. Furthermore, to a reasonable degree of scientific certainty, glyphosate based formulations, including Roundup, cause NHL.

Beate Ritz, M.D., Ph.D.

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References cited

1. De Roos AJ, Zahm SH, Cantor KP, et al. Integrative assessment of multiple pesticides as risk factors for non-Hodgkin's lymphoma among men. *Occup Environ Med.* 2003;60(9):E11.
2. Eriksson M, Hardell L, Carlberg M, Akerman M. Pesticide exposure as risk factor for non-Hodgkin lymphoma including histopathological subgroup analysis. *Int J Cancer.* 2008;123(7):1657-1663.
3. Portier CJ, Armstrong BK, Baguley BC, et al. Differences in the carcinogenic evaluation of glyphosate between the International Agency for Research on Cancer (IARC) and the European Food Safety Authority (EFSA). *J Epidemiol Community Health.* 2016;70(8):741-745.
4. IARC Monographs Program. *Some organophosphate insecticides and herbicides.* 26 January 2017.
5. Dancik BP. Importance of Peer Review. *The Serials Librarian.* 1991;19(3-4):91-94.
6. Bekelman JE, Li Y, Gross CP. Scope and impact of financial conflicts of interest in biomedical research: a systematic review. *JAMA.* 2003;289(4):454-465.
7. Ahn R, Woodbridge A, Abraham A, et al. Financial ties of principal investigators and randomized controlled trial outcomes: cross sectional study. *BMJ.* 2017;356:i6770.
8. Trafimow D, Marks M. Editorial. *Basic and Applied Social Psychology.* 2015;37(1):1-2.
9. Ziliak ST, McCloskey DN. *The cult of statistical significance: How the standard error costs us jobs, justice, and lives.* University of Michigan Press; 2008.
10. Anscombe F. The summarizing of clinical experiments by significance levels. *Stat Med.* 1990;9(6):703-708.
11. Berkson J. Tests of significance considered as evidence. *Int J Epidemiol.* 2003;32(5):687-691.
12. Evans S, Mills P, Dawson J. The end of the p value? *Br Heart J.* 1988;60(3):177.
13. Gelman A, Loken E. The Statistical Crisis in Science Data-dependent analysis—a "garden of forking paths"—explains why many statistically significant comparisons don't hold up. *Am Sci.* 2014;102(6):460.
14. Gelman A, Stern H. The difference between "significant" and "not significant" is not itself statistically significant. *The American Statistician.* 2006;60(4):328-331.
15. Gigerenzer G. Mindless statistics. *The Journal of Socio-Economics.* 2004;33(5):587-606.
16. Goodman SN. Toward evidence-based medical statistics. 1: The P value fallacy. *Ann Intern Med.* 1999;130(12):995-1004.
17. Greenland S. Nonsignificance plus high power does not imply support for the null over the alternative. *Ann Epidemiol.* 2012;22(5):364-368.
18. Grieve AP. How to test hypotheses if you must. *Pharmaceutical statistics.* 2015;14(2):139-150.
19. Hoekstra R, Finch S, Kiers HA, Johnson A. Probability as certainty: Dichotomous thinking and the misuse ofp values. *Psychonomic Bulletin & Review.* 2006;13(6):1033-1037.
20. Kaye DH. Is Proof of Statistical Significance Relevant? 1986.
21. Lecoutre M-P, Poitevineau J, Lecoutre B. Even statisticians are not immune to misinterpretations of Null Hypothesis Significance Tests. *International Journal of Psychology.* 2003;38(1):37-45.
22. Lew MJ. Bad statistical practice in pharmacology (and other basic biomedical disciplines): you probably don't know P. *Br J Pharmacol.* 2012;166(5):1559-1567.
23. Matthews JN, Altman DG. Statistics Notes: Interaction 2: compare effect sizes not P values. *BMJ.* 1996;313(7060):808.

24. Poole C. Beyond the confidence interval. *Am J Public Health*. 1987;77(2):195-199.
25. Rozeboom WW. The fallacy of the null-hypothesis significance test. *Psychol Bull*. 1960;57(5):416.
26. Salsburg DS. The religion of statistics as practiced in medical journals. *The American Statistician*. 1985;39(3):220-223.
27. Sterne JA, Cox D, Smith GD. Sifting the evidence—what's wrong with significance tests? Another comment on the role of statistical methods. *BMJ*. 2001;322(7280):226-231.
28. Thompson B. The "significance" crisis in psychology and education. *The Journal of Socio-Economics*. 2004;33(5):607-613.
29. Walker AM. Reporting the results of epidemiologic studies. *Am J Public Health*. 1986;76(5):556-558.
30. Rothman KJ, Greenland S, Lash TL. *Modern epidemiology*. 3rd ed. Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2008.
31. Zahm SH, Weisenburger DD, Babbitt PA, et al. A case-control study of non-Hodgkin's lymphoma and the herbicide 2,4-dichlorophenoxyacetic acid (2,4-D) in eastern Nebraska. *Epidemiology*. 1990;1(5):349-356.
32. Hoar SK, Blair A, Holmes FF, et al. Agricultural herbicide use and risk of lymphoma and soft-tissue sarcoma. *JAMA*. 1986;256(9):1141-1147.
33. Pahwa M, Freeman LB, Demers PA, et al. An evaluation of glyphosate use and the risks of NHL major histological subtypes in the North American Pooled Project. International Society for Environmental Epidemiology; August 31, 2015; Sao Paulo, Brazil.
34. Schinasi L, Leon ME. Non-Hodgkin lymphoma and occupational exposure to agricultural pesticide chemical groups and active ingredients: a systematic review and meta-analysis. *Int J Environ Res Public Health*. 2014;11(4):4449-4527.
35. McDuffie HH, Pahwa P, McLaughlin JR, et al. Non-Hodgkin's lymphoma and specific pesticide exposures in men: cross-Canada study of pesticides and health. *Cancer Epidemiol Biomarkers Prev*. 2001;10(11):1155-1163.
36. Hardell L, Eriksson M, Nordstrom M. Exposure to pesticides as risk factor for non-Hodgkin's lymphoma and hairy cell leukemia: pooled analysis of two Swedish case-control studies. *Leuk Lymphoma*. 2002;43(5):1043-1049.
37. De Roos AJ, Blair A, Rusiecki JA, et al. Cancer incidence among glyphosate-exposed pesticide applicators in the Agricultural Health Study. *Environ Health Perspect*. 2005;113(1):49-54.
38. Orsi L, Delabre L, Monnereau A, et al. Occupational exposure to pesticides and lymphoid neoplasms among men: results of a French case-control study. *Occup Environ Med*. 2009;66(5):291-298.
39. Hardell L, Eriksson M. A case-control study of non-Hodgkin lymphoma and exposure to pesticides. *Cancer*. 1999;85(6):1353-1360.
40. Nordstrom M, Hardell L, Magnuson A, Hagberg H, Rask-Andersen A. Occupational exposures, animal exposure and smoking as risk factors for hairy cell leukaemia evaluated in a case-control study. *Br J Cancer*. 1998;77(11):2048-2052.
41. Hohenadel K, Harris SA, McLaughlin JR, et al. Exposure to multiple pesticides and risk of non-Hodgkin lymphoma in men from six Canadian provinces. *Int J Environ Res Public Health*. 2011;8(6):2320-2330.
42. Cocco P, Satta G, Dubois S, et al. Lymphoma risk and occupational exposure to pesticides: results of the Epilymph study. *Occup Environ Med*. 2013;70(2):91-98.
43. Cantor KP, Blair A, Everett G, et al. Pesticides and other agricultural risk factors for non-Hodgkin's lymphoma among men in Iowa and Minnesota. *Cancer Res*. 1992;52(9):2447-2455.
44. Lee WJ, Cantor KP, Berzofsky JA, Zahm SH, Blair A. Non-Hodgkin's lymphoma among asthmatics exposed to pesticides. *Int J Cancer*. 2004;111(2):298-302.

45. Blair A, Zahm SH. Patterns of pesticide use among farmers: implications for epidemiologic research. *Epidemiology*. 1993;4(1):55-62.
46. Morabia A, Stellman SD, Wynder EL. Smoking prevalence in neighborhood and hospital controls: implications for hospital-based case-control studies. *J Clin Epidemiol*. 1996;49(8):885-889.
47. Ruano-Ravina A, Perez-Rios M, Barros-Dios JM. Population-based versus hospital-based controls: are they comparable? *Gac Sanit*. 2008;22(6):609-613.
48. Sadetzki S, Bensal D, Novikov I, Modan B. The limitations of using hospital controls in cancer etiology--one more example for Berkson's bias. *Eur J Epidemiol*. 2003;18(12):1127-1131.
49. Neupane B, Walter SD, Krueger P, Loeb M. Community controls were preferred to hospital controls in a case-control study where the cases are derived from the hospital. *J Clin Epidemiol*. 2010;63(8):926-931.
50. Bridger RS, Sparto P, Marras WS. Spade design, lumbar motions, risk of low-back injury and digging posture. *Occupational Ergonomics*. 1998;1(3):157-172.
51. Maeda K, Okazaki F, Suenaga T, Sakurai T, Takamatsu M. Low back pain related to bowing posture of greenhouse farmers. *J Hum Ergol (Tokyo)*. 1980;9(2):117-123.
52. Riihimaki H. Low-back pain, its origin and risk indicators. *Scand J Work Environ Health*. 1991;17(2):81-90.
53. Alavanja MC, Sandler DP, McMaster SB, et al. The Agricultural Health Study. *Environ Health Perspect*. 1996;104(4):362-369.
54. SEER Cancer Statistics Review, 1975-2013. Table 19.7: Non-Hodgkin Lymphoma, Incidence and mortality rates by age. 2016; http://seer.cancer.gov/csr/1975_2013/, based on November 2015 SEER data submission, posted to the SEER web site, April 2016. Accessed March 27, 2017.
55. Woodburn AT. Glyphosate: production, pricing and use worldwide. *Pest Management Science*. 2000;56(4):309-312.
56. Coupe RH, Capel PD. Trends in pesticide use on soybean, corn and cotton since the introduction of major genetically modified crops in the United States. *Pest management science*. 2015.
57. Aspelin AL, Grube AH, Torla R. *Pesticides industry sales and usage: 1996 and 1997 market estimates*. Biological and Economic Analysis Division, Office of Pesticide Programs, Office of Prevention, Pesticides and Toxic Substances, US Environmental Protection Agency; 1999.
58. Grube A, Donaldson D, Kiely T, Wu L. *Pesticide industry sales and usage: 2006 and 2007 market estimates*. Washington, DC: US Environmental Protection Agency;2011.
59. Myers JP, Antoniou MN, Blumberg B, et al. Concerns over use of glyphosate-based herbicides and risks associated with exposures: a consensus statement. *Environ Health*. 2016;15:19.
60. Feng JC, Thompson DG. Fate of glyphosate in a Canadian forest watershed. II: Persistence in foliage and soils. *Journal of Agricultural and Food Chemistry*. 1990;38(4):1118-1125.
61. Newton M, Howard KM, Kelpsas BR, Danhaus R, Lottman CM, Dubelman S. Fate of glyphosate in an Oregon forest ecosystem. *Journal of Agricultural and Food Chemistry*. 1984;32(5):1144-1151.
62. Tiefenbacher JP. Mapping the pesticide driftscape: Theoretical patterns of the drift hazard. *Geographical Environment Model*. 1998;2(1):83-102.
63. Yates W, Akesson N, Bayer D. Drift of glyphosate sprays applied with aerial and ground equipment. *Weed Science*. 1978:597-604.
64. Office of Pesticide Programs. *Reregistration eligibility decision (RED): Glyphosate* US Environmental Protection Agency (EPA);1993.

65. Battaglin W, Meyer M, Kuivila K, Dietze J. Glyphosate and its degradation product AMPA occur frequently and widely in US soils, surface water, groundwater, and precipitation. *JAWRA Journal of the American Water Resources Association*. 2014;50(2):275-290.
66. Rose G. Sick individuals and sick populations. *Int J Epidemiol*. 1985;14(1):32-38.
67. Chang ET, Delzell E. Systematic review and meta-analysis of glyphosate exposure and risk of lymphohematopoietic cancers. *J Environ Sci Health B*. 2016;51(6):402-434.
68. Curwin BD, Hein MJ, Sanderson WT, et al. Urinary pesticide concentrations among children, mothers and fathers living in farm and non-farm households in iowa. *Ann Occup Hyg*. 2007;51(1):53-65.
69. Weber J, Phaneuf D, Samuel O, Guillot J, Manca D. Etude de l'exposition professionnelle des travailleurs forestiers exposés au glyphosate. *Centre de toxicologie du Québec, Québec*. 1988.
70. Jauhiainen A, Rasanen K, Sarantila R, Nuutinen J, Kangas J. Occupational exposure of forest workers to glyphosate during brush saw spraying work. *Am Ind Hyg Assoc J*. 1991;52(2):61-64.
71. Bolognesi C, Carrasquilla G, Volpi S, Solomon KR, Marshall EJ. Biomonitoring of genotoxic risk in agricultural workers from five colombian regions: association to occupational exposure to glyphosate. *J Toxicol Environ Health A*. 2009;72(15-16):986-997.
72. Vigfusson NV, Vyse ER. The effect of the pesticides, Dexon, Captan and Roundup, on sister-chromatid exchanges in human lymphocytes in vitro. *Mutat Res*. 1980;79(1):53-57.
73. Bolognesi C, Bonatti S, Degan P, et al. Genotoxic activity of glyphosate and its technical formulation Roundup. *Journal of Agricultural and food chemistry*. 1997;45(5):1957-1962.
74. El-Shenawy NS. Oxidative stress responses of rats exposed to Roundup and its active ingredient glyphosate. *Environ Toxicol Pharmacol*. 2009;28(3):379-385.
75. Gasnier C, Dumont C, Benachour N, Clair E, Chagnon MC, Seralini GE. Glyphosate-based herbicides are toxic and endocrine disruptors in human cell lines. *Toxicology*. 2009;262(3):184-191.

EXHIBIT A

CURRICULUM VITAE
April 2017

Beate R. Ritz, MD, Ph.D.
Professor
Departments of Epidemiology and Environmental Health
UCLA School of Public Health
Box 951772
Los Angeles, CA 90095-1772

EDUCATION

1995	Ph.D. in Epidemiology, School of Public Health, UCLA
1993	M.P.H. in Epidemiology, School of Public Health, UCLA
1987	Doctoral Degree in Medical Sociology, University of Hamburg.
1983	Medical Examination Certificate, Registration as a Physician (M.D.), Board of Health in Hamburg
1977-1983	Medical School, University of Hamburg, Germany

PROFESSIONAL POSITIONS AND APPOINTMENTS

2012- 2015	Chair, Department of Epidemiology, School of Public Health, University of California Los Angeles (UCLA)
2006-current	Professor, Departments of Epidemiology, Environmental Health, and Center for Occupational and Environmental Health, School of Public Health, and Neurology, School of Medicine, UCLA
2005-2012	Vice Chair, Department of Epidemiology, School of Public Health, University of California Los Angeles (UCLA)
2004-current	Appointment in the Department of Neurology, School of Medicine, UCLA
2002-current	Co-director of the UCLA-CGEP (UCLA center for Parkinson 's Disease Environmental Research (CCPDER- CNS)
2001 -2006	Associate Professor, Department of Epidemiology, Department of Environmental Health, and Center for Occupational and Environmental Health, School of Public Health, UCLA
1995-2001	Assistant Professor, Department of Epidemiology and Center for Occupational and Environmental Health, School of Public Health, UCLA
1993-1995	Assistant Researcher, Department of Epidemiology, School of Public Health, UCLA
1989-1991	Hochschulassistentin (Assistant Professor), Institute of Medical-Sociology, University of Hamburg, Germany.
1987-1988	Research Fellow and Resident, Psychiatric University-Hospital Eppendorf, Hamburg, Germany
1984-1986	Research Fellow, Institute of Medical Sociology, University Hospital Eppendorf, Hamburg, Germany

OTHER HONORARY PROFESSIONAL APPOINTMENTS

2002-2008	Editorial Board: EPIDEMIOLOGY
2004-2009	Editorial Board: Epidemiologic Perspectives & Innovations
2007-2010	Editorial Board: Environmental Health
2001-current	Chair (since 2005) and Member (since 2001) of the external advisory committee for the NCI/NIEHS Agricultural Health Cohort Study
2001-current	Board of Directors for the 'R. Lemelson Foundation for Psychocultural Research.' Annual awards of $800,000 for research and training including a UCLA training grant for cross-disciplinary studies in anthropology, psychology and neuroscience

2001-2002	Member of the external advisory committee for the California Biomonitoring Planning Project conducted by the Environmental Health Laboratory's Biomonitoring Project (CDHS)
2002	Member of the EPA Science Advisory Board for Human Health Research Strategy (HHRS)
2002-2004	Member of the external advisory committee for the California Environmental Health Surveillance System (Governor Davis appointee to expert working group for SB 702)
2003-2006	Member of the Ethic Committee for the International Society for Environmental Epidemiology
2003-2004	Member of NAS, IOM Committee on Gulf War and Health, Phase 3: Literature Review of Selected Environmental Particulates, Pollutants, and Synthetic Chemical Compounds
2002-2004	Member of the external advisory committee for the California Environmental Health Surveillance System (Governor Davis appointee to expert working group for SB 702)
2006	Member of NAS, IOM Committee on Gulf War and Amyotrophic Lateral Sclerosis
2006	Member of the Scientific Steering Committee for Pediatric BioBank in California
2007	Robert M. Zweig M.D. Memorial Award (Clean Air Award) from the California South Coast Air Quality Management District
2007	Appointed as a Collegium Ramazzini Fellow
2007	Scientific Organizing committee for the PPTOX conference in Faroe Island
2008	Scientific Organizing committee for the ISEE conference in Pasadena
2008	Member of the Environmental Exposures Working Group conducted by RTI International for the PhenX project of GWA research at NIH
2009	Member of NAS, IOM Committee on Gulf War and Health, Phase 4
2008-09	Member of the U.S. EPA CO standard setting panel for (CASAC: *Carbon Monoxide National Ambient Air Quality Standards*)
2009-2012	Elected Councilor for the International Society for Environmental Epidemiology (ISEE)
2010-current	Member of the Conference Organizing committee of the ISEE
2009	Award from the American Parkinson's Disease Association (APDA) for outstanding contributions to the medical and scientific communities towards the advancement of Parkinson's disease research
2010-2013	Member of the External Advisory Board for the Superfund site center grant at University of Washington
2010-2013	Member of the External Review Board for the Swiss Tropical and Public Health Institute in Basel
2013	Scientific Organizing committee for the ISEE conference in Basel/Switzerland
2012-current	Member of CA-EPA Scientific Review Panel on Toxic Air Contaminants
2012	Affiliate member of the Institute of the Environment and Sustainability
2014	Scientific Organizing committee for the ISEE conference in Seattle Washington
2014-current	Member of NAS/IOM committee on Incorporating 21st Century Science into Risk-Based Evaluations

FUNDED RESEARCH

NNH12ZDA006O-EVI3
Agency: NASA (PI: Ritz)
Total Direct Costs to UCLA: $1,294,244
Multi-Angle Imager for Aerosols (MAIA) 08/01/16-11/30/25
This project will assess air pollution and adverse birth outcomes using exposure data provided by Dr. Diner's group from the MAIA NASA project. UCLA researchers will be responsible for the modeling the effects of prenatal air pollution exposures on adverse birth outcomes derived from vital statistics records for multiple locations across the world.

1 U01 HD087221 (PI: Devaskar/UCLA Ob-GYN)
Agency: NIH/NICHD Period: 01/01/16-12/30/19
Total Direct Costs: $2,999,640
Imaging Innovations for Placental Assessment in Response to Environmental Pollution
The objective of this proposal is to develop and evaluate a suit of cutting-edge multi-parametric magnetic resonance imaging (mp-MRI) technologies and translate these novel placental imaging modalities to assessing the impact of environmental pollution exposure on prediction of placental insufficiency.

Psychosocial stressors, air pollution and childhood respiratory health in LAFANS
Agency: NIEHS R03ES025908 (PI: Ritz) Period: 07/01/15-06/30/17
Total Direct Costs $100,000
This study will add to the previous literature by constructing a more holistic measure of the stress perceived by the child, and use that measure to determine if a child's perceived stress modifies their risk of asthma or reduced lung function from air pollution.

Pesticide Exposures and Risk of Cerebral Palsy
Agency: NIEHS R03ES025904 (PI: Ritz) Period: 07/01/15-06/30/17
Total Direct Costs $100,000
Using records from the California Department of Developmental Services (DDS), we will identify children born 1995-2007 and diagnosed with CP in California until 2010. For ~10,000 CP cases we will randomly select 1:10 matched controls from the California birth certificates. Ambient pesticide exposure estimates pre-pregnancy, during pregnancy and/or first year of life for each child will be estimated using a Geographic Information System (GIS) model we previously developed based on the California Pesticide Use Reporting (PUR) system. We will examine specific vulnerable periods in pregnancy (trimesters or months of pregnancy) to assess pesticide exposure effects on CP.

Autism, Metabolomics, and Environment (AIME)
Agency: NIEHS R21ES25573 (PI: Ritz) Period: 07/01/15-06/30/17
Total Direct Costs $275,000
We will assess whether autism risk factors can be identified using metabolomic biomarkers of exposure in stored maternal serum samples from mid-pregnancy from 200 case and 200 control pregnancies in Central California and compare biomarker exposure patterns with modelled air pollution and pesticide exposures. Metabolomics analyses will be performed in a targeted as well as untargeted manner with high-resolution metabolomics that uses mass spectrometry and advanced data extraction algorithms to quantify up to 20,000 chemicals in small biologic extracts.

Air Pollution and Childhood Autism
Agency: NIEHS R21ES024006 (PI: Ritz/Ehrenstein – multiple PI) Period: 07/01/15-06/30/17
Total Direct Costs $275,000
We use highly sophisticated modeling and analytical techniques for the detailed spatial and temporal assessment of air pollution to examine their influence on neurodevelopment in a California birth cohort linked to autistic disorder records of the CA Department of Developmental Services.

Environment and cognitive decline in older Hispanics
Multi-PI: Ritz/Haan
Agency: NIEHS Type: R01- RES023451A Period: 04/01/15-03/31/19
Total Direct Costs: $ 2,000,000
The goal of the proposed research is to investigate whether long-term exposure to two ubiquitous environmental exposures, air pollution and pesticides, contribute to cognitive decline and dementia in elderly Mexican Americans (MA) from the "Sacramento Area Latino Study on Aging" (SALSA) cohort. We capitalize upon our expertise in modeling air pollution and pesticide exposure and plan to model 1) long and short term regional, local, and traffic related air pollution using monitored criteria pollutants, CALINE4 - emissions and land use regression (LUR) models; and 2) long-term exposures to pesticides of specific chemical classes with our GIS model; and 3) assess impairment in cognitive domains and the onset of dementia longitudinally based on multiple complex environmental exposure patterns while taking into account vulnerability due to genetic and physiologic risk factors for dementia.

Air Pollution and Autism in Denmark
PI: Ritz
Agency: NIEHS Type: R21 Period: 04/01/15-03/31/17
Total Direct Costs: $ 275,000
The goal of the proposed research is to utilize Danish nationwide population-based registers and sophisticated individual-level air pollution exposure measures to assess whether early life exposure to traffic-related and particulate air pollution during critical periods of fetal development are associated with autism risk. We will use the Danish National Birth Cohort (DNBC) which enrolled pregnant women and collected extensive prospective risk factor data during pregnancy and early life for ~100,000 children

among whom 720 are already diagnosed with ASD to examine potential confounding bias for a large number of risk factors assessed in pregnancy.

Air Pollution and Cardiovascular Diseases: Identification of Novel Biomarkers
Agency: NIEHS R21 ES024560 (PI: Zhu) Period: 05/01/15-04/30/17
Total Direct Costs $275,000
Objectives: The goal of this project is to identify novel and sensitive biomarkers of cardiovascular health effects, in association to air pollution exposures.
Role: Co-I

Environmental exposure, DNA methylation, and Parkinson's disease

Agency: NIEHS 21ES024356 (PI: Ritz/ Horvath) Period: 08/06/14 – 07/31/16

Total Direct Costs: $ 250,000

Environmental exposure, DNA methylation, and Parkinson's disease
Here we use a powerful new tool and systems biology analytic methods to identify signatures for toxic exposures that evoke long-term biologic responses. Using DNA methylation we will investigate specific epigenetic markers (CpGs) correlate with toxic exposures and the role these epigenetic changes play in PD progression using epigenome wide technologies combined with analytic tools to integrate these data. We will investigate epigenetic determinants of Parkinson's disease in over 800 subjects with existing biospecimens.
Role: PI

Maternal comorbidities, prescription drug use in pregnancy, and childhood cancer (COMPAC): a record linkage study in Denmark
PI: Heck
Agency: NIH/NCI Type: R21CA175959 Period: 04/01/14-03/31/16
Total Direct Costs: $ 275,000
This study aims to link several large-scale databases in Denmark to examine maternal health and medication use in pregnancy in relation to childhood cancers. We propose to examine common pregnancy conditions that have been linked to cancers in adults and children in other studies as well as common medications taken in pregnancy which are suspected carcinogens or linked to cancer in other studies.
Role: Co-I

Inflammatory Cytokine Polymorphisms, Air Pollution, and Very Preterm Birth
PI: von Ehrenstein
Agency: NIEHS Type: R21ES022734 Period: 07/01/13 - 06/30/15
Total Direct Costs: $ 275,000
We examine the hypotheses that maternal exposure to air pollutants during pregnancy is associated with an increased risk of very preterm birth (VPTB, <32 weeks gestation), and that polymorphisms in inflammatory genes modify the influence of air pollution on the risk of VPTB. We use data from the CA Very Preterm Birth (CVPTB) Study, a nested case-control study of VPTB from 5 counties in Southern CA known for high particulate matter, ozone, and traffic exposures that has genotyped SNPs related to PTB in 26 inflammatory/immune response pathway genes in mother-infant pairs and will utilize a combination of extensive air monitoring data and air pollution modeling approaches (land use regression (LUR), CALINE4, kriging) to estimate air pollution exposures in pregnancy for CVPTB Study subjects.
Role: CO-I

Pesticide Exposure and Childhood Autism
PI: von Ehrenstein
Agency: NIEHS Type: R21ES022389 Period: 01/01/14 - 12/31/15
Total Direct Costs: $ 275,000
We examine the hypothesis that exposure to specific pesticides during vulnerable periods, particularly during fetal development, determines risks of subsequent development of autistic disorder (AD). We developed a geographic pesticide exposure assessment tool (GRAPES) that utilizes the unique California Pesticide Use Report system, in combination with agricultural land-use maps, to derive record-based estimates of historical residential exposures, and expect to identify >20,000 autism cases with diagnoses up to the age of 72

months from the CA-DDS database born in CA 1997-2009 and >1,700 from agricultural areas as well as 1:10 age-sex match controls from birth records, the largest cohort ever to address hypotheses that exposures to specific chemicals (e.g. neurotoxic or endocrine disrupting agents) contribute to AD during vulnerable periods of development.
Role: CO-I

Parkinson's Susceptibility Genes and Pesticides (PEG-Renewal)
Principal Investigator: Ritz
Agency: NIEHS/NINDS Type:R01ES010544 03/01/11-11/30/15
Total Direct Costs: $ 2,500,000
In this renewal of an epidemiologic population-based case-control study we recruit 500 additional PD patients in three rural California counties and will assessed their exposures to pesticide exposures and the effects of gene-pesticide interactions.
Role: PI

Systems genetic and reverse phenotypic analysis of age and retirement.
PI: Horvath (UCLA)
Agency: NIA Type: R01AG042511-02 07/01/13 - 06/30/17
Total Direct Costs: $ 1,000,000
We will apply/develop state of the art computational, statistical, and bioinformatic approaches with which to investigate the association between genetic data and aging- related phenotypes. Specifically, the study uses data from the Health and Retirement Study (HRS) and a systems biology approach to identifying relevant SNPs and genetic pathways and machine learning techniques and reverse phenotyping methods to better understand the complex relationship between genetics and aging outcomes including cognition and wealth.
Role: CO-I

Exposure to C8-chemicals and autism, ADHD, and cerebral Palsy in the Danish Birth Cohort
PI: Jorn Olsen (UCLA and Aarhus University, Denmark)
Agency: Danish Medical Council
Total Direct Costs (at UCLA): $ 250,000 01/01/11 - 08/31/15
The overall goal of the project is to assess the impact of C8 persistent organic pollutants in maternal serum during pregnancy and childhood outcomes of autism, ADHD and cerebral palsy in the Danish Birth cohort using follow-up data from the National Danish medical registry systems.
Role: CO-I

A Cohort Study on Air Pollution and Breast Cancer in Los Angeles County
IIR13262718 Wu (co-PI) 02/13/14-02/150/17
Susan G Komen $217,728
The overall objective is to examine the role of air pollution and risk of breast cancer among whites and non-whites in Los Angeles using the large Multiethnic Cohort Study
Role: Co-Principal Investigator

Improvements in Air Quality and Health Outcomes among California Medicaid Enrollees Due to Goods Movement Actions — Phase I: Assessing Air Quality Changes
PI: Meng , UCLA
Agency: Health Effects Institute (HEI) #: 4914-RFA11-1/2-6 09/01/12 – 08/31/15
This phase of the project will evaluate the effect of goods movement emission reduction actions on ambient air quality in goods movement corridors, non-goods movement corridors, and areas outside of these two corridors in 10 major California counties between the 2003-2007 pre-policy and 2008-2012 post-policy years.

COMPLETED RESEARCH
Assessing and Reducing Taxi Drivers' Exposure to Ultrafine Particles
PI: Yifang Zhu (UCLA) Type: R21OH10196 09/01/12–08/31/14
Agency: CDC/NIOSH
Total Direct Costs: $ 275,000

Goal: The major goals of this project are to develop ultrafine particle exposure assessment instrument and explore novel low-cost ultrafine particle exposure mitigation strategies for taxi drivers.
Role: Co-I

Air Pollution and PD in Denmark
PI: Ritz Type: R21-ES022391 12/01/12-30/11/14
Agency: NIEHS
Total Direct Costs: $ 275,000
This study will use a sophisticated and validated GIS-based dispersion model, AirGIS, to assess exposure to traffic-related air pollution in PASIDA participants; i.e. NO_2/NO_x. Specific aims are to: (1) assess the influence of long-term traffic-related air pollution exposure on PD risk for 1,867 cases and 1,920 population controls combining existing PASIDA data with new exposure measures from AirGIS; and (2) investigate the combined action of air pollution and genetic variants in inflammatory genes previously linked to PD.
Role: PI

Parental Occupation and Childhood Cancers in Denmark
PI: Heck (UCLA) TYPE: R03 ES021643 4/15/12-3/31/14
Agency: NIEHS
Total Direct Costs: $ 50,000
The specific aims of this study are: 1) Create a linked database of all childhood cancers in Denmark diagnosed 1965-2010 with recorded information on parental employment. 2) Examine the relation between parental employment and childhood cancers focusing on maternal occupational exposures. 3) Examine specific hypotheses in childhood cancer risk (occupational social contact; contact with animals; organic dust; welding fumes; bitumen fumes; outdoor work; and several associations seen in previous literature (solvents, paints and pigments, motor vehicle exhaust related occupations)).
Role: Co-I

Pesticides and Childhood Cancers
Principal Investigator: Ritz (UCLA)
NIEHS R21- ES019986 4/1/11 – 12/31/13
Total Direct Costs: $ 275,000
The specific aims of this study are to examine associations between prenatal exposure to pesticides and specific childhood cancers in California between 1980-2009 using ambient measurement data using our GIS model of pesticide exposures based on land use maps and pesticide use report (PUR) data.

UCLA Center for Centers for Neurodegeneration Science (CNS; former CGEP)
Director: Chesselet, UCLA; Co-director: Ritz
NIEHS P01ES016732 09/15/08-08/31/13
Total Direct Costs: $5,000,000
We have previously shown associations between high levels of exposure to specific environmental pesticides and Parkinson's disease and will build on this knowledge to determine the mechanisms of action that may be causing this association. We will use an integrated, multidisciplinary approach to identify additional agricultural pesticides that are disrupting similar molecular pathways, and determine whether these also increase the risk of Parkinson's. This work is expected to shed light on the pathological processes involved in sporadic Parkinson's disease, the most frequent form of the disorder, and could have public health implications for precautions in the use of some pesticides.
Project 4: Pesticides and Genes in PD: Studies in Humans
Principal Investigator: Ritz
NIEHS 09/15/08-08/31/13
Total Direct Costs: $1,250,000
This project will use the existing PEG data to test biological candidate genes and newly identified putative environmental toxicants for association with PD. We will recruit and collect biological (DNA) samples from and construct exposures estimates for 400 additional population controls. This will enable us to test new hypotheses for rarer exposures to specific toxins and will allow us to investigate gene-gene (GxG) and gene-environment (GxE) interactions with sufficient power. Targeted toxins are either (a) interfering with the ubiquitin proteasomal system (UPS), (b) altering microtubule integrity, and/or (c) inhibiting the aldehyde/alcohol dehydrogenase. Targeted genes include UBE1 and UBE1L2; PSMC2, 3, 4, and 5; HIP2; SKP1A; GSK3B; CDK5; MAPT, Sirt2, and ALDH and ADH gene clusters.

Registry of Parkinson's Disease Study In Denmark (PASIDA)
Principal Investigator: Ritz
NIEHS RO1 - ES013717 09/01/06-08/31/13
Total Direct Costs: $5,600,000
We conduct 1) a case-control study of ~13,000 PD cases and age-gender matched controls from the Danish population via passive record linkage by unique ID between the National Patient Register, Pharmacy Database, and National Pension fund to identify risk factor information contained in these records (e.g. occupations, medication use, diseases prior to PD onset); and 2) recruit actively ~2500 of the most recently registered PD patients and population controls to collect additional risk factor information per interview and biological materials for gene-environment interaction analyses and to characterize PD patients phenotypically.

Air Pollution and Childhood Cancers
Principal Investigator: Heck (UCLA)
NIEHS R21- ES018960 4/1/10 – 12/31/13
Total Direct Costs: $250,000
The specific aims of this study are to examine associations between prenatal exposure to motor vehicle related air pollution toxics and specific childhood cancers in Los Angeles County and all of California between 1980-2009 using ambient measurement data, land use based regression (LUR) and CALINE4 models.

California Parkinson's Disease Registry Pilot Feasibility Study
Principal Investigator: Ritz
DOD 09/01/07-04/30/12
Total Direct Costs: $390,000
The primary goal is to conduct a pilot study for the legally mandated statewide population-based PD registry. We will identify PD cases in Kern, Tulare and Fresno counties from legally mandated sources (pharmacists, health care institutions, physicians and other providers). A secure prototype database will be established, and associations between PD and toxicant chemical exposure will be determined by linking to a database of toxicant chemicals established previously by UCLA based on California state data (e.g. the pesticide use databases).

UCLA UDALL Parkinson's Disease center
Principal Investigator: Chesselet, UCLA
NINDS Type: P50 NS38367 04/01/06-03/31/12
Total Direct Costs: $7,500,000
Project 6 within the center (budget of $ 500,000 annual direct costs): Progression and Health Impacts of PD Motor and Non-Motor Manifestations (C-PI Ritz)
Research goals are to assess whether development and progression of PD motor and non-motor manifestations in 300 PD patients ascertained in the PEG study (PI: Ritz see below) are influenced by environmental, behavioral, and social factors and by genetic variants of ApoE and serotonin transporter alleles; and to determine the relative contributions of progression of motor and non-motor manifestations of PD to changes in HRQOL over time.

Sunlight exposure and variations in vitamin D metabolic genes in Parkinson's disease
Principal Investigator: Ritz
NIEHS R03- ES017139 09/01/09-08/31/11
Total Direct Costs: $100,000
The goal of the proposed research based on the PEG study population is to examine the hypothesis that long-term low levels of vitamin D either through inadequate sunlight exposure or alterations in metabolic genes that influence physiological vitamin D levels increase the risk of PD. We will test associations between long-term UV exposure measures and PD and examine whether genetic alterations presumed to result in different physiological vitamin D activity in genes critical to the vitamin D pathway (VDR, CYP27B1 and CYP24A1) increase the risk of PD.

Traffic-Related Air Pollution and Ultrasound Measures of Fetal Growth
Principal Investigator: Wilhelm Turner (UCLA)

NIEHS R03- ES017314 04/01/09-03/31/11
Total Direct Costs: $100,000
The specific aims of this study are to estimate prenatal exposures to O3 and PM10 and pollutants originating from traffic (NOx) using CALINE4 air dispersion modeling and examine associations with fetal size throughout pregnancy using ultrasound measures to examine associations with weight, length, head circumference, fetal growth ratio, ponderal index, and cephalization index at birth.

Ambient Air Toxics and Adverse Birth Outcomes
Principal Investigator: Wilhelm Turner (UCLA)
NIEHS R03 ES017119-01 12/15/08 – 12/30/10
Total Direct Costs: $100,000
The specific aims of this study are to: (1) examine associations between prenatal exposure to motor vehicle air toxics and low birth weight (LBW) and preterm birth in women residing in Los Angeles County, California between 1994-2006 using both ambient measurement data and land use based regression (LUR) models; and (2) gain information about how LUR models built on NOx measurements reflect exposures to specific toxins thought to have biological relevance for these outcomes.

Exposure to mobile source air pollution and adverse birth outcomes in the Los Angeles Air Basin
Principal Investigator : Jun Wu (UCI)
NIEHS R21 ES016379 9/11/08 -12/31/10
Total Direct Costs: $250,000
The overall goal of the project is to improve exposure assessment of air pollution exposure in pregnant women and investigate the impact of air pollution exposure on adverse reproductive outcomes, such as preterm birth, low birth weight, and intrauterine growth retardation.

Disparity in asthma among Californians from pollutant exposures.
Principal Investigator: Meng, UCLA
California Air Resources Board 04/22/08- 12/31/10
Direct Costs: $270,000
The goal of the research is to conduct a population-based study to examine the effects of long-term air pollution exposure near residence on chronic severe asthma and asthma-like symptoms in vulnerable populations.

Development of Exposure and Health Outcome Indicators for Those with Asthma or Other Respiratory Problems
Principal Investigator: Meng, UCLA
EPA- R833629 09/01/07-12/31/10
Direct Costs: $410,000
The goal of this research is to investigate the feasibility of combining existing environmental monitoring and health survey data to develop indicators that signal trends in exposures and health for those with asthma or other respiratory problems

Neighborhood Effects on Children's Health & Access to Care
Principal Investigator: A. Pebley, UCLA
HRSA 09/01/07- 8/31/10
Total Direct Costs: $500,000
The goal of this study is to significantly advance our knowledge about the relative importance of specific family and neighborhood characteristics in the development of major child health problems. This project is based on the Los Angeles Family and Neighborhood Survey (L.A.FANS), a longitudinal study of neighborhoods, families, adults, and children in Los Angeles County

Traffic-Related Air Pollution and Asthma in Economically Disadvantaged and High Traffic Density Neighborhoods in Los Angeles County, California (with LA F.A.N.S.)
Principal Investigator: Ritz
California Air Resources Board 01/06/05-09/30/09
Total Direct Costs: $420,000
The objectives of this research are: (1) to conduct NO_x and NO_2 monitoring at 200 locations within LA County neighborhoods with varying levels of economic disadvantage and varying exposures to air

pollution originating from vehicular sources; (2) to use these monitoring data to help inform land use-based regression (LUR) models developed to predict traffic pollutant exposures; (3) to use geostatistical models to estimate regional background concentrations of O_3 and $PM_{2.5}$; (4) to evaluate associations between exposure to NO_x, NO and NO_2 and measures of lung function and asthma prevalence, exacerbation and possibly incidence in children ages 0-17 years in conjunction with the Los Angeles Family and Neighborhood Survey (L.A. FANS) study; and (5) to evaluate whether concentrations of the more regionally distributed background pollutants (O_3 and $PM_{2.5}$) confound or modify the effects of exposure to the more heterogeneously distributed traffic-related pollutants (NO_x, NO and NO_2) on lung function and asthma.

Aggregate Exposure Assessment: Longitudinal Surveys of Human Exposure-Related Behavior
Principal Investigator: Irva Hertz-Picciotto, UC Davis
EPA 01/12/04-11/30/09
Direct Direct Costs: $388,111
This project develops data collection platforms for longitudinal assessment of exposure-related behavior. The data characterize short-term, seasonal, and long-term changes in time-activities, food consumption habits, and use of household and personal care products. We assess exposure-related behaviors at multiple collection points over time, and evaluate a number of data collection methods for validity (accuracy), precision, completion rates, cost, feasibility, and user acceptability.

UCLA Center for Gene-Environment Studies in Parkinson's Disease (CGEP-part of the NIEHS CCPDER)
Director: Chesselet, UCLA; Co-director: Ritz
NIEHS 09/01/02-08/31/09
Total Direct Costs: $7,000,000
The overall objective of this Center is to understand how the detrimental effects of pesticides, a suspected environmental risk factor for Parkinson's disease, are modulated by genetic variations that impact dopamine homeostasis in nigrostriatal neurons. The center integrates 3 RO1 research projects that investigate these questions in fly, mouse, cell culture models and applies the results also to human genetics (project 1: PI Ritz)
Research Project I within the CGEP center "Environmental toxins and genes that influence dopamine in Drosophila and humans"
Principal Investigator: Ritz
NIEHS 09/01/02-08/31/09
Total Direct Costs: $1,000,000
This project examines interindividual variability of dopamine vesicular transporter (VMAT) expression due to promoter variants in two human populations in parallel with a reporter gene assay. These populations will be genotyped for functional VMAT2 variants and association analyses of gene-environment interactions and pesticide exposures collected in the parent grant will be conducted. In addition, Drosophila genetics will be used to determine how the expression of VMAT affects dopamine-mediated toxicity and identify genes that modulate VMAT function, which will then be examined in the human population for their relevance to increase risk of PD.

Parkinson's Susceptibility Genes and Pesticides (PEG)
Principal Investigator: Ritz
NIEHS/NINDS 10/01/00-09/30/07
Total Direct Cost: $2,653,852
We are testing the gene-environment interaction hypothesis for Parkinson's disease by conducting an epidemiologic population-based case-control study of 400 newly diagnosed PD patients from three rural California counties matched to population controls; in addition we are collecting data for unaffected sibling controls. Environmental and occupational pesticide exposure estimate are derived from California pesticide-use reporting (PUR) and other data. We are examining the effects of gene-environment interactions by testing for associations of PD using multiallelic repeat markers and genotyping intragenic single nucleotide polymorphisms (SNPs) and/or deletions in 50 candidate genes.

PD Consortium: Genetic and Environmental Factors in Parkinson's Disease
Principal Investigator: L. Nelson, Stanford
MJ Fox Foundation 10/01/04-09/30/07

Total Direct Costs $50,000
We established the Consortium for the Study of Genetic and Environmental Factors in Parkinson's disease, with the goal of organizing the collaborative efforts of five investigative groups that have who have conducted (or are conducting) seven case-control studies of PD. For approximately 1700 PD cases and 2100 gender- and age-matched control subjects, we investigate how the risk of developing PD varies according to tobacco and caffeine intake, as well as variants in ten candidate genes that code for proteins that may be involved in conferring the protective effect of these agents.

Alpha Synuclein and Environmental Exposures: A Study in Humans
Principal Investigator: Langston, The Parkinson's Institute
MJ Fox Foundation 01/01/05-12/31/07
Total Direct Costs $100,000
We are investigating the joint effects of: (1) consequences of alpha-synuclein over-production and enhanced mapping of the SNCA promoter region and (2) the biologic effects specific toxicants (e.g., rotenone, paraquat, organochlorine pesticides). We take advantage of two unique cohorts at high risk for pesticide exposure currently evaluated by members of the NIEHS-funded Collaborative Centers for Parkinson's Disease Environmental Research (CCPDER) at the Parkinson's Institute (PI) and UCLA, the Agricultural Health Study cohort and a population-based study of PD and pesticide exposure in rural Central California (the PEG study).

Prostate Cancer and Pesticide Exposure in Diverse Populations in California's Central Valley
Principal Investigator: Cockburn, USC
DOD 05/01/06-12/31/07
Total Direct Costs: 250,000$
This is a pilot study bringing an innovative collaborative approach to prostate cancer research. Specifically, this study will apply novel methods of pesticide exposure assessment using Geographical Information Systems (GIS), examine whether our proposed method of recruiting and approaching cases and controls for a large population-based case-control study will result in acceptable response rates, or whether our sample will be biased with respect to socioeconomic status, race, and disease characteristics, and whether we will be able to obtain sufficient DNA from mailed (Oragene) spit collection kits to assess effect modification by known relevant genes, and have sufficient stored DNA to assess the impact of genes that may be discovered in future.

Traffic-related Air Pollution and Adverse Birth Outcomes
Principal Investigator: Ritz
NIEHS 07/15/01-06/14/07
Total Direct Costs: $641,612
The objectives of this project are to determine whether exposures to elevated and traffic-related ambient air pollution during pregnancy result in low birth weight, preterm birth, intrauterine and postneonatal mortality, or cardiac defects in infants born to women living in the South Coast Air Basin (SoCAB). We performed a cohort study of all births (between 1995 and 1999), fetal and infant deaths (between 1989 and 1997), and conducted a nested case-control study of 2600 women who delivered children in LA in 2003 to collect additional exposure, confounder, and effects modifier data.

Ergonomic Interventions for Sewing Machine Operators
Principal Investigator: Ritz
CDC/NIOSH 10/01/02-09/31/06
Total Direct Costs: $868,262
We are conducting a randomized trial of a newly developed ergonomic intervention in sewing machine operators working in LA garment shops. The ergonomic intervention package includes changes in work-station design, training of employees, and suggestions of improvement in work procedures. We are examining whether interventions can reduce rates of upper extremity, neck (and lower back) musculoskeletal disorders, severity of pain and impairment, and lost-time compared to 'placebo' (control) interventions. This study will provide employers, employees and public agencies with evidence of the effectiveness of ergonomic interventions in order to guide health and safety policy.

Traffic-Related Air Pollution and Acute Respiratory Diseases and Asthma in Children Ages 0-5 in the SoCAB From 1990-2000

Principal Investigator: Ritz
California Air Resources Board 01/06/04-09/30/05
Total Direct Costs: $55,000
The aims of this study are to estimate the transient effects of traffic related and background air pollution in the South Coast Air Basin (SoCab) on the risk for hospitalization for acute respiratory illness and asthma in children ages 0-5 using a case- crossover study design and a time-series analysis.

Assessment of In-Traffic Exposures and Human Reproductive Health
Pilot project Principal Investigator: Ritz; SCEHSC Center Principal Investigator: Froines, UCLA
EPA 07/01/04-06/30/05
Total Direct Costs Pilot Project within the PM-center: $28,000
The goal of this project is to evaluate whether maternal in-vehicle air pollutant exposures during commutes (either in passenger cases, buses or other means of public transportation) affected the risk of low birth weight (LBW) and preterm birth in infants born to women living in Los Angeles County, California between 2003-2004. Commuting behavior (travel time, mileage and/or modeled routes) will be used to evaluate exposure to motor vehicle exhaust pollutants while in-transit

Molecular Epidemiology and Gene-Environment Interaction
Principal Investigator: Zhang, UCLA
NIH/NIEHS R21 ES 011667 04/01/02-03/31/05
Total Direct Costs: $450,000
This was a planning grant for molecular epidemiology in Environmental genome. The award was to establish a molecular epidemiology research program focusing on environmental genome.

Uncontrolled Asthma and Exposure to Air Pollutants: Linking Chronic Disease and Environmental Data Sources
Principal Investigator: Meng, UCLA
CDC/NIOSH/ 10/01/02-09/01/05
Total Direct Costs: $600,000
Based on the California Health Interview Survey (CHIS 2001) data, an extensive air monitoring network, and detailed information on traffic density we are conducting a population-based epidemiologic case-control study to: (1) ascertain the relationship between control of asthma and exposure to air pollutants in Los Angeles County and San Diego County, California; and (2) build and enhance the partnerships between public health and environmental agencies and local communities.

Center of Excellence for Environmental Public Health Tracking
Principal Investigator: Balmes, UCSF
CDC/ATSDR 10/01/02-09/01/05
Total Direct Costs (UCLA only): $300,000
The UCLA part of this center grant uses the data from 5,200 California Health Interview Survey (CHIS 2001) respondents who reported having been diagnosed with asthma at some point in their lives and live in the Greater Bay Area, San Joaquin Valley, and Los Angeles County. Criteria pollutant averages are employed as measures of background ambient air quality and linked with sociodemographic information and data on asthma management, access to care, and risk behaviors collected through CHIS for each targeted respondent.

Community Response to Maternal/Child Heath Disparities
Principal Investigator: Hobel, Cedars Sinai
NIH 04/1/03-9/30/05
The major goals of this study are to examine the interrelating biological and social-behavioral factors that contribute to health disparities in pregnancy outcomes and infant and early childhood mortality and morbidity. We will participate as one of five selected sites in the nation to plan for a multi-centered, community-based study examining the relationship between environmental factors and child health disparities.

Extension of the Rocketdyne/Al Worker Cohort Through 1999
Principal Investigator: Ritz
California Cancer Research Program 07/01/00-06/30/04

CRP award #00-00781V-20218
Total Direct Cost: $324,508
We extended the mortality follow-up of two previously established cohorts of workers employed at Rocketdyne/Atomics International (now Boeing North American) facility for an additional 5 years and added a cancer incidence component for the period 1972-1998. This study allowed evaluating the impact of radiation and some known animal carcinogens on cancer mortality and morbidity.

Assessment Scale for End-of-Life Care in End-Stage Dementia
Principal Investigator: Ackerman, UCLA
Alzheimer's Association 10/01/00-09/30/03
Total Direct Costs: $217,583
This pilot project developed a scale to assess end-of-life care for end-stage dementia patients and evaluated its performance using mortality data.

Pilot grant from Southern California Center for Airborne Particulate Matter (SCCAPM)
Principal Investigator: Froines, UCLA; Pilot grant Principal Investigator: Ritz
U.S.-EPA-Star grant 07/01/01-12/31/02
Total Direct Cost: $12,000
The pilot grant supported exposure assessment for an epidemiologic study of traffic related adverse birth outcomes.

Evaluation and Validation of Pesticide Use Reporting in California
Principal Investigator: Ritz
UC Toxic Substances Research & Teaching Program 07/01/99-06/30/01
Total Direct Costs: $ 50,000
The goal of this pilot grant was to use biomarker data to evaluate the validity of pesticide exposures estimates derived from geographic models of environmental exposure based on pesticide use reports and land use maps in California residents.

Identify and Reduce Work Hazards in Home Health Care Workers
Principal Investigator: Ritz
Institute of Labor and Employment Pilot Study 02/01/01-30/08/01
Total Direct Costs: $ 7,500
This pilot project developed and tested a survey instrument and collected preliminary data for a study of job hazards in 74,000 home health care workers in LA county.

Pilot Study for Gene-Environment Interaction and Parkinson's Disease Study
Principal Investigator: Ritz
APDA Center Pilot Grant 03/01/99-12/31/00
Total Direct Costs: $35,000
This pilot project involved establishing data resources to improve exposure measures for pesticides, and setting up of a county-wide networks to reach incident Parkinson's cases in rural California.

Development of a Temporary Parkinson's Disease Registry for Southern California
Principal Investigator: Ritz
APDA/Pilot Grant from the PD-center at UCLA 03/01/99-12/31/00
Total Direct Costs: $10,000
This pilot project established mechanisms to obtain incident Parkinson's cases in rural California using information provided by local health care providers, Parkinson's disease foundations, clinics, and Medicare, and to determine which data sources exist for the application of capture-recapture methods to validate coverage of a future PD registry.

Modeling Air Pollution and Birth Defects
Principal Investigator: Ritz
CBDMP Grant/SCEHS/NIEHS Pilot Grant 07/01/00-09/30/00
Total Direct Costs: $5,600
The objective of this project was to examine the usefulness of some advanced statistical modeling procedures in order to determine whether exposures to elevated levels of ambient air pollutants (PM10,

CO) at the levels found in the South Coast Air basin (SoCAB) basin caused defects of the cardiac system of fetuses.

Pesticide Exposure Modeling Based on Historical Use Reporting in California to Investigate Long-Term Health Effects
Principal Investigator: Ritz
UCLA-USC NIEHS-Center Pilot Grant 05/01/99-04/30/00
Total Direct Costs: $18,000
The objectives of this pilot grant were to develop a geographic model for pesticide exposure of California residents between 1950 and 1990 using satellite images of crops, aerial photographs, and Pesticide Use Reporting Data from the California Department of Pesticide Regulations.

Epidemiologic Study to Determine Possible Adverse Health Effects on Rockwell/Rocketdyne Workers from Exposure to Radioactive and Hazardous Substances
Principal Investigator: Morgenstern, UCLA
CPHF/DOE/DE-FG-03-91SF18983 01/10/93-03/31/99
Total Direct Costs: $740,000
The major goal of this study was to test the hypothesis whether exposure to toxic chemicals and ionizing radiation among Rockwell/Rocketdyne workers caused an excess of cancer mortality.

Hazard Surveillance in the Defense Nuclear Industry
Principal Investigator: Froines, UCLA
CDC/NIOSH/R01-CCR912034 09/01/95-08/31/99
Total Direct Costs: $1,244,745
The major goals of this project were to develop an integrated theory, approach, and methodology to exposure assessment and hazard surveillance in the U.S. defense nuclear industry.

The Influence of Air Pollution in the Los Angeles Metropolitan Area on the Occurrence of Birth Defects, 1990-1993
Principal Investigator: Ritz
SCEHSC/NIEHS/UCLA-USC NIEHS-Center Pilot Grant 09/01/97-09/30/98
Total Direct Costs: $24,000
The objective of this pilot project were to examine whether the exposure of pregnant women to elevated levels of ambient air pollutants (Ozone, NO2, PM10, CO) at the levels found in the Los Angeles Metropolitan Area or the South Coast Air basin (SoCAB) basin cause low birth weight or preterm birth.

RESEARCH CONDUCTED IN GERMANY (1984-1989)
Health effects of airborne-dioxin exposure in Hamburg nursery schools
Rheumatic disorders, working conditions and coping behaviors in female office workers
Work-related knee-joint and elbow injuries in pipe-fitters and welders
Back and neck pain, psycho-social and ergonomic stresses in nursing professions

HONORS AND AWARDS

1999	UCLA Faculty Career Development Award
1999	'Rothman' award presented at SER by C. Poole
1989-1992	Post-doctoral fellowship received from DAAD ("German Academic Exchange Office of the Ministry of Research and Technology")
2001	Delta-Omega Award
2007	Robert M. Zweig M.D. Memorial Award (Clean Air Award) from the South Coast Air Quality Management District (AQMD)
2009	Award from the American Parkinson's Disease Association for outstanding contributions to the medical and scientific communities and for my work towards the advancement of Parkinson's disease research

TEACHING

UCLA, School of Public Health, graduate courses, 1995-present
Epidemiology Methods (Core methods course (200B) in the UCLA Epidemiology program)
Environmental Epidemiology
Occupational Epidemiology
Advanced Methods in Occupational and Environmental Epidemiology
Seminar: Occupational and Environmental Cancers
Seminar: Policy Issues in Occupational and Environmental Health

University of Hamburg, Medical School, 1984-89
Lectures and seminars in Medical Sociology for medical students
Lectures and seminars in Psychiatry for medical students

ADVISING AND MENTORING OF DOCTORAL STUDENTS (PH.D) AND POSTDOCTORAL FELLOWS (SUBJECT OF DISSERTATION OR FELLOWSHIP)– *note: this list only includes primary advisees (i.e. chair of committee and not member of dissertation committee) and does not include master level students*
At UCLA:

1997 - 2001	Kurt Straif (Cancer mortality in the German rubber industry)
1998 - 2000	Timothy Clary (Pancreatic cancer mortality and pesticide use in California)
1998 - 2004	Michelle Wilhelm (Traffic-related air pollution and pregnancy related health effects)
1998 - 2004	Rudy Rull (GIS modeling of pesticide exposure and neural tube defects)
1998 - 2004	Anusha Krishnadsan (Occupational physical activity and prostate cancer incidence)
2001 - 2004	Yingxu Zhao (Work place exposures to chemicals and cancer incidence)
2003 - 2004	Gail Asleson Kang (*Movement Disorder Fellow*: Clinical characteristics of PD patients)
2002 - 2006	Pin-Chieh Jason Wang (Ergonomic interventions and health effects in LA garment workers)
2003 - 2006	Chad Lewis (TTHM contamination in drinking water and adverse birth outcomes)
2003 - 2005	Kathrine Hoggatt (co-mentored with Dr Greenland: Air pollution and adverse birth outcomes)
2004 - 2008	Angelika Wahner (Doctoral student & postdoctoral fellow: Parkinson's disease, genetic factors and anti-inflammatory drug use)
2004 - 2008	Marie Sharp (The Latina Paradox in Birth Outcomes)
2004 - 2008	Sadie Costello (Parkinson's disease and life style factors)
2005 - 2008	Shannon Rhodes (Doctoral student & postdoctoral fellow: Iron genetics and Parkinson's disease)
2008 - 2010	Nicole Gatto (Postdoctoral fellow: Vitamin D, sunlight and Parkinson's disease)
2004 - 2008	Amanda Colligan (Residential pesticide exposure and Parkinson's disease)
2005 - 2012	Anthony Wang (Occupational pesticide exposures and Parkinson's disease)
2007- 2011	JoKay Ghosh (Air toxics and adverse birth outcomes)
2008- 2013	Tracy Becerra (Autism and race ethnicity in Los Angeles)
2008- 2013	Erin Jacob-Marcotte (Pesticides in pregnancy and childhood cancers)
2011-2012	Anshu Shresta; post-doctoral fellow (Childhood cancers and the environment)
2011-2013	Pei Chen Lee; postdoctoral fellow (Air pollution and pregnancy biomarkers)
2009-2014	Shilpa Narayan (Progression in Parkinson's disease)
2009-2014	Christina Lombardi (Air pollution and childhood cancers)
2011-2014	Zeyan Liew: PFOA exposures in the Danish birth cohort and ADHD and autism)
2012 -present	Gretchen Bandoli (Stress, asthma and birth outcomes in LA)
2012 -present	Kristina Vanderwaal Hool (breast cancer and methylation patterns)
2011- present	Kim Paul (Gene-environment interactions in Parkinson's – PASIDA study)
2011- present	Xin Cui (Bias analysis in the PASIDA study of Parkinsons)
2011- present	Andrew Park (Pesticides and childhood cancers)
2012- present	Vivian Alonso (Nutrition, vitamins use and reproductive health)
2013- present	Yu-Hsuan Chuang (Parkinsons, gene methylation, and gene-environment interactions)
2013- present	Xiaoqing Xu (Pharmaceuticals and childhood cancers in Denmark)
2013- present	Matt Feaster (Occupations risk factors for childhood cancers)
2013- present	I-Fan Shih (Parkinsons and physical activity)
2013- present	Negar Omid (Childhood cancer risk factors)

2013- present Aline Duarte (Parkinson's non-motor symptoms)
2013- present Chenxiao Ling (Bias analysis in environmental epidemiology)
2014- present Cynthia Kuster (Parkinsons' and estrogen receptors)
2014- present Zuelma Esquivel (Childhood cancer risk factors)

At University of Washington:

2004-2006 Kathrine Carr (*Postdoctoral Fellow*: Bronchiolitis and air pollution in LA infants)

At UCI:

2011-2013 Jun Wu (junior faculty mentor for W. Rosenblith award given by HEI)

At the University of Copenhagen, Denmark:

2008-present Line Kenborg (Parkinson's disease and outdoors work and sunlight exposures)
2007-2009 Kathrine Rugbjerg (Parkinson's disease and head trauma and auto-immune diseases)

University of Umea/Sweden

2014 Opponent for doctoral student David Olsson (Air pollution and PTB and preeclampsia in Stockholm)

PARTICIPATION IN GRANT AND CENTER REVIEWS

Reviewer on a NCI Special Emphasis Panel "Improving Exposure Assessment in Environmental and Occupational Epidemiology of Cancer", May 2001
Reviewer of the NIEHS-funded Columbia University Environmental Health Sciences Center, May 2002
Reviewer of the Charles Harkin Award Application for Research in Thyroid Cancer, NIH, April 2003
Reviewer of the Wellcome Trust Application "Pre and post-natal exposure to particulate matter and pregnancy and infant outcomes: an historical cohort study", 2003
Reviewer of the Health Effects Institute's (HEI) Walter Rosenblith New Investigator Award application, April 2003
Reviewer of pilot grants for the Southern California NIEHS center grant (2004 and 2005)
Reviewer of pilot grants for the UCLA-CCPDER center (NIEHS funded) (2003 and 2005 and 2008)
Reviewer for NCI, Epidemiology of Cancer (2004/05 Council EPIC)
Reviewer for several NIH, Department of Health & Human Services meeting applications, 2003-2005
Reviewer (Chair of Review Committee) for a NIEHS-PO1 application (2004)
Appointment to Review Committee of the European Science Foundation (ESF) (2005)
Annual Review of SCEHSC Pilot Project Submission (permanent member 2004-current)
Institutional Patient-Oriented Career Development Programs in the Environmental Health Sciences [K12] (ES06-005). (2007)
Conference grant applications (2004-2007)
NIH reviewer for Outstanding New Environmental Scientist (ONES) award in the Environmental Health Sciences (2006)
Member of the EPA's Clean Air Scientific Advisory Committee (CASAC) Carbon Monoxide (CO) Review Panel (2008-current)
Grant review for an internal NIEHS scientist's application (Dr. Chen) (2007 and 2008)
Grant review for NIEHS special emphasis panels 2009-2010
Grant review for NIH-BCHI 2011
Pilot grant review for the Northern California Center for the National Children's Study –Pilot Projects Program August 2011
External Review of the Neurology Department at Columbia (NY), 2011
Scientific Review of Superfund Site Projects as EAC member for University of Washington, 2012
External Review of the Swiss Tropical and Public Health Institute (TPH), 2012 and 2013
External Review of the Epidemiology Branch at NIEHS, 2013
Review for Harvard NIEHS center pilot grant, 2014
Review of applications for Health Effects Institute (HEI Boston), Rosenblith awardees, 2014
Review for Mount Sinai (NY) NIEHS center pilot grants, 2014
Review for NIEHS USC-UCLAEnvironmental Health Science center pilot grants, 2014
Review of NIEHS conference grants July 2015
Review of Parkinson's disease grant for Parkinson's UK foundation in Great Britain

JOURNAL REVIEWER FOR:

American Journal of Epidemiology
Epidemiology
International Journal of Epidemiology
Annals of Epidemiology

Environmental Health Perspectives
Environmental Health
Occupational and Environmental Medicine
Archives of Neurology
Annals of Neurology
Neurology
Movement Disorders
Pediatrics
JAMA
Lancet
Parkinson's and Related Disorders
Pharmacogenetics and Genomics
Journal of the Air & Waste Management Association
Journal of Exposure Analysis and Environmental Epidemiology
Chemosphere
Zeitschrift Sozial- und Präventivmedizin (SPM)
Human Reproduction
Women & Health
Etc.

INVITED SEMINARS AND LECTURES (SELECTED)

1. The Health Effects of Low-level Ionizing Radiation, USC, Health Sciences 1996
2. Work Environment and Health, UCLA Health Sciences 1996
3. The Effects of Carbon Monoxide Exposure on Low Birth Weight in the LA Metropolitan Area, 1989-1993, USC, Southern California Environmental Health Sciences, 1997
4. Cancer Mortality in Radiation Workers, USC Southern California Environmental Health Sciences, 1997.
5. Basic Principles of Reproductive Epidemiology, European School of Risk Assessment in Reproduction" in Florence/Italy December, 1997.
6. The Rocketdyne/Al Worker Health Study: Results and Lesson's Learned, California Department of Health Services, Occupational Health Branch, 1998
7. Air Pollution and Low Birth Weight in Southern California, GSF Munich Germany, 1998.
8. Air Pollution and Adverse Birth Outcomes: Methodological Issues and First Results, Southern California Environmental Health Science Center, USC, 1998.
9. Gene-Environment Interaction and Parkinson's Disease, Neurology Grand Rounds, UCLA 1998
10. Air Pollution and Adverse Birth Outcomes in Southern California, Dept. of Reproductive Epidemiology, University of Michigan, East Lansing, 1999.
11. Methodologic Issues in Studying of Gene-Environment Interaction, GSF Munich Germany, 1999
12. Methodologic Aspects of Studying Cancer Mortality in Radiation Workers, Dept. of Epidemiology, University of Michigan, East Lansing, 2000.
13. Cancer Mortality in Fernald Uranium Workers, NIOSH, Cincinnatti, 2000.
14. GIS Modeling of Pesticide Exposures in California, Dept. Environmental Epidemiology, GSF Munich Germany, 2000
15. Traffic-related Air Pollution and Adverse Birth Outcomes in Southern California, Dept. Environmental Epidemiology, GSF Munich Germany, 2000
16. Studying Parkinson's disease in Populations; American Parkinson's Disease Association conference for patients and care providers at UCLA, 2001
17. From the Epidemiology of Parkinson's Disease to Gene-Environment Interactions, VA-PD conference, Woodland Hills, 2001
18. GIS Modeling of Air Pollution and Pesticide Exposures in California, USC-UCLA NIEHS Town hall meeting; Dec, 2001
19. GIS Modeling in the context of a Gene-Environment Interaction study of Parkinson's disease, Dept. Environmental Epidemiology, GSF Munich Germany, 2001
20. The Epidemiology of Parkinson's Disease, Conference of the Society for Research on Amyotrophic Lateral Sclerosis, Colorado May 2002
21. Traffic-related Air Pollution and Reproductive Health Effects: An Overview; Environmental Health Sciences seminar at UC Riverside, Feb. 2002
22. Reproductive Health Effects due to Carbon Monoxide Air Pollution in Southern California, NRC

Subcommittee on Health Effects from CO pollution meeting at UC Irvine, April 2002
23. Traffic-related Air Pollution and GIS Modeling in Southern California, USC-GIS Workshop Pasadena, May 2002
24. Health Effects Modeling with GIS, USC-GIS Workshop Public Forum at USC, May 2002
25. Dopamine Imbalance and Oxidative Stress in Parkinson's Disease, VA Research Conference on PD and Movement Disorders, Los Angeles 2002
26. The Center for Gene Environment Interaction in Parkinson's disease (CGEP) at UCLA: Dopamine Imbalance in Parkinson's Disease, Inaugural NIEHS Conference at the Parkinson's Institute in Sunnyvale CA, August 2002
27. Air pollution effects on birth outcomes: An overview. Health Effects Institute, Annual conference held at Georgetown University; 2003
28. Linking air pollution effects and adverse birth outcomes in the Los Angeles basin throughout the 1990s. U.S. EPA, Chapel Hill, NC; 2003
29. Air Pollution and Adverse Birth Outcomes in the South Coast Air Basin, 1989-2000; Conference of the Czech NAS meeting on air pollution effects (Dr. Sram), Prague, 2003.
30. Air pollution and adverse birth outcomes, an update on recent developments. Department of Preventive Medicine at the University of Southern California, 2003
31. GIS modeling of environmental exposures: applications to air pollution and pesticide exposures. Department of Environmental Health, Harvard, 2004
32. Air pollution models of adverse birth outcomes. Department of Epidemiology at the University of North Carolina, 2004
33. Parkinson's disease, metals and pesticides. Department of Toxicology, Symposium on Toxics Risks and Aging, Duke 2005
34. Air pollution and adverse birth outcome research in the SoCAB from 1995-2005. California Air Resources Board, Sacramento, Sept 2005
35. Parkinson's disease and pesticide exposure assessment in farming communities in the California Central Valley. Symposium of the Ramazzini Conference, Bologna, Italy Sept. 2005
36. Parkinson's disease and aging. UCLA Center on Aging Research Conference on Aging 2006.
37. Air Pollution and Asthma in Children. AQMD Asthma Impacts of Air Pollution Conference Los Angeles, Feb. 2006
38. Parkinson's disease and pesticides in the Central California Valley. NIEHS center at Columbia University, NY 2007
39. Assessing pesticides exposures for prostate cancers in the Central California Valley. IARC, Lyon 2007
40. Air pollution and adverse birth outcomes in LA. INSERM, Paris 2007
41. Gene Environment Interactions in Parkinson's disease. CREAL Institute, Barcelona 2008
42. Latest results on Gene Environment Interactions in Parkinson's disease. INSERM, Paris 2008
43. Re-assessing Gene Environment Interactions in Parkinson's disease. MDS conference symposium, Chicago 2008
44. Methodological Issues in studying risk factor for Parkinson's disease in populations. MDS conference symposium, Chicago 2008.
45. Environmental and occupational health studies in California. University of Dublin 2008
46. Air pollution, pregnancy and child health; Healthy Development and Ageing Workshop; British Foreign & Commonwealth Office, LA 2009
47. Air pollution, pregnancy and child health; Physician's for Social Responsibility Environmental training 2009
48. Air pollution and adverse pregnancy outcomes in LA; Annenberg School of Journalism 2009
49. Parkinson's disease and pesticides. George Washington University Environmental Health Program 2009
50. LUR model for traffic related exposures and adverse birth outcomes in LA. Helmholtz Center Munich 2010
51. Parkinson's disease and gene–pesticide interactions. Symposium on Predictive Health, Human Health: Molecules to Mankind. Emory University Atlanta Dec 2010
52. Air Pollution and Adverse Birth Outcomes, invited speaker at HEI annual conference Boston 2011
53. Parkinson's disease in Denmark; the PASIDA study; University of Odense Denmark, May 2011
54. Gene-environment interactions in Parkinson's disease, invited symposium speaker at the International Society for Environmental Epidemiology (ISEE), Barcelona 2011
55. Air Pollution and the Brain; invited plenary speaker at the annual conference of the International Society for Environmental Epidemiology (ISEE), South Carolina 2012

56. Air Pollution and Autism; invited speaker at the University of Aarhus, Denmark 2012
57. Air Pollution, Children and Women's Health in LA; invited speaker at the SCAMQD conference for stakeholders, LA 2013
58. How to be an Epidemiologist, invited speaker at SER, Boston 2013
59. Pesticides and Neurodegeneration; invited speaker at the Conference on safety of fumigated container shipping in Berlin, Germany 2014
60. History of Environmental and Occupational Epidemiology, invited speaker at SER, Seattle 2014
61. History of Air Pollution, Adverse Birth Outcomes and Children's Health in California; Invited Plenary Speaker for the ISEE Young Researcher Conference, Barcelona 2014
62. Environmental Causes of Adverse Neurodevelopment; Invited Speaker at the B-Debate Barcelona (Environment and Child Brain Development: the Challenges in the Global Context) Conference, Barcelona 2014
63. Autism Epidemiology; invited speaker at the annual CART meeting UCLA 2014
64. Epidemiology of Parkinson's disease, invited speaker at annual GEO-PD meeting Vancouver CA, 2014
65. Parkinson's Disease Epidemiology: a Gene-Environment Perspective, invited speaker at the Neurogenetics Institute of Luebeck/Germany, 2015

PUBLICATIONS

PEER REVEIWED JOURNAL ARTICLES (*indicates mentored students/fellows)

1. **Ritz B**. Humeral Epicondylitis Among Gas- And Waterworks Employees. Scandinavian Journal of Work, Environment and Health, 1995 Dec, 21(6): 478-86.
2. **Ritz B**, Heinrich J, Wjst M, Wichmann E, Krause C. Effect Of Cadmium Body Burden On Immune Response Of School Children. Archives of Environmental Health 1998,Jul-Aug; Vol 53: 272-280
3. **Ritz B**, Morgenstern H, Froines J, Young B. Effects Of Exposure To External Ionizing Radiation On Cancer Mortality In Nuclear Workers Monitored For Radiation At Rocketdyne/Atomics International. AJIM 1999, Jan; Vol 35: 21-31.
4. **Ritz B**, Yu F. The Effect Of Ambient Carbon Monoxide On Low Birth Weight Among Children Born In Southern California Between 1989 and 1993. Environmental Health Perspectives 1999 Jan, 107(1):17-25. PMCID: PMC1566307
5. Heinrich J, Hoelscher B, Wjst M, **Ritz B**, Cyrys J, Wichmann HE. Respiratory Diseases And Allergies In Two Polluted Areas In East Germany. Environmental Health Perspectives 1999,Jan; 107(1):53-62. PMCID: PMC1566314
6. **Ritz B**, Morgenstern H, Moncau J. Age At Exposure Modifies The Effects Of Low-Level Ionizing Radiation On Cancer Mortality In An Occupational Cohort. Epidemiology 1999, Mar; 10(2):135-140.
7. **Ritz B**. Radiation Exposure and Cancer Mortality In Uranium Processing Workers. Epidemiology, 1999, Sep; 10:531-538
8. **Ritz B**. Cancer Mortality Among Workers Exposed To Chemicals During Uranium Processing. JOEM 1999, Jul;41(7):556-566.
9. **Ritz B**, Morgenstern H, Froines J., Moncau J. Chemical Exposures Of Rocket Engine Test Stands Personnel And Cancer Mortality In A Cohort Of Aerospace Workers. JOEM, 1999 Oct; 41(10): 903-910.
10. Jacob B, **Ritz B**, Heinrich J, Hoelscher B, Wichmann HE. The Effect Of Low-Level Blood Lead On hematologic parameters In Children. Environmental Research, 2000 Feb, 82 (2): 150-159.
11. **Ritz B**, Yu F. Parkinson's Disease Mortality And Pesticide Exposure In California 1984-1994. International Journal of Epidemiology, 2000 Apr, Vol. 29:323-329.
12. Hoelscher B, Heinrich J, Jacob B, **Ritz B**, Wichmann HE. Gas Cooking, Respiratory Health And White Blood Cell Counts In Children. Int. J. Hygiene and Environ Health, 2000 Mar; 203 (1): 29-37.
13. **Ritz B**, Morgenstern H, Crawford-Brown D,Young B.The Effects Of Internal Radiation Exposure On Cancer Mortality In Nuclear Workers At Rocketdyne/Atomics International. Environ Health Perspect, 2000 Aug; 108(8):743-751. PMCID: PMC1638302
14. **Ritz B**, Yu F, Chapa G, Fruin S. Effect Of Air Pollution On Preterm Birth Among Children Born In Southern California Between 1989 And 1993. Epidemiology, 2000 Sep; 11(5):502-511.
15. Morgenstern H, **Ritz B**. Effects of Radiation And Chemical Exposures On Cancer Mortality Among Rocketdyne Workers: A Review of Three Cohort Studies. Occup. Med. 2001 Apr-Jun;16(2): 219-237.
16. **Ritz B**, Yu F, Chapa G, Fruin S, Shaw G, Harris J. Ambient Air Pollution And Risk of Birth Defects in Southern California. Am J Epidemiol 2002 Jan 1;155:17–25.

17. **Ritz B**, Hoelscher B, Frye C, Meyer I, Heinrich J. Allergic sensitization owing to 'second-hand' cat exposure in schools. Allergy 2002 Apr;57(4):357-61
18. Jacob B, **Ritz B,** Gehring U, Koch A, Bischof W ,Wichmann HE, Heinrich J for the INGA-Study group. Indoor Exposure To Molds And Allergic Sensitization. Environ Health Perspect. 2002 Jul;110(7):647-53. PMCID: PMC1240910
19. Clary T, **Ritz B**. Pancreatic Cancer Mortality And Organochlorine Pesticide Exposure In California, 1989-1996. Am J Ind Med. 2003 Mar;43(3):306-13.
20. Wilhelm M, **Ritz B.** Residential Proximity To Traffic And Adverse Birth Outcomes In Los Angeles County, California, 1994-1996. Environ Health Perspect. 2003 Feb; 111(2):207-16. PMCID: PMC1241352
21. Rull R, **Ritz B**. Historical Pesticide Exposure In California Using Pesticide Use Reports And Land-Use Surveys: An Assessment Of Misclassification Error And Bias. Environ Health Perspect. 2003 Oct; 111(13):1582-9. PMCID: PMC1241678.
22. Hashibe M, **Ritz B**, Le AD, Li G, Sankaranarayanan R, Zhang ZF. Radiotherapy For Oral Cancer As A Risk Factor For Second Primary Cancers. Cancer Letters 2005 Apr 8; 220(2):185–195.
23. **Ritz,B**, Tager I, Balmes J. Can Lessons From Public Health Disease Surveillance Be Applied To Environmental Public Health Tracking? Environ Health Perspect. 2005 Mar; 113(3):243-9. PMCID: PMC1253746
24. Kang G, Bronstein JM, Masterman DL, Redelings M, Crum JA, **Ritz B**. Clinical Characteristics In Early Parkinson's Disease In A Central Californian Population-Based Study. Mov Disord. 2005 Sep; 20(9):1133-42. PMCID: PMC3643967
25. Ponce NA, Hoggatt KJ, Wilhelm M, **Ritz B**. Preterm Birth: The Interaction Of Traffic-Related Air Pollution With Economic Hardship In Los Angeles Neighborhoods. Am J Epidemiol. 2005 Jul 15;162(2):140-8.
PMCID: PMC3636775
26. Wilhelm M, **Ritz, B**. Local Variations In CO And Particulate Air Pollution And Adverse Birth Outcomes In Los Angeles County, California, USA. Environ Health Perspect; 2005 Sep;113(9):1212-21. PMCID: PMC1280404
27. Rull RP, **Ritz B**, Shaw GM. Validation Of Self-Reported Proximity To Agricultural Crops In A Case-Control Study Of Neural Tube Defects. Journal of Exposure Analysis and Environmental Epidemiology; J Expo Sci Environ Epidemiol. 2006 Mar;16(2):147-55.
28. Zhao Y, Krishnadasan A, Kennedy N, Morgenstern H. **Ritz B**. Estimated effects of solvents and mineral oils on cancer incidence and mortality in a cohort of aerospace workers. Am J Ind Med. 2005 Oct;48(4):249-58.
29. Lewis C, Suffet I, **Ritz B**. Estimated Effects Of Disinfection By-Products On Birth Weight In A Population Served By A Single Water Utility. Am J Epidemiol. 2006 Jan 1;163(1):38-47.
30. Karr C, Lumley T, Shepherd K, Davis R, Larson T, **Ritz B**, Kaufman J. A Case Crossover Study Of Wintertime Ambient Air Pollution And Infant Bronchiolitis. Environ Health Perspect. 2006 Feb;114(2):277-81. PMCID: PMC1367844
31. **Ritz B,** Zhao Y, Krishnadasan A, Kennedy N, Morgenstern H. Estimated Effects of Hydrazine Exposure on Cancer Incidence and Mortality in Aerospace Workers. Epidemiology. 2006 Mar;17(2):154-61.
32. Rull RP, **Ritz B**, Shaw GM. Neural Tube Defects And Maternal Residential Proximity To Agricultural Pesticide Applications. Am J Epidemiol. 2006 Apr 15;163(8):743-53.
33. Glatt CE, Wahner AD, White DJ, Ruiz-Linares A, **Ritz B**. Gain Of Function Haplotypes In The Vesicular Monoamine Transporter Promoter Are Protective For Parkinson Disease In Women. Hum Mol Genet. 2006 Jan 15;15(2):299-305. PMCID:PMC3643966
34. Marusek JC, Cockburn MG, Mills PK, **Ritz B**. Control Selection And Pesticide Exposure Assessment Via GIS In Prostate Cancer Studies. Am J Prev Med. 2006 Feb;30(2 Suppl):S109-16.
35. **Ritz B**, Wilhelm M, Zhao Y. Air pollution and infant death in southern California, 1989-2000. Pediatrics 2006 Aug;118(2);493-502. PMCID: PMC3636770
36. Schernhammer E, Chen H, **Ritz B**. Circulating Melatonin Levels: Possible Link Between Parkinson's Disease And Cancer Risk? 2006 May;17(4):577-82.
37. Karr C, Lumley T, Schreuder A, Davis R, Larson T, **Ritz B**, Kaufman J. Effect of Subchronic and Chronic Exposure to Ambient Air Pollutants on Infant Bronchiolitis. Am J Epidemiol. 2007 Mar 1;165(5):553-60.
38. **Ritz B**, Ascherio A, Checkoway H, Marder KS, Nelson LM, Rocca WA, Ross GW, Strickland D, Van Den Eeden SK, Gorell J. Pooled Analysis Of Tobacco Use And Risk Of Parkinson Disease. Arch Neurol. 2007 Jul;64(7):990-7.

39. **Ritz B,** Costello S. Geographic model and biomarker-derived measures of pesticide exposure and Parkinson's disease. Ann N Y Acad Sci. 2006 Sept;1076:378-87. PMCID: PMC3656600
40. Elbaz A, Nelson LM, Payami H, Ioannidis JPA, Fiske BK, Annesi G, Belin AC, Factor SA, Ferrarese C, Hadjigeorgiou GM, Higgins DS, Kawakami H, Krüger R, Marder KS, Mayeux RP, Mellick GD, Nutt JG, **Ritz B**, Samii A, Tanner CM, Van Broeckhoven C, Van Den Eeden SK, Wirdefeldt K, Zabetian CP, Dehem M, Montimurro JS, Myers RM, Southwick A, Trikalinos TA. Lack Of Replication Of Thirteen Single-Nucleotide Polymorphisms Implicated In Parkinson's Disease: A Large-Scale International Study. Lancet Neurol. 2006 Nov; 5(11):917-23. PMCID: PMC3636768
41. Rempel DM, Wang PC, Janowitz I, Harrison RJ, Yu F, **Ritz B**. A Randomized Controlled Trial Evaluating the Effects of New Task Chairs on Shoulder and Neck Pain among Sewing Machine Operators: The Los Angeles Garment Study. 2007 Apr 20. Spine; 32(9): 931–938
42. Wahner AD, Sinsheimer JS, Bronstein JF, **Ritz B**. Inflammatory Cytokine Gene Polymorphisms And Increased Risk of Parkinson disease. Arch Neurol. 2007 Jun;64(6):836-40.
43. Wahner AD, Glatt CE, Bronstein JM, **Ritz B**. Glutathione S-Transferase Mu, Omega, Pi, And Theta Class Variants And Smoking In Parkinson's Disease. Neurosci Lett. 2007 Feb 21;413(3):274-8. PMCID: PMC1864949
44. Lewis C, Suffet HI, Hoggatt KJ, **Ritz B**. Estimated Effects of Disinfection By-products On Preterm Birth in a Population Served by a Single Water Utility. Environ Health Perspect. 2007 Feb;115(2):290-5. PMCID: PMC1831522
45. Krishnadasan A, Kennedy N, Zhao Y, Morgenstern H, **Ritz B**. Nested Case-Control Study of Occupational Chemical Exposures and Prostate Cancer in Aerospace and Radiation Workers. Am J Ind Med. 2007 May; 50(5):383-90.
46. Meng YY, Wilhelm M, Rull R, English P, **Ritz B**. Traffic And Outdoor Air Pollution Levels Near Residences And Poorly-Controlled Asthma In Adults. Ann Asthma, Allergy, Immunol; 2007 May, 98(5), 455-63.
47. Wang PC, Rempel DM, Harrison RJ, Chan J, **Ritz B**. Work-Organizational And Personal Factors Associated With Upper Body Musculoskeletal Disorders Among Sewing Machine Operators. Occup Environ Med. 2007 Dec;64(12):806-13. Epub 2007 May 23 PMCID: PMC2095384
48. **Ritz B**, Wilhelm M, Hoggatt KJ, Ghosh JKC. Ambient Air Pollution And Preterm Birth In the Environment And Pregnancy Outcomes Study at the University of California, Los Angeles. Am J Epidemiol. 2007 Nov 1;166(9):1045-52.
49. Wahner AD, Bronstein JM, Bordelon YM, **Ritz B**. Nonsteroidal Anti-Inflammatory Drugs May Protect Against Parkinson Disease. Neurology. 2007 Nov 6;69(19):1836-42.
50. Wahner AD, Bronstein JM, Bordelon YM, **Ritz B**. Statin Use and the Risk of Parkinson's Disease. Neurology. 2008 Apr 15;70(16 Pt 2):1418-22. PMCID: PMC3690297
51. Krishnadasan A, Kennedy N, Zhao Y, Morgenstern H, **Ritz B**. Nested Case-control Study of Occupational Physical Activity and Prostate Cancer Among Workers Using a Job Exposure Matrix. Cancer Causes Control. 2008 Feb;19(1):107-14.
52. **Ritz B**, Wilhelm M. Ambient Air Pollution And Adverse Birth Outcomes: Methodologic Issues In An Emerging Field. Basic Clin Pharmacol Toxicol. 2008 Feb;102(2):182-90. PMCID: PMC3656653
53. Meng YY, Wilhelm M, Rull RP, English P, Nathan S, **Ritz B**. Are frequent asthma symptoms among low-income individuals related to heavy traffic near homes, vulnerabilities, or both? Ann Epidemiol. 2008 May;18(5):343-50.
54. Wilhelm M, Qian L, **Ritz B**. Outdoor air pollution, family and neighborhood environment, and asthma in LA FANS children. Health Place. 2009 Mar;15(1):25-36. PMCID: PMC2658528
55. Heck JE, **Ritz B**, Hung R, Hashibe M, Boffetta P. The Epidemiology of Neuroblastoma: A Review. Paediatr Perinat Epidemiol. 2009 Mar;23(2):125-43.
56. Wilhelm M, Meng YY, Rull RP, English P, Balmes J, **Ritz B.** Environmental public health tracking of childhood asthma using California health interview survey, traffic, and outdoor air pollution data. Environ Health Perspect 2008 Sep;116(9):1254-60. PMCID: PMC2535631
57. Wang PC, **Ritz, B**, Janowitz I, Harrison RJ, Yu F, Chan J, Rempel DM. A Randomized Controlled Trial of Chair Interventions on Back and Hip Pain Among Sewing Machine Operators: The Los Angeles Garment Study. J Occup Environ Med. 2008 Mar;50:255–262.
58. Wang PC, Rempel DM, Hurwitz EL, Harrison RJ, Janowitz I, **Ritz B**. Self-Reported Pain And Physical Signs For Musculoskeletal Disorders In The Upper Body Region Among Los Angeles Garment Workers. Work. 2009;34(1):79-87.
59. Rhodes SL, **Ritz, B**. Genetics of Iron Regulation and the Possible Role of Iron in Parkinson's Disease. In Neurobiol Dis. 2008 Nov;32(2):183-95. PMCID: PMC3643980

60. Goldberg DW, Wilson JP, Knoblock CA, **Ritz B**, Cockburn MG. An effective and efficient approach for manually improving geocoded data. International Journal of Health Geographics 2008 Nov 26, 7:60. PMCID: PMC2612650.
61. **Ritz B**, Rull R. Assessment of Environmental Exposures from Agricultural Pesticides in Childhood Leukemia Studies: Challenges and Opportunities. Radiat Prot Dosimetry. 2008;132(2):148-55.
62. Rugbjerg K, **Ritz B**, Korbo L, Martinussen N, Olsen JH. Risk for Parkinson's disease after hospital contact for head injury: a population-based case–control study. BMJ. 2008 Dec 15;337. PMCID: PMC2603581
63. Costello S*, Cockburn M., Bronstein J, Zhang X, **Ritz B.** Parkinson's disease and residential exposure to Maneb and Paraquat from agricultural applications in the central valley of California. Am J Epidemiol. 2009 Apr 15;169(8):919-26. PMCID: PMC2727231.
64. Hoggatt KJ, Greenland S, **Ritz B**. Adjustment for response bias via two-phase analysis: an application. Epidemiology. 2009 Nov;20(6):872-9. PMCID: PMC3656648
65. Wang PC, Harrison RJ, Yu F, Rempel DM, **Ritz B**. Follow-up Of Neck And Shoulder Pain Among Sewing Machine Operators: the Los Angeles Garment Study. Am J Ind Med. 2010 Apr;53(4):352-60.
66. **Ritz B**, Manthripragada A, Costello S, Lincoln SJ, , Farrer M, Cockburn M, Bronstein J. Dopamine transporter genetic variants and pesticides in Parkinson's disease. Environ Health Perspect 2009 Jun;117(6):964-9 PMCID: PMC2702414.
67. Meng YY, Rull RP, Wilhelm M ,Lombardi C,Balmes J, **Ritz B**. Outdoor air pollution and uncontrolled asthma in the San Joaquin Valley, California. J Epidemiol Community Health. 2010 Feb;64(2):142-7.
68. Manthripragada A, Cockburn M, Costello S, Bronstein J, **Ritz B**. Paraoxonase 1, agricultural organophosphate exposure, and Parkinson disease. Epidemiology. 2010 Jan;21(1):87-94. PMCID: PMC3117899
69. Su JS, Jerrett M, Beckerman B, Wilhelm M, Ghosh JK, **Ritz B**. Predicting traffic-related air pollution in Los Angeles using a distance decay regression selection strategy. Environ Res. 2009; Aug; 109(6):657-70. PMCID: PMC 3656661
70. Wu J, Ren C , Delfino R, Chung J, Wilhelm M, **Ritz B**. Association between local traffic-generated air pollution and preeclampsia and preterm delivery in the South Coast Air Basin of California. Environ Health Perspect. 2009 Nov;117(11):1773-9. PMCID: PMC2801174.
71. Gatto N, Cockburn M, Bronstein J, Manthripragada A, **Ritz B**. Well Water Consumption and Parkinson's Disease in Rural California. Environ Health Perspect 2009 Dec; 117: 1912–1918 PMCID: PMC2799466.
72. Rugbjerg K, Friis S, **Ritz B**, Schernhammer ES, Korbo L, Olsen JH. Autoimmune disease and risk for Parkinson's disease: a population based case–control study. Neurology. 2009 Nov 3;73(18):1462-8. PMCID: PMC2779008
73. Rod-Nielsen N, Schernhammer E, Hansen J, **Ritz B**. Major life events and risk of Parkinson's disease. Mov Disord. 2010 Aug 15;25(11):1639-45. PMCID: PMC2928859
74. Plaitakis A, Latsoudis H, Kanavouras K, **Ritz B**, Bronstein JM, Skoula I, Mastorodemos V, Papapetropoulos S, Borompokas N, Zaganas I, Xiromerisiou G, Hadjigeorgiou GM, Spanaki C. Gain-of-function variant in GLUD2 glutamate dehydrogenase modifies Parkinson's disease onset. Eur J Hum Genet. 2010 Mar;18(3):336-41. PMCID: PMC2987208
75. **Ritz B,** Rhodes SL, Qian L, Schernhammer E, Olsen J, Friis, S. L-type Calcium Channel blockers and Parkinson disease in Denmark. Ann Neurol. 2010 May;67(5):600-6. PMCID: PMC2917467
76. Gosh JKC, Wilhelm M, Dunkel-Shetter C, Lombardi C*, **Ritz B**. Paternal support and preterm birth, and the moderation of effects of chronic stress: a study in Los Angeles county mothers. Arch Womens Ment Health. 2010 Aug;13(4):327-38.PMCID: PMC2896639
77. Costello S, Bordelon Y, Bronstein J, **Ritz B.** Familial Associations of Alzheimer Disease and Essential Tremor with Parkinson Disease. Eur J Neurol. 2010 Jun 1;17(6):871-8. PMCID: PMC2895681
78. Wu J, Hou H, **Ritz B**, Chen Y Exposure to Polycyclic Aromatic Hydrocarbons and Missed Abortion in Early Pregnancy in a Chinese Population. Science of the Total Environment 2010 May 1;408(11):2312-8.
79. **Ritz B,** Mandripragada A, Qian L, Schernhammer E, Olsen J, Wermuth L, Friis S. Statin use and Parkinson's Disease in Denmark. Mov Disord. 2010 Jul 15;25(9):1210-6. PMCID: PMC2910157
80. Rugbjerg K, Friis S, Jorgensen T, **Ritz B**, Korbo L, Olsen JH. Risk of Parkinson disease among patients with osteoarthritis: a Danish cohort study. Mov Disord. 2010 Oct 30;25(14):2355-60. PMCID:PMC2992436

81. Gatto NM, Rhodes SL, Manthripragada AD, Bronstein J, Cockburn M, Farrer M, **Ritz B**. a-Synuclein Gene May Interact with Environmental Factors in Increasing Risk of Parkinson's Disease. Neuroepidemiology. 2010;35(3):191-5. PMCID: PMC2945263
82. Wu X, Bennett DH, **Ritz B**, Frost J, Cassady D, Lee K, Hertz-Picciotto I. Residential Insecticide Usage in Northern California Homes with Young Children. J Expo Sci Environ Epidemiol. 2011 Jul-Aug;21(4):427-36.
83. Jacob EL, Gatto NM, Thompson A, Bordelon Y, **Ritz B.** Occurrence of Depression and Anxiety prior to Parkinson's Disease. Parkinsonism Relat Disord. 2010 Nov;16(9):576-81. PMCID: PMC2963655
84. Wu X, Bennett DH, **Ritz B**, Cassady DL, Lee K, Hertz-Picciotto I. Usage Pattern of Personal Care Products in California Households. Food Chem Toxicol. 2010 Nov;48(11):3109-19.
85. Rhodes SL, Sinsheimer JS, Bordelon Y, Bronstein JM, **Ritz B**. Replication of GWAS associations for GAK and MAPT in Parkinson's disease. Annals of Human Genetics. Ann Hum Genet. 2011 Mar;75(2):195-200.
PMCID: PMC3074465
86. Kenborg L, Funch C, **Ritz B**, Schernhammer E, Hansen J, Gatto N, Olsen JH. Outdoor work and risk for Parkinson disease: a population-based case–control study. Occup Environ Med. 2011 Apr;68(4):273-8. PMCID: PMC3667158
87. Hertz-Picciotto I, Cassady D, Lee K, Bennett DH, **Ritz B**, Vogt R. Study of Use of Products and Exposure-Related Behaviors (SUPERB): study design, methods, and demographic characteristics of cohorts. Environ Health. 2010 Aug 29;9:54. PMCID: PMC2940867
88. Sapkota A, Chelikowski A, Nachman K, Cohen A, **Ritz B**. Exposure to Particulate Matter and Adverse Birth Outcomes: A Comprehensive Review and Meta Analysis. Air Quality, Atmosphere and Health; 2012, Vol 5, Issue 4; 369-381
89. Cockburn M, Mills P, Zhang X, Zadnick j, Goldberg D, **Ritz B**. Prostate cancer and ambient pesticide exposure in agriculturally intensive areas in California. Am J Epidemiol. 2011 Jun 1;173(11):1280-8 PMCID: PMC3121318
90. Popat R, Van Den Eeden SK, Tanner CM, Kamel F, Umbach D, Marder K, Mayeux R, **Ritz B**, Ross GW, Petrovitch H, Topol B, McGuire V, Costello S, Manthripragada AD, Southwick A, Myers RM, Nelson LM. Coffee, ADORA2A, and CYP1A2: the caffeine connection in Parkinson's disease. Eur J Neurol. 2011 May;18(5):756-65. PMCID: PMC3556904
91. Lewis C, Hoggatt KJ, **Ritz B**. The Impact of Different Causal Models on Estimated Effects of Disinfection By-Products on Preterm Birth. Environ Res. 2011 Apr;111(3):371-6.
92. Lee PC, Talbott EO; Roberts JM, Catov JM, Sharma RK, **Ritz B.** Particulate Air Pollution Exposure and C-Reactive Protein during Early Pregnancy. Epidemiology. 2011 Jul;22(4):524-31.
93. Schernhammer E, Hansen J, Rugbjerg K, Wermuth L, **Ritz B**. Diabetes and the risk of developing Parkinson's disease in Denmark. Diabetes care. 2011 May;34(5):1102-8. PMCID:PMC3114482
94. Wang A, Costello S, Cockburn M, Zhang X, Bronstein J, **Ritz B**. Parkinson's Disease risk from ambient exposure to pesticides. Eur J Epidemiol. 2011 Jul;26(7):547-55. Epub 2011 Apr 20. PMCID: PMC3643971
95. Manthripragada A, Schernhammer ES, Qiu J, Friis S, Wermuth L, Olsen J, **Ritz B**. Non-steroidal anti-inflammatory drug use and the risk of Parkinson's Disease. Neuroepidemiology. 2011;36(3):155-61. PMCID:PMC3095838
96. Wu X, Bennett DH, Lee K, Cassady DL, **Ritz B**, Hertz-Picciotto I. Feasibility of Using Web Surveys to Collect Time-Activity Data. Journal Of Exposure Science And Environmental Epidemiology. J Expo Sci Environ Epidemiol. 2012 Mar-Apr;22(2):116-25.
97. Gatto NM, Bordelon Y, Gatz M, **Ritz B**. Personality Characteristics and Motor Skills Attributed to Occupations in Parkinson Disease. Cognitive and Behavioral Neurology. Cogn Behav Neurol. 2011 Mar; 24(1):18-25.PMCID: PMC3656654
98. Wu J, Wilhelm M, Chung J, **Ritz B**. Comparing exposure assessment methods for traffic-related air pollution in an adverse pregnancy outcome study. Environ Res. 2011 Jul;111(5):685-92. PMCID: PMC3114297
99. McGuire V, Van Den Eeden SK, Tanner CM, Kamel F, Umbach D, Marder K, Mayeux R, **Ritz B**, Ross GW, Petrovitch H, Topol B, Popat RA, Costello S, Manthripragada AD, Southwick A, Myers RM, Nelson LM, Association of DRD2 and DRD3 Polymorphisms with Parkinson's Disease in a Multiethnic Consortium. J Neurol Sci. 2011 Aug 15;307(1-2):22-9. PMCID: PMC3155471
100. Wilhelm M, Ghosh JK, Su J, Cockburn M, Jerrett M, **Ritz B**. Traffic-related air toxics and preterm birth: a population-based case-control study in Los Angeles County, California. Environmental Health. Environ Health. 2011 Oct 7;10:89. PMCID:PMC3204282

101. Hamza TH, Chen H, Hill-Burns EM, Rhodes SL, Montimurro J, Kay DM, Tenesa A, Kusel VI, Sheehan P, Eaaswarkhanth M, Yearout D, Samii A, Roberts JW, Agarwal P, Bordelon Y, Park Y, Wang L, Gao J, Vance JM, Kendler KS, Bacanu SA, Scott WK, Ritz B, Nutt J, Factor SA, Zabetian CP, Payami HGenome-Wide Gene-Environment Study Identifies Glutamate Receptor Gene GRIN2A as a Parkinson's Disease Modifier Gene via Interaction with Coffee. PLoS Genet. 2011 Aug;7(8):e1002237. PMCID: PMC3158052
102. Armes MN, Liew Z, Wang A, Wu X, Bennett DH, Hertz-Picciotto I, **Ritz B.** Residential Pesticide Usage in Older Adults Residing in Central California. International Journal of Environmental Research and Public Health. Int J Environ Res Public Health. 2011 Aug;8(8):3114-33. PMCID:PMC3166730.
103. Wilhelm M, Gosh J, Su J, Cockburn M, Jerret M, **Ritz B**. Traffic-Related Air Toxics and Term Low Birth Weight in Los Angeles County, California. Environ Health Perspect. 2012 Jan;120(1):132-8. PMCID:PMC3261935
104. Wu X, Bennett DH, Lee K, Cassady DL, **Ritz B**, Hertz-Picciotto I. Longitudinal variability of time-location/activity patterns of population at different ages: a longitudinal study in California. Environmental Health 2011 Sep 20;10:80 PMCID: PMC3184256
105. Hoggatt KJ, Sharp M, Wilhelm M, Solorio R, **Ritz B**. The Latina Epidemiologic Paradox revisited: the role of birthplace and acculturation in predicting infant low birth weight for Latinas in Los Angeles, CA. Journal of Immigrant and Minority Health (JOIH). J Immigr Minor Health. 2012 Oct;14(5):875-84. PMCID: PMC3643973
106. Gosh JK, Wilhelm M, Su J, Goldberg D, Cockburn M, Jerrett J, **Ritz B**. Assessing the influence of traffic-related air pollution on risk of term low birth weight on the basis of land-use-based regression models and measures of air toxics. Am J Epidemiol. 2012 Jun 15;175(12):1262-74. PMCID: PMC3372317
107. Nielsen HH, Qiu J, Friis S, Wermuth L**, Ritz B**. Treatment of Helicobacter Pylori infection and risk of Parkinson's disease in Denmark. Eur J Neurol. 2012 Jun;19(6):864-9. PMCID: PMC3330170
108. Wermuth L, Lassen CF, Himmerslev L, Olsen J, **Ritz B.** Validation of hospital register-based diagnosis of Parkinson's disease. Dan Med J. 2012 Mar;59(3):A4391. PMCID: PMC3643969
109. Rugbjerg K, Friis S, Lassen CF, **Ritz B**, Olsen J. Malignant melanoma, breast cancer and other cancers in patients with Parkinson's disease. 2012 Oct 15;131(8):1904-11. PMCID: PMC3636769
110. Heck JE, Lombardi CA, Cockburn M, Meyers TJ, Wilhelm M, **Ritz B**. Epidemiology of rhabdoid tumors of early childhood. Pediatr Blood Cancer. 2013 Jan;60(1):77-81. PMCID: PMC3399923
111. Li L, Wu J, Wilhelm M, **Ritz B**. Use of Generalized Additive Models and Cokriging of Spatial Residuals to Improve Land-Use Regression Estimates of Nitrogen Oxides in Southern California. Atmos Environ 2012 Aug 1;55:220-228. PMCID: PMC3579670
112. Lee PC, Roberts JM, Catov JM, Talbott EO, **Ritz B**. First trimester exposure to ambient air pollution, pregnancy complications and adverse birth outcomes in Allegheny County, PA. Matern Child Health J. 2013 Apr;17(3):545-55. PMCID: PMC3636771
113. Bennett DH, Wu X, Teague C, Lee K, Cassady DL, **Ritz B**, Hertz-Picciotto I. Passive Sampling Methods to Determine Household and Personal Care Product Use. J Expo Sci Environ Epidemiol. 2012 Mar-Apr;22(2):148-60.
114. **Ritz B.** Rhodes SL, Bordelon Y, Bronstein J. α-Synuclein genetic variants predict faster motor symptom progression in idiopathic Parkinson disease. PLoS One. 2012;7(5):e36199. PMCID: PMC3352914
115. Lee PC, Talbott EO; Roberts JM; Catov JM Bilonick RA; Stone RA; Sharma RK; **Ritz B**. Ambient Air Pollution Exposure and Blood Pressure Changes during Pregnancy. Environ Res. 2012 Aug;117:46-53. PMCID: PMC3656658
116. Gosh JK, Wilhelm M, **Ritz B**. Effects of residential indoor air quality and household ventilation on preterm birth and term low birth weight in Los Angeles County, California. Am J Public Health. 2013 Apr;103(4):686-94. PMCID: PMC3643965
117. Heck JE, Lombardi CA, Meyers TJ, Cockburn M, Wilhelm M, **Ritz B**. Perinatal characteristics and retinoblastoma. 2012 Sep;23(9):1567-75. PMCID: PMC 3429932
118. Lee PC, Bordelon Y, Bronstein J, **Ritz B**. Traumatic Brain Injury, Paraquat Exposure, and their Relationship to Parkinson Disease. Neurology. 2012 Nov 13;79(20):2061-6. PMCID: PMC3511918
119. Mata IF, Checkoway H, Hutter CM, Samii A, Roberts JW, Kim HM, Agarwal P, Alvarez V, Ribacoba R, Pastor P, Lorenzo-Betancor O, Infante J, Sierra M, Gómez-Garre P, Mir P, **Ritz B**, Rhodes SL, Colcher A, Van Deerlin V, Chung KA, Quinn JF, Yearout D, Martinez E, Farin FM, Wan JY, Edwards KL, Zabetian CP.Common Variation in the LRRK2 Gene is a Risk Factor for Parkinson's Disease. Mov Disord. 2012 Dec;27(14):1822-5. PMCID: PMC3536918

120. Block ML, Elder A, Auten RL, Bilbo SD, Chen H, Chen JC, Cory-Slechta DA, Costa D, Diaz-Sanchez D, Dorman DC, Gold DR, Gray K, Jeng HA, Kaufman JD, Kleinman MT, Kirshner A, Lawler C, Miller DS, Nadadur SS, **Ritz B**, Semmens EO, Tonelli LH, Veronesi B, Wright RO, Wright RJ. The outdoor air pollution and brain health workshop. Neurotoxicology. 2012 Oct;33(5):972-84. PMCID: PMC3726250
121. Rod-Nielsen N, Bordelon Y, Thompson A, Marcotte E, **Ritz B**. Major life events and development of major depression in Parkinson's disease patients. Eur J Neurol. 2013;20(4):663-70. PMCID: PMC3566278
122. Vogt R, Bennett D, Cassady D, Frost J, **Ritz B**, Hertz-Picciotto I. Cancer and non-cancer health effects from food contaminant exposures for children and adults in California: a risk assessment. Environ Health 2012 Nov 9 ;11:83. PMCID: PMC3551655
123. Becerra T, Wilhelm W, Olsen J, Cockburn M, **Ritz B**. Ambient Air Pollution and Autism in Los Angeles County, California. Environ Health Perspect. 2013 Mar;121(3):380-6. PMCID: PMC3621187
124. Fitzmaurice AG, Rhodes SL, Lulla A, Murphy NP, Lam HA, O'Donnell KC, Barnhill L, Casida JE, Cockburn M, Sagasti A, Stahl MC, Maidment NT, **Ritz B**, Bronstein JM. Aldehyde dehydrogenase inhibition as a pathogenic mechanism in Parkinson disease. Proc Natl Acad Sci U S A. 2013 Jan 8;110(2):636-41. PMCID: PMC3545765
125. Lim SS, et al. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet. 2012 Dec 15;380(9859):2224-60. PMCID: PMC4156511
126. Clark AJ, **Ritz BR**, Prescott E, Rod NH. Psychosocial risk factors, pre-motor symptoms, and first-time hospitalization with Parkinson's Disease: a prospective cohort study. Eur J Neurol 2013 Aug;20(8):1113-20. PMCID: PMC3664243
127. Shrestha A, **Ritz B,** Ognjanovic S, Lombardi CA, Wilhelm M, Heck JE. Early life factors and risk of childhood rhabdomyosarcoma. Front Public Health. 2013 May 31;1:17. PMCID: PMC3854857.
128. Li L, Wu J, Ghosh JK, **Ritz B**.Estimating Spatiotemporal Variability of Ambient Air Pollutant Concentrations with A Hierarchical Model. Atmospheric Environment 2013 Jun 1;71:54-63. PMCID: PMC3627373
129. Liew Z, Wang A, Bronstein B, **Ritz B**. Job Exposure Matrix (JEM) derived estimates of life-time occupational pesticide exposure and the risk of Parkinson's Disease. Arch Environ Occup Health. 2014;69(4):241-51. PMCID: PMC3916959
130. Lee PC, Rhodes SL, Sinsheimer JS, Bronstein J, **Ritz B**. Functional Paraoxonase 1 Variants Modify the Risk of Parkinson's Disease due to Organophosphate Exposure. Environ Int. 2013 Jun;56:42-7. PMCID: PMC3690300
131. Schernhammer E, Qiu J, Wermuth L, Funch Lassen C, Friis S, **Ritz B**. Gout and the risk of Parkinson's disease in Denmark. European Journal of Epidemiology. 2013 Apr;28(4):359-60. PMCID:PMC3655156
132. Lombardi C, Heck JE, Cockburn M, **Ritz B**. Solar UV radiation and cancer in young children. Cancer Epidemiol Biomarkers Prev. 2013 Jun;22(6):1118-28 PMCID:PMC369030
133. von Ehrenstein OS, Wilhelm M**, Ritz B.** Maternal Occupation and Term Low Birth Weight in a Predominantly Latina Population in Los Angeles, California. J Occup Environ Med. 2013 Sep;55(9):1046-51.
134. Gosh JK, Heck J, Cockburn M, Su J, Jerrett M, **Ritz B**. Prenatal exposure to traffic-related air pollution and risk of early childhood cancers. Am J Epidemiol. 2013 Oct 15;178(8):1233-9. PMCID:PMC3792733
135. von Ehrenstein OS, Wilhelm M, **Ritz B**. Preterm Birth and Prenatal Maternal Occupation: Preterm Birth and Prenatal Maternal Occupation: The Role of Hispanic Ethnicity and Nativity in a Population Based Sample in Los Angeles, California. Am J Public Health. 2014 Feb;104 Suppl 1:S65-72. PMCID: PMC4011103
136. Chen H, Burton EA, Ross GW, Huang X, Savica R, Abbott RD, Ascherio A, Caviness JN, Gao X, Gray KA, Hong JS, Kamel F, Jennings D, Kirshner A, Lawler C, Liu R, Miller GW, Nussbaum R, Peddada S, Rick AC, **Ritz B**, Siderowf AD, Tanner CM, Tröster AI, Zhang J. Research on the pre-motor symptoms of Parkinson's disease Clinical and etiological implications. Environ Health Perspect. 2013 Nov-Dec;121(11-12):1245-52. PMCID: PMC3855519
137. Rhodes SL, Fitzmaurice AG, Cockburn M, Bronstein JM, Sinsheimer JS, **Ritz B**. Pesticides that Inhibit the Ubiquitin-Proteasome System: Effect Measure Modification by Genetic Variation in SKP1 in Parkinson's Disease. Environ Res. 2013 Oct; 126:1-8. PMCID: PMC3832349

138. Narayan S, Liew Z, Paul K, Lee PC, Sinsheimer JS, Bronstein JM, **Ritz B.** Household Organophosphorus Pesticide Use and Parkinson's Disease. Int J Epidemiol. 2013 Oct;42(5):1476-85. PMCID:PMC3807617
139. Murray CJ et al. (125 US Burden of Disease Collaborators). The state of US health, 1990-2010: burden of diseases, injuries, and risk factors. JAMA. 2013 Aug 14;310(6):591-608.
140. Roede JR, Uppal K, Park YH, Lee K, Tran V, Strobel FH, Rhodes SL, **Ritz B,** Jones DP. Serum Metabolomics of Slow vs. Rapid Motor Progression Parkinson's Disease: a Pilot Study. PLoS One. 2013 Oct 22;8(10):e77629. PMCID:PMC3805572
141. Nielsen M, Hansen J, **Ritz B**, Nordahl H, Schernhammer E, Wermuth L, Rod NH. Cause-specific mortality among spouses of Parkinson disease patients. Epidemiology. 2014 Mar;25(2):225-32.
142. Heck JE, Wu J, Lombardi CA, Meyers TJ, Wilhelm M, Cockburn M, **Ritz B.** Childhood cancer and traffic-related air pollution exposure in pregnancy and early life. Environ Health Perspect. 2013 11-12;121(11-12):1385-1391. PMCID: PMC3855517
143. Heck JE, Park AS, Qiu J, Cockburn M, **Ritz B**. An exploratory study of ambient air toxics exposure in pregnancy and the risk of neuroblastoma in offspring. Environ Res. 2013 Nov;127:1-6. PMCID: PMC3960946
144. Rhodes SL, Buchanan D, Ahmed I, Taylor KD, Loriot MA, Sinsheimer JS, Bronstein J, Elbaz A, Mellick G, Rotter JI, **Ritz B**. Pooled Analysis of Iron-related Genes in Parkinson's Disease: Association with Transferrin. Neurobiol Dis. 2014 Feb;62:172-8. PMCID: PMC3968945
145. Wu XM, Bennett DH, **Ritz B**, Tancredi DJ, Hertz-Picciotto I. Temporal variation of residential pesticide use and comparison of two survey platforms: a longitudinal study among households with young children in Northern California. Environ Health. 2013 Aug 20;12(1):65. PMCID: PMC3765515
146. Heck JE, Cockburn M, **Ritz B**. Case-Control Study of Birth Characteristics and the Risk of Hepatoblastoma. Cancer Epidemiol. 2013 Aug;37(4):390-5. PMCID: PMC3679264
147. Heck JE, Park AS, Qiu J, Cockburn M, **Ritz B.** Retinoblastoma and ambient exposure to air toxics in the perinatal period. J Expo Sci Environ Epidemiol. 2013 Nov 27 PMCID: PMC4059784
148. Fitzmaurice AG, Rhodes SL, Cockburn M, **Ritz B**, Bronstein JM. Aldehyde dehydrogenase variation enhances effect of pesticides associated with Parkinson disease. Neurology. 2014 Feb 4;82(5):419-26. PMCID: PMC3917685
149. Liew Z, **Ritz B**, Rebordosa C, Lee PC, Olsen J. Acetaminophen use during pregnancy, behavioral problems and Hyperkinetic disorders. JAMA Pediatr. 2014 Apr;168(4):313-20.
150. Marcotte E, **Ritz B.** Cockburn M, Clarke CA , Heck JE. Birth Characteristics and Risk of Lymphoma in Young Children. Cancer Epidemiology PMCID: PMC4100477
151. Wang A, Cockburn M, Ly TT, Bronstein J, **Ritz B.** The Association Between Ambient Exposure to Organophosphates and Parkinson's Disease Risk. Occup Environ Med. 2014 Apr;71(4):275-81. PMCID:PMC4351788
152. Heck JE, Park AS, Qiu J, Cockburn M, **Ritz B**. Risk of leukemia in relation to exposure to ambient air toxics in pregnancy and early childhood. Int J Hyg Environ Health. 2014 Jul;217(6):662-8. PMCID: PMC4071125
153. Shresta A, **Ritz B**, Wilhelm M, Qiu J, Cockburn M, Heck JE. Prenatal exposure to air toxics and risk of Wilms' tumor in 0-5 year old children. J Occup Environ Med. 2014 Jun;56(6):573-8 PMCID: PMC4204106
154. **Ritz B**, Qiu J, Lee PC, Lurmann F, Penfold B, Weiss RE, McConnell R, Arora C, Hobel C, Wilhelm M. Prenatal Air Pollution Exposure and Ultrasound Measures of Fetal Growth in Los Angeles, California. Environ Research. 2014 Apr;130:7-13. PMCID: PMC4016959
155. Greene N, Lassen C, Rugbjerg K, **Ritz B**. Reproductive factors and Parkinson's disease risk in Danish women. Eur J Neurol. 2014 Sep;21(9):1168-77, e68.
156. Liew Z, **Ritz B**, Bonefeld EC, Henriksen TB, Nohr EA, Bech BH, Fei C, Bossi R, von Ehrenstein O, Streja E, Uldall P, Olsen J. Prenatal Exposure to Perfluoroalkyl Substances and Risk of Congenital Cerebral Palsy in Children. Am J Epidemiol. 2014 Sep 15;180(6):574-81.
157. Becerra T, von Ehrenstein O, Heck JE, Olsen J, Arah O, Jeste S, Rodriguez M, **Ritz B**. Autism and Maternal Race/Ethnicity and Nativity in Los Angeles. Pediatrics. 2014 Jul;134(1):e63-71.PMCID: PMC4067639
158. Marcotte E, Heck J, Cockburn M, Yu F, **Ritz B**. Exposure to Infections and Risk of Leukemia in Young Children. Cancer Epidemiol Biomarkers Prev. 2014 Jul;23(7):1195-203 PMCID: PMC4100471
159. Burdick DJ, Watson GS, Siderowf A, Trojanowski JQ, Weintraub D, **Ritz B**, Rhodes S, Rausch HR, Factor SA, Wood-Siverio C, Quinn JF, Chung K, Cholerton B, Srivatsal S, Edwards KL, Montine TJ, Zabetian CP, Leverenz JB. People with Parkinson's disease and normal MMSE score have a broad range of cognitive performance. Mov Disord. 2014 Sep;29(10):1258-64. PMCID: PMC4162839

160. Mata IF, Leverenz JB, Weintraub D, Trojanowski JQ, Hurtig HI, Van Deerlin V, **Ritz B**, Rausch R, Rhodes SL, Factor SA, Wood-Siverio C, Quinn JF, Chung KA, Peterson AL, Espay AJ, Revilla FJ, Devoto J, Hu SC, Cholerton BA, Montine TJ, Edwards KL, Zabetian CP. APOE, MAPT, and SNCA Genes and Cognitive Performance in Parkinson Disease. JAMA Neurology. 2014 Nov;71(11):1405-12. PMCID: PMC4227942
161. Krøigård T, Christensen J, Wermuth L, **Ritz B**, Lassen CF. The use of antidepressant medication in Parkinson's disease patients is not affected by the type of anti-parkinson medication. J Parkinsons Dis. 2014;4(3):327-30.
162. **Ritz B**, Lee PC, Lassen FC, Arah O. Ease of quitting is an early sign of Parkinson's Disease: Parkinson's and smoking revisited. Neurology. 2014 Oct 14;83(16):1396-402. PMCID: PMC4206154
163. Shelton JF, Geraghty EM, Tancredi DJ, Delwiche LD, Schmidt RJ, Hansen R, **Ritz B,** Hertz-Picciotto I. Neurodevelopmental Disorders and Prenatal Residential Proximity to Agricultural Pesticides: The CHARGE Study. Environ Health Perspect. 2014 Oct;122(10):1103-9. PMCID:PMC4181917
164. von Ehrenstein O, Aralis H, Cockburn M, **B Ritz**. In Utero Exposure to Toxic Air Pollutants and Risk of Childhood Autism. Epidemiology. 2014 Nov;25(6):851-8.PMCID: PMC4698150
165. Gatto N, Deapen D, Stoyonoff S; Pinder R, Narayan S, Bordelon Y, **Ritz B**. Lifetime Exposure to Estrogens and Parkinson's Disease in California Teachers. Parkinsonism Relat Disord. 2014 Nov;20(11):1149-56.
166. Ahmed I, Lee PC, Lill CN, Nielsen SS, Artaud F, Gallagher LG, Loriot MA, Mulot C, Nacfer M, Liu T, Biernacka JM, Armasu S, Anderson K, Farin FM, Lassen CF, Hansen J, Olsen JH, Bertram L, Maraganore DM, Checkoway H, **Ritz B**, Elbaz A. Lack of replication of the GRIN2A-by-coffee interaction in Parkinson's disease. PLoS Genet. 2014 Nov 20;10(11):e1004788. PMCID: PMC4238979
167. Lee PC, Bordelon Y, Bronstein J, Sinsheimer JS, Farrer M; **Ritz B**. Head injury, alpha-synuclein genetic variability and Parkinson's disease. Eur J Neurol. 2015 May;22(5):874-8. PMCID: PMC4390403
168. Kenborg L, Rugbjerg K; Lee PC; Ravnskjær L; Christensen J; **Ritz B**; Lassen CF. Head injury and risk for Parkinson disease: results from a Danish case- control study. Neurology. 2015 Mar 17;84(11):1098-103 PMCID:PMC4371406
169. Kenborg L, Lassen CF, **Ritz B**, Andersen KK, Christensen J, Schernhammer ES, Hansen J, Wermuth L, Rod NH, Olsen JH. Lifestyle, Family History, and Risk for Idiopathic Parkinson Disease: a Large Danish Case-Control Study. Am J Epidemiol. 2015 May 15;181(10):808-16 PMCID:PMC4423523
170. Liew Z, **Ritz B**, von Ehrenstein OS, Bech BH, Nohr E, Fei C, Bossi R, Henriksen TB, Bonefeld-Jørgensen EC, Olsen J. Attention Deficit/Hyperactivity Disorder and Childhood Autism in Association with Prenatal Exposure to Perfluoroalkyl Substances: A Nested Case–Control Study in the Danish National Birth Cohort. Environ Health Perspect. 2015 Apr;123(4):367-73.
171. Liew Z, Olsen J, Cui X**, Ritz B**, Arah OA. Bias from conditioning on live birth in pregnancy cohorts: an illustration based on neurodevelopment in children after prenatal exposure to organic pollutants. Int J Epidemiol. 2015 Feb;44(1):345-54.
172. Bandoli G, von Ehrenstein OS, Flores M, **Ritz B**. Breastfeeding and Asthmatic Symptoms in the offspring of Latinas - the role of maternal nativity. J Immigr Minor Health. 2015 Dec;17(6):1739-45. PMCID:PMC4499015
173. Lill CM, Rengmark A, Pihlstrøm L, Fogh I, Shatunov A, Sleiman PM, Wang LS, Liu T, Lassen CF, Meissner E, Alexopoulos P, Calvo A, Chio A, Dizdar N, Faltraco F, Forsgren L, Kirchheiner L, Kurz A, Larsen JP, Liebsch M, Linder J, Morrison KE, Nissbrandt H, Otto M, Pahnke J, Partch A, Restagno G, Rujescu D, Schnack C, Shaw CE, Shaw PJ, Tumani H, Tysnes OB, Valladares O, Silani V, van den Berg LH, van Rheenen W, Veldink JH, Lindenberger U, Steinhagen-Thiessen E, SLAGEN Consortium, Teipel S, Perneczky R, Hakonarson H, Hampel H, von Arnim CAF, Olsen JH, Van Deerlin VM, Al-Chalabi A, Toft M, **Ritz B**, Bertram L. The role of TREM2 R47H as a risk factor for Alzheimer's disease, frontotemporal lobar degeneration, amyotrophic lateral sclerosis, and Parkinson's disease. Alzheimers Dement. 2015 Apr 29. pii: S1552-5260(15)00122-3.
174. Lombardi C, Ganguly A, Bunin GR, Azary S, Alfonso V, **Ritz B**, Heck JE. Maternal Diet during Pregnancy and Unilateral Retinoblastoma: A Report from the Children's Oncology Group. Cancer Causes Control. 2015 Mar;26(3):387-97. PMCID: PMC4334703
175. Bronstein JM, Paul K, Yang L, Hass RH, Shults CW, **Ritz B.** Platelet Mitochondrial Activity and Pesticide Exposure in Early Parkinson's Disease. Mov Disord. 2015 May;30(6):862-6. PMCID: PMC4439327
176. Srivatsal S, Cholerton B, Leverenz JB, Wszolek ZK, Uitti RJ, Weintraub D, Trojanowski JQ, Van Deerlin VM, Quinn JF, Chung KA, Peterson AL, Factor SA,Wood-Siverio C, Goldman JG, Stebbins

GT, Bernard B, **Ritz B**, Rausch R, Espay AJ, Revilla FJ, Devoto J, Rosenthal LS, Dawson TM, Albert MS, Mata IF, Hu SC, Montine KS, Johnson C, Montine TJ, Edwards KL, Zabetian CP. Cognitive Profile of LRRK2-related Parkinson's Disease. Mov Disord. 2015 Apr 15;30(5):728-33. PMCID: PMC4397146

177. Su JG, Jerrett M, Meng YY, Pickett M, **Ritz B**. Integrating smart-phone based momentary location tracking with fixed site air quality monitoring for personal exposure assessment. Sci Total Environ. 2015 Feb 15; 506-507:518-26.
178. **Ritz B,** Lee PC, Hansen J, Lassen CF, Ketzel M, Sørensen M, Raaschou-Nielsen O. Traffic-Related Air Pollution is a Risk Factor for Parkinson's Disease in Denmark. Environ Health Perspect. 2016 Mar;124(3):351-6.
179. Paul KC, Sinsheimer JS, Rhodes SL, Cockburn M, Bronstein JM**, Ritz B.** Organophosphate Pesticide Exposures, Nitric Oxide Synthase Gene Variants, and Gene-Pesticide Interactions in a Case-Control Study of Parkinson's Disease, California (USA). Environ Health Perspect. 2015 Sep 18. [Epub ahead of print]
180. Lill CM, Hansen J, Olsen JO, Binder H**, Ritz B**, Bertram L. Impact of Parkinson's disease risk loci on age at onset. Mov Disord. 2015 May;30(6):847-50.
181. Gatto NM, Sinsheimer JS, Cockburn M, Escobedo LA, Bordelon Y, **Ritz B**. Vitamin D receptor gene polymorphisms and Parkinson's disease in a Population with High Ultraviolet Radiation Exposure. J Neurol Sci. 2015 May 15;352(1-2):88-93.
182. Kannarkat GT, Cook DA, Lee JK, Chang J, Chung V, Sandy E , Paul KC, **Ritz B**, Bronstein J, Factor SA, Boss JM, Tansey MG. Common Genetic Variant Association with Altered HLA Expression, Synergy with Pyrethroid Exposure, and Risk for Parkinson's Disease: An Observational and Case-Control Study. npj Parkinson's Disease (2015) 1, 15002; doi:10.1038/npjparkd.2015.2; published online 22 April 2015
183. Heck JE, Park AS, Cockburn M, **Ritz B**. Can the "Hispanic paradox" shed light on childhood cancer risk? Cancer Epidemiol Biomarkers Prev. 2015 Apr;24(4):764-5.
184. Pearce NE, Blair A, Vineis P, Ahrens W, Andersen A, Anto JM, Armstrong BK, Baccarelli AA, Beland FA, Berrington A, Bertazzi PA, Birnbaum LS, Brownson RC, Bucher JR, Cantor KP, Cardis E, Cherrie JW, Christiani DC, Cocco P, Coggon D, Comba P, Demers PA, Dement JM, Douwes J, Eisen EA, Engel LS, Fenske RA, Fleming LE, Fletcher T, Fontham E, Forastiere F, Frentzel-Beyme R, Fritschi L, Gerin M, Goldberg M, Grandjean P, Grimsrud TK, Gustavsson P, Haines A, Hartge P, Hansen J, Hauptmann M, Heederik D, Hemminki K, Hemon D, Hertz-Picciotto I, Hoppin JA, Huff J, Jarvholm B, Kang D, Karagas MR, Kjaerheim K, Kjuus H, Kogevinas M, Kriebel D, Kristensen P, Kromhout H, Laden F, Lebailly P, LeMasters G, Lubin JH, Lynch CF, Lynge E, 't Mannetje A, McMichael AJ, McLaughlin JR, Marrett L, Martuzzi M, Merchant JA, Merler E, Merletti F, Miller A, Mirer FE, Monson R, Nordby KK, Olshan AF, Parent ME, Perera FP, Perry MJ, Pesatori AC, Pirastu R, Porta M, Pukkala E, Rice C, Richardson DB, Ritter L, **Ritz B**, Ronckers CM, Rushton L, Rusiecki JA, Rusyn I, Samet JM, Sandler DP, de Sanjose S, Schernhammer E, Seniori Constantini A, Seixas N, Shy C, Siemiatycki J, Silvermann DT, Simonato L, Smith AH, Smith MT, Spinelli JJ, Spitz MR, Stallones L, Stayner LT, Steenland K, Stenzel M, Stewart BW, Stewart PA, Symanski E, Terracini B, Tolbert PE, Vainio H, Vena J, Vermeulen R, Victora CG, Ward EM, Weinberg CR, Weisenburger D, Wesseling C, Weiderpass E, Zahm SH. IARC Monographs: 40 Years of Evaluating Carcinogenic Hazards to Humans. Environ Health Perspect. 2015 Feb 24. [Epub ahead of print]
185. Schernhammer ES, Lassen CF, Kenborg L, **Ritz B**, Olsen JH, Hansen J. Night shift work and Parkinson's disease in Denmark. Scand J Work Environ Health. 2015 Jul 1;41(4):377-83.
186. Walker RF, Liu JS, Peters BA, **Ritz BR**, Ophoff R, Horvath S. Epigenetic age analysis of blood from "Peter Pan" children". Aging (Albany NY). 2015 May;7(5):334-9.
187. von Ehrenstein, Aralis H, Flores MS, **Ritz B**. Fast Food Consumption in Pregnancy and Subsequent Asthma Symptoms in Young Children. Pediatr Allergy Immunol. 2015 Sep;26(6):571-7.
188. Coker ES, Beckerman B, Ghosh JC, Gomez-Rubio V, Jerrett M, Li A, Liverani S, **Ritz B**, Su J, Molitor J. Modeling spatial effects of PM2.5 on term low birth weight in Los Angeles County. Environ Res. 2015 Jul 17;142:354-364.
189. Narayan S, Sinsheimer JS, Paul KC, Liew Z, Cockburn M, Bronstein JM, **Ritz B**. Genetic Variability in ABCB1, Occupational Pesticide Exposure, and Parkinson's Disease. Environ Res. 2015 Nov;143 (Pt A):98-106.
190. Mata IF, Leverenz JB, Weintraub D, Trojanowski JQ, Chen-Plotkin A, Van Deerlin VM, **Ritz B**, Rausch R, Factor SA, Wood-Siverio C, Quinn JF,Chung KA, Peterson-Hiller AL, Goldman JG, Stebbins GT, Bernard B, Espay AJ, Revilla FJ, Devoto J, Rosenthal LS, Dawson TM, Albert MS, Tsuang D, Huston H, Yearout D, Hu SC, Cholerton BA, Montine TJ, Edwards KL, Zabetian CP. GBA

variants are associated with a distinct pattern of cognitive deficits in Parkinson disease. Mov Disord. 2016 Jan;31(1):95-102.

191. von Ehrenstein OS, Heck JE, Park A, Cockburn M, Escobedo L, **Ritz B**. In Utero and Early-Life Exposure to Ambient Air Toxics and Childhood Brain Tumors: A Population-Based Case-Control Study in California, USA. Environ Health Perspect. 2016 Jul;124(7):1093-9. PMCID: PMC4937846
192. Virk J, Liew Z, Olsen J, Nohr E, Catov JM, **Ritz B**. Preconceptional and Prenatal Supplementary Folic Acid and Multivitamin Intake and Autism Spectrum Disorders. Autism. 2016 Aug;20(6):710-8.
193. Bandoli G, von Ehrenstein OS, Gosh JKC, Flores M, Dunkel-Schetter C**, Ritz B**. Prenatal maternal stress and the risk of lifetime wheeze in young offspring: An examination by stressor and maternal race/ethnicity. J Immigr Minor Health. 2016 Oct;18(5):987-95.
194. Heck JE, Azary S, **Ritz B**, Bunin GR, Ganguly A. A case-control study of sporadic retinoblastoma in relation to maternal health conditions and reproductive factors. BMC Cancer. 2015 Oct 19;15:735. PMCID: PMC4615328
195. Virk J, **Ritz B,** Li J, Obel C, Olsen J. Childhood Bereavement and Type 1 Diabetes: A Danish National Register Study. Paediatr Perinat Epidemiol. 2016 Jan;30(1):86-92.
196. Julvez J, Paus T, Bellinger D, Eskenazi B, Tiemeier H, Pearce N, **Ritz B**, White T, Ramchandani P, Gispert JD, Desrivières S, Brouwer R, Boucher O, Alemany S, López-Vicente M, Suades-González E, Forns J, Grandjean P, Sunyer J. Environment and Brain Development: Challenges in the Global Context. Neuroepidemiology. 2015 Dec 19;46(2):79-82.
197. Wermuth L, Cui X, Greene NH, Schernhammer ES, **Ritz BR**. Medical Record Review to Differentiate between Idiopathic Parkinson's Disease (IPD) and Parkinsonism: A Danish Record Linkage Study with 10 Years of Follow-up. Parkinsons Dis. 2015;2015:781479.
198. Liew Z, **Ritz B**, Virk J, Olsen J. Maternal Use of Acetaminophen During Pregnancy and Risk of Autism Spectrum Disorders in Childhood: a Danish National Birth Cohort Study. Autism Res. 2016 Sep;9(9):951-8.
199. Horvath S, **Ritz BR.** Increased epigenetic age and granulocyte counts in the blood of Parkinson's disease patients. Aging (Albany NY). 2015 Dec;7(12):1130-42.
200. Liew Z, **Ritz B**, Virk J, Arah O, Olsen J Prenatal Use of Acetaminophen and Child IQ: a Danish Cohort Study. Epidemiology. 2016 Nov;27(6):912-8.
201. Heck JE, Park AS, Contreras ZA, Davidson TB, Hoggatt KJ, Cockburn M, **Ritz B**. Cancer in the Children of US and Foreign-born Hispanics: a test of the "Hispanic paradox" JAMA Pediatr. 2016 Jun 1;170(6):585-92.
202. Paul KC, Rausch R, Creek MM, Sinsheimer JS, Bronstein JM, Bordelon Y, **Ritz B.** APOE, MAPT, and COMT genetic variants and cognitive symptom progression in a Parkinson's disease patient cohort. J Parkinsons Dis. 2016 Apr 2;6(2):349-59.
203. **Ritz B**, Paul KC, Bronstein JM. Of Pesticides and Men: A California Story of Genes and Environment in Parkinson's Disease. Curr Environ Health Rep. 2016 Mar;3(1):40-52.
204. Coker E, Liverani S, Ghosh J, Jerrett M, Beckerman B, Su J, Li A, **Ritz B,** Molitor J. A. Multi-Pollutant Exposure Profiles Associated with Term Low Birth Weight in Los Angeles County. Environ Int. 2016 May;91:1-13.
205. Heck JE, Contreras ZE, Park AS, Cockburn M, **Ritz B**. Smoking in pregnancy and risk of cancer among young children: a population-based study. Int J Cancer. 2016 Aug 1;139(3):613-6.
206. Azary S, Ganguly A, Bunin GR, Lombardi C, Park AS, **Ritz B**, Heck JE. Sporadic Retinoblastoma and Parental Smoking and Alcohol Consumption before and after Conception: A Report from the Children's Oncology Group. PLoS One. 2016 Mar 18;11(3):e0151728
207. Alfonso VH, Bandoli G, von Ehrenstein O, **Ritz B**. The influence of pre-natal supplement initiation on preterm birth among majority Hispanic women in Los Angeles County: the role of nativity. Matern Child Health J. 2016 Sep;20(9):1861-8.
208. Bandoli G, Ghosh J, von Ehrenstein O, **Ritz B**. Psychosocial stressors and lung function in youth ages 10-17: an examination by stressor, age and gender. J Public Health (Oxf). 2016 May 8. pii: fdw035. [Epub ahead of print]
209. Bandoli G, Ghosh J, von Ehrenstein O, **Ritz B.** Synergistic effects of air pollution and psychosocial stressors on adolescent lung function. J Allergy Clin Immunol. 2016 Apr 30. pii: S0091-6749(16)30196-8. [Epub ahead of print]
210. Shih IF, Liew Z, Krause N, **Ritz B**. Lifetime Occupational and Leisure Time Physical Activity and Risk of Parkinson's Disease Parkinsonism & Related Disorders. Parkinsonism Relat Disord. 2016 Jul;28:112-7.

211. Contreras ZA, **Ritz B**, Virk J, Cockburn M, Heck JE. Maternal diabetes, obesity, weight gain in pregnancy, and risk of childhood cancer in offspring: a population-based study in California. Cancer Causes Control. 2016 Oct;27(10):1273-85.
212. Levine ME, Lu AT, Chen BH, Hernandez DG, Singleton AB, Ferrucci L, Bandinelli S, Salfati E, Manson JE, Quach A, Kusters CDJ, Kuh D, Wong A, Teschendorff AE, Widschwendter M, **Ritz BR**, Absher D, Assimes T, Horvath S.. Menopause accelerates biological aging. Proc Natl Acad Sci U S A. 2016 Aug 16;113(33):9327-32.
213. Kettner LO, Kesmodel US, Ramlau-Hansen CH, Bay B, **Ritz B**, Matthiesen NB, Brink Henriksen T. Fertility Treatment and Childhood Epilepsy: a Nationwide Cohort Study of 565,166 Live Births. Paediatr Perinat Epidemiol. 2016 Sep;30(5):488-95.
214. Hill-Burns EM, Ross OA, Wissemann WT, Ortolaza AI, Mellick GD, Scherzer CR, **Ritz B**, Marthi V, Zareparsi S, Zabetian CP, Factor SA, Payami H. Identification of genetic modifiers of age-at-onset for familial Parkinson's disease. Hum Mol Genet. 2016 Jul 11. pii: ddw206.
215. Su J, Meng YY, Pickett M, Seto E**, Ritz B,** Jerrett M. Identification of the effects of regulatory actions on improvements in air quality in the goods movement corridors. Environ Sci Technol. 2016 Aug 16;50(16):8687-96.
216. Horvath S, Gurven M, Levine ME, Trumble BC, Kaplan B, Allayee H, **Ritz BR**, Chen B, Lu AT, Rickabaugh TM, Jamieson BD, Sun D, Li S, Chen W, Quintana-Murci L, Fagny M, Kobor MS, Tsao PS, Reiner AP, Edlefsen KL, Absher D, Assimes TL. An epigenetic clock analysis of race/ethnicity, sex, and coronary heart disease. Genome Biol. 2016 Aug 11;17(1):171.
217. Lee PC, Raaschou-Nielsen O, Lill CM, Bertram L, Sinsheimer JS, Hansen J, **Ritz B**. Gene-environment interactions linking air pollution and inflammation in Parkinson's disease. Environ Res. 2016 Nov;151:713-720.
218. Contreras ZA, **Ritz B**, Virk J, Cockburn M, Heck JE. Maternal pre-pregnancy and gestational diabetes, obesity, gestational weight gain, and risk of cancer in young children: a population-based study in California. Cancer Causes Control. 2016 Oct;27(10):1273-85
219. A European Respiratory Society & American Thoracic Society Policy Statement: What Constitutes an Adverse Health Effect of Air Pollution? An analytical framework Joint ERS/ATS statement'
220. Gatto NM, Paul K, Sinsheimer JS, Bronstein JM, Bordelon Y, Rausch R, Ritz B., **Ritz B**. Vitamin D receptor gene polymorphisms and cognitive decline in Parkinson's disease. J Neurol Sci. 2016 Nov 15;370:100-106.
221. Liew Z, Bach CC, Asarnow RF, **Ritz B**, Olsen J. Paracetamol use during pregnancy and attention and executive function in offspring at age 5. International Journal of Epidemiology 2016;
222. Chuang YH, Lill CM, Lee PC, Hansen J, Lassen CF, Bertram L, Greene N, Sinsheimer JS, **Ritz B.** Gene-environment interaction in Parkinson's disease: coffee, ADORA2A, and CYP1A2. Accepted in Neuroepidemiology.
223. Malmqvist E, Liew Z, Källén K, Rignell-Hydbom A, Rittner R, Rylander L, **Ritz B.** Fetal growth and air pollution -A study on ultrasound and birth measures. Environ Res. 2016 Oct 11;152:73-80.
224. Hall C, **Ritz B**, Cockburn M, Davidson TB, Heck JE. Risk of malignant childhood germ cell tumors in relation to demographic, gestational, and perinatal characteristics. Accepted for publication in Cancer Epidemiology
225. Lee PC, Liu LL, Sun Y, Chen YA, Liu CC, Li CY, Yu HL, **Ritz B.** Traffic-related air pollution increased the risk of Parkinson's disease in Taiwan: A nationwide study. Environ Int. 2016 Nov;96:75-81.
226. Chuang YH, Austin Quach A, Absher D, Assimes T, Horvath S, **Ritz B**. Coffee consumption is associated with DNA methylation levels of human blood. Accepted: European Journal of Human Genetics
227. Virk J, Liew Z, Olsen J, Nohr EA, **Ritz B**. Pre-conceptual and Prenatal Supplementary Folic Acid and Multivitamin Intake, Behavioral Problems and Hyperkinetic Disorders, A Study Based on the Danish National Birth Cohort (DNBC). Accepted in Nutritional Neuroscience
228. Xu X, **Ritz B**, Cockburn M, Lombardi C, Heck J. Maternal Preeclampsia and Odds of Childhood Cancers in Offspring — A California Statewide Case-Control Study. Paediatric and Perinatal Epidemiology
229. Omidakhsh N, Ganguly A, Bunin GR, **Ritz B,** Ehrenstein O, Heck JE.. Residential pesticide exposures in pregnancy and the risk of sporadic retinoblastoma: a report from the Children's Oncology Group. Journal of Ophthalmology
230. Quach A, Levine M, Tanaka T, Lu A, Chen B, Ferrucci L, **Ritz B**, Neuhouser M, Beasly J, Snetselaar L, Wallace R, Tsao P, Absher D, Assimes T, Stewart J, Li Y, Hou L, Baccarelli A, Whitsel E, Horvath S. Epigenetic clock analysis of diet, exercise, education, and lifestyle factors. Aging.

231. Shih I, Starhof C, Lassen CF, Hansen J, Liew Z, **Ritz, B**.Occupational and Recreational Physical Activity and Parkinson's Disease in Denmark. In Press: Scand J Work Environ Health
232. McAllister K, Mechanic LE, Amos C, Aschard H, Blair I, Chatterjee N, Conti D, Gauderman WG, Hsu L, Hutter CM, Jankowska M, Kerr J, Kraft P, Montgomery SB, Mukherjee B, Papanicolaou GJ, Patel CJ, Ritchie MD, **Ritz BR**, Thomas DC, Wei P, Witte JS on behalf of GxE meeting participants. Current Challenges and New Opportunities for Gene-Environment Interaction Studies of Complex Diseases. Accepted: AJE
233. **Ritz BR**, Chatterjee N, Garcia-Closas M, Gauderman JW, Pierce BL, Kraft P, Tanner CM, Mechanic LE, McAllister K. Lessons Learned from Past Gene-Environment (GxE) Interaction Successes. Accepted: AJE
234. Narayan S, Sinsheimer JS, Paul KC, Liew Z, Cockburn M, Bronstein JM, **Ritz B**. Occupational Pesticide Use and Parkinson's Disease in the Parkinson Environment Gene (PEG) Study. Accepted in: Environment International
235. Mata, Johnson, Leverenz, Weintraub, Trojanowski, Van Deerlin, **Ritz**, Rausch, Factor, Wood-Siverio, Quinn, Chung, Peterson-Hiller, Espay, Revilla, Devoto, Yearout, Hu, Cholerton, Montine, Edwards, Zabetian. Large-scale Exploratory Genetic Analysis of Cognitive Impairment in Parkinson's Disease. Accepted: Neurobiology of Aging
236. Sanders LH, Paul KC, Howlett EH, Lawal H, Boppana S, Bronstein J, **Ritz B**, Greenamyre TJ. Base excision repair variants and pesticide exposure increase Parkinson's disease risk. Accepted: Toxicological Sciences

MANUSCRIPTS CURRENTLY UNDER REVIEW

1. Chuang YH, Paul K, Bronstein J, Horvath S, Ritz B. EWAS in Parkinson's disease. Movement Disorders.
2. Paul KC, Ling C, Haan M, Ritz B. Organophosphate pesticides exposure and cognitive decline in SALSA. EHP
3. Paul KC, Sinsheimer JS, Cockburn M, Bronstein JM, Bordelon Y,Ritz BR. Organophosphate pesticide exposure and PON1 L55M in Parkinson's disease progression. Environment International
4. Paul KC, Sinsheimer JS, Cockburn M, Bronstein JM, Bordelon Y, Ritz B. NFE2L2, PPARGC1α, and Oxidative Stress in Parkinson's disease susceptibility and progression. Environ Health
5. Reading SR, Arun S Karlamangla,; Tara L Gruenewald,; Natalie Slopen, David R Williams, Dallas T Swendeman; Beate R Ritz, Brandon Koretz; Teresa E Seeman. Relationship between Psychosocial Stressors and Allostatic Load: Findings from the MIDUS Study. Annals of Behavioral Medicine.
6. Alfonso,VH, Bandoli G, von Ehrenstein O, Ritz B. Early folic acid supplement initiation and risk of adverse early childhood respiratory health: A Los Angeles population-based study. Maternal and Child Health Journal
7. Contreras ZA, Hansen J, Ritz B, Olsen B, Yu F, Heck JE. Parental age and childhood cancer risk: A Danish population-based registry study. Cancer Causes Controls
8. Alfonso,VH, Wang MC, von Ehrenstein O, Bandoli G, Ritz B. Enrollment in the Special. Supplemental Program for Women, Infants and Children reduces risk of recurrent preterm birth among eligible California siblings. IJE
9. Lee PC, Nielsen S, Loriot MA, Hansen J, Lill C, Checkoway H, Elbaz A, Ritz B. Meta-analysis of head injuries and *SNCA* interactions in Parkinson Disease. Neurology
10. Lee PC, Ahmed I, Loriot MA, Mulot C, Lambert JC, Ritz B, Elbaz A. Smoking and Parkinson's disease: evidence for gene-by-smoking interactions. Neurology
11. Patel CJ, Kerr J, Thomas DC, Mukherjee B, Ritz BR, Chatterjee N, Jankowska M, Madan J, Karagas MR, McAllister K, Leah E. Mechanic10, M. Daniele Fallin11, Chris Ladd-Acosta11, Ian Blair12, Susan Teitelbaum13, Amos CI. Opportunities and Challenges for Environmental Exposure Assessment in Population-Based Studies. AJE
12. Wojcik KY, Escobedo LA, Wysong A, Heck JE, Ritz B, Cockburn M. High Birth Weight, Early UV exposure, and Melanoma Risk in Children, Adolescents and Young Adults. Pediatrics.
13. Park AS, B Ritz, C Ling, M Cockburn, JE Heck. Exposure to Ambient Dichloromethane in Pregnancy and Infancy from Industrial Sources and Childhood Cancers in California.
14. Omidakhsh N, Heck JE, **Ritz B**, Kennedy N, Ehrenstein OS, Krause N, Ganguly A, Bunin GR.. Parental occupational exposures and the risk of childhood sporadic retinoblastoma: a report from the Children's Oncology Group. Occupational and Environmental Medicine
15. Li L, Lurmann F, Habre R, Urman R, Rappaport E, **Ritz B**, Chen JC, Gilliland FD, Wu J. Constrained Mixed-Effect Models with Ensemble Learning for Prediction of Nitrogen Oxide Concentrations at a High

Spatiotemporal Resolution. Environmental Science & Technology.

INVITED COMMENTARIES AND EDITORIAL (peer reviewed)

1. **Ritz B.** Environmental Toxins and Neurodegenerative Diseases: A Challenge for Epidemiologists. Epidemiology. 2006 Jan;17(1):2-3.
2. Kheifets, L, **Ritz B.** Electromagnetic Fields, Science and Public Concern. Soz Praeventive Med 51 (2006): 1-2.
3. **Ritz, B**. Wahner A*, Bordelon Y, Bronstein J. Can Anti-Inflammatory Agents Protect Against Parkinson's Disease? Future Neurology 2008
4. Chesselet M-F, **Ritz B**. Transcriptional regulation of α-synuclein: insights from blood? Commentary on: GATA transcription factors directly regulate the Parkinson's disease-linked gene alpha-synuclein; Scherzer et al. Future Neurology, March 2009, Vol. 4, No. 2, Pages 145-147
5. **Ritz, B.** Birth defects and ambient air pollution, opportunities and challenges. Editorial; Occup Environ Med. 2010 Apr;67(4):221-2.
6. **Ritz B**, Rhodes SL. After half a century of research on smoking and PD, where do we go now? Neurology. 2010 Mar 16;74(11):870-1.
7. Bower J, **Ritz B**. Is the answer for Parkinson disease already in the medicine cabinet? Unfortunately not. Neurology. 2011 Mar 8;76(10):854-5.
8. Blair A, **Ritz B**, Wesseling C, Beane Freeman L. Pesticides and human health. Occup Environ Med. 2015 Feb;72(2):81-2.

BOOKS AND MONOGRAPHS

1. Karmaus W, Glaser-Möller N, Hullmann B, **Ritz B**, Schäfer K-H, Sonn E: Arbeitsbedingte rheumatische Erkrankungen, Büroarbeit und Bewältigung. Ergebnisse einer Längsschnittstudie von weiblichen Angestellten. *("Working Conditions, Health Behaviour and Rheumatic Disorders II; Results of a Longitudinal Study on Female Office Workers")* Forschungsbericht des BMFT, HDA 01 HA 033/4, 1987.
2. Hullmann B, Karmaus W, Osterholz U, **Ritz B**: Work-Related Musculo-Skeletal Disorders. Proceedings of an International Symposium. HDA, Tagungsbericht TB 48, Wirtschaftsverlag NW, Bremerhaven, 1987.
3. Osterholz U, Patjens S, **Ritz B**: Forschungsdokumentation "Rheuma und Arbeit" *"Research Documenation on Working Conditions and Musculo-Skeletal Disorders"*). Arbeitspapier Nr 10, Projektgruppe HdA des WSI, Eds.: Geschäftsführung des WSI, Düsseldorf, 1987.

PEER REVIEWED REPORTS

1. Morgenstern H, Froines J., **Ritz B**, Young B. Epidemiologic Study to Determine Possible Adverse Effects to Rocketdyne/AI Workers from Exposure to Selected Chemicals. July 1998
2. Morgenstern H, Froines J., **Ritz B**, Young B. Epidemiologic Study to Determine Possible Adverse Effects to Rocketdyne/AI Workers from Exposure to Ionizing Radiation. June 1997.
3. Sloss E, Geschwind SA, McCaffrey DF, **Ritz B**. Groundwater Recharge with Reclaimed Water - An Epidemiologic Assessment in Los Angeles County, 1987-1991. Rand Technical Report DRR-1192-WRDSC, 1995
4. Karmaus W, Glaser-Moeller N, Hullmann B, **Ritz B**, Schäfer K-H, Sonn E: Final Report of the project "Arbeitsbedingte rheumatische Erkrankungen in der Verwaltung" *("Work Related Rheumatic Disorders in Administrative Jobs")* Schriftenreihe der Bundesanstalt fuer Arbeitsschutz, Forschung Fb 608, Bonn, 1990.
5. Sloss E, McCaffrey DF, Fricker RD, Geschwind, SA, **Ritz B**. Groundwater Recharge with Reclaimed Water - Birth Outcomes in Los Angeles County, 1982-1993. Rand Technical Report, 1999.
6. **Ritz, B.** X- & Gamma Radiation and Neutrons. In: Report on Carcinogens, 11th edition. Carcinogen Profiles. U.S. Department of Health and Human Services, Public Health Service, National Toxicology Program. 2004.
7. Meng YY, Rull RP, Wilhelm M, **Ritz B**, English P, Yu H, Nathan S, Kuruvilla M, Brown ER. Living near heavy traffic increases asthma severity. Policy Brief UCLA Cent Health Policy Res. 2006 Aug:1-5.

8. Molitor J, Coker E, Jerrett M, **Ritz B**, Li A; Health Review Committee. Part 3. Modeling of Multipollutant Profiles and Spatially Varying Health Effects with Applications to Indicators of Adverse Birth Outcomes.Res Rep Health Eff Inst. 2016 Apr;(183 Pt 3):3-47.

CHAPTERS OR SECTIONS IN BOOKS

1. Appelt H, **Ritz B**: Medikamentengebrauch und -abhängigkeit bei Frauen ("FemaleDrug Abuse and Dependency"). In: Medikamente und Sucht, Berichtsheft zur Arbeitstagung der Hamburgischen Landesstelle gegen die Suchtgefahren e.V.(Eds.) Hamburg 1984.
2. **Ritz B**, Karmaus W, Ellinger S: Schmerz-,Beruhigungs-und Schlafmittel - die verordnete Normalität ("Pain Killers, Sleeping Pills and Tranquilizers - Prescribed Norms"). In: Jahresheft 1984 Hamburgische Landesstelle gegen die Suchtgefahren e.V.(Eds.) Hamburg 1984.
3. Glaser N, **Ritz B**: Lungenkrebs, Rauchen und Schadstoffbelastung bei Hamburger Gaswerkern; Risikoabschätzung anhand der logistischen Regression ("Lung Cancer, Smoking and Air Pollutants of Workers Employed at the Hamburg Gas Company "). In: Muß Arbeit krank machen? Eds: G.Elsner, W.Karmaus, L.Lißner, VSA-Verlag,Hamburg 1986.
4. **Ritz B:** Zur Epidemiologie degenerativer rheumatischer Erkrankungen im Zusammenhang mit Arbeitsbedingungen: Halswirbelsäulenveränderungen bei weiblichen Verwaltungsangestellten ("The Epidemiology of Musculo-Skeletal Disorders and Working Conditions of Female Office Workers: Work-Related Neck Disorders"). In: Rheuma und Krebs; Beiträge zur wissenschaftlichen Jahrestagung der Deutschen Gesellschaft für Sozialmedizin Eds: E.O. Krasemann, U.Laaser, E.Schach, Springer Verlag, Heidelberg, München 1987.
5. **Ritz B**: Methodological Aspects in Studying Musculo- Skeletal Disorders and Working Conditions in Office Work Places. In: Work-related musculo-skeletal disorders. Proceedings of an International Symposium. HDA, Tagungsbericht TB 48, Wirtschaftsverlag NW, Bremerhaven, 1987.
6. **Ritz B**, Hullmann B: How Women Office Workers Deal with Stress In: Health Promotion in the Working World. Springer-Verlag Berlin Heidelberg 1989.
7. **Ritz B**: Chapter 3 - Health and Regulatory Considerations In: Using Reclaimed Water to Augment Potable Water Resources. Water Environment Federation, Virginia 1998.
8. **Ritz B**, Karmaus W: Die Nutzung von Surveillance-programmen und Registern fuer umweltbezogene Fragestellungen (The use of surveillance programs and registries for environmental health research: a historical perspective). In Press: Buch zur Verabschiedung von Heidrun Kaupen-Haas, Mabuse Verlag 2002
9. Van Den Eeden S, **Ritz B**, Cobb K. Measurement and Analysis. In: Neuroepidemiology; From Principles to Practice. Eds: Nelson L, Tanner C, Van Den Eeden S, McGuire V. Oxford University Press 2004.
10. **Ritz B**, and other Committee Members: Chapter 4 Cancer: Gulf War and Health volume 3, Fuels, Combustion products, and Propellants, The National Academies Press Washington, D.C., 2005
11. **Ritz B**, and other Committee Members: Amyotrophic Lateral Sclerosis in Veterans. Review of the scientific literature. IOM, NAS National Academy Press, Washington DC, 2006

LETTERS AND OTHER PUBLICATIONS

1. Morgenstern H, **Ritz B.** Workplace Radiation is Indeed Harmful (letter). Los Angeles Times, March 2, 1998, p S6.
2. Morgenstern H, **Ritz B**. Alarming But Neither Absurd nor Amusing (letter). Washington Post, Febuary 11, 1998, p S6.
3. **Ritz B**: Der Einfluß sozialer und struktureller Bedingungen an Büroarbeitsplätzen auf den Gebrauch psychotroper Medikamente; Ergebnisse einer epidemiologischen Untersuchung *("The Influence of Psycho-Social Factors and Job Latitudes on the Use of Psychotropic Medication")*. Ph.D.Dissertation, Hamburg 1986.
4. Meng YY, Rull RP*, Wilhelm M, **Ritz B**, English P, Yu H, Nathan S, Kuruvilla M, Brown ER. Living near heavy traffic increases asthma severity. Policy Brief UCLA Cent Health Policy Res. 2006 Aug;1-5

5. Grandjean B, Bellinger D, Bergman A, Cordier S, Davey-Smith G, Eskenazi B, Gee D, Gray K, Hanson M, Van den Hazel P, Heindel JJ, Heinzow P, Hertz-Picciotto I, Hu H, Huang TK, Kold Jensen T, Landrigan PJ, McMillen IC, Murata K, **Ritz B**, Schoeters G, Skakkebæk NE, Skerfving S, Weihe P. The Faroes Statement: Human Health Effects of Developmental Exposure to Chemicals in Our Environment. Basic & Clinical Pharmacology & Toxicology, 2007
6. Slama R, Darrow L, Parker J, Woodruff TJ, Strickland M, Nieuwenhuijsen M, Glinianaia S, Hoggatt KJ*, Kannan S, Hurley F, Kalinka J, Srám R, Brauer M, Wilhelm M, Heinrich J, **Ritz B**. Meeting report: atmospheric pollution and human reproduction. Environ Health Perspect. 2008 Jun;116(6):791-8
7. Popat RA, Van Den Eeden SK, Tanner CM, Kamel F, Umbach DM, Marder K, **Ritz B**, Webster Ross G, Petrovitch H, Topol B, McGuire V, Nelson LM. Response to Hill-Burns et al. letter: An attempt to replicate interaction between coffee and CYP1A2 gene in connection to Parkinson's disease. Eur J Neurol. 2011 Sep;18(9):e109.
8. Liew Z, **Ritz B**, Olsen J. Characteristics of acetaminophen users compared with nonusers during pregnancy, behavioral problems, and hyperkinetic disorders--reply. JAMA Pediatr. 2014 Sep;168(9):865-6.
9. Liew Z, Olsen J, Cui X, **Ritz B**, Arah OA. Response to Werler and Parker letter: Comment on live-birth bias in pregnancy cohorts. Int J Epidemiol. 2015 Jun;44(3):1080-1
10. Bennett D, Bellinger DC, Birnbaum LS, Bradman A, Chen A, Cory-Slechta DA, Engel SM, Fallin MD, Halladay A, Hauser R, Hertz-Picciotto I, Kwiatkowski CF, Lanphear BP, Marquez E, Marty M, McPartland J, Newschaffer CJ, Payne-Sturges D, Patisaul HB, Perera FP, **Ritz B**, Sass J, Schantz SL, Webster TF, Whyatt RM, Woodruff TJ, Zoeller RT, Anderko L, Campbell C, Conry JA, DeNicola N, Gould RM, Hirtz D, Huffling K, Landrigan PJ, Lavin A, Miller M, Mitchell MA, Rubin L, Schettler T, Tran HL, Acosta A, Brody C, Miller E, Miller P, Swanson M, Witherspoon NO. 2016. Project TENDR: Targeting Environmental Neuro-Developmental Risks. Project TENDR: Targeting Environmental Neuro-Developmental Risks The TENDR Consensus Statement. Environ Health Perspect. 2016 Jul 1;124(7):A118-22.
11. Thurston GD, Kipen H, Annesi-Maesano I, Balmes J, Brook RD, Cromar K, De Matteis S, Forastiere F, Forsberg B, Frampton MW, Grigg J, Heederik D, Kelly FJ, Kuenzli N, Laumbach R, Peters A, Rajagopalan ST, Rich D, **Ritz B,** Samet JM, Sandstrom T, Sigsgaard T, Sunyer J, Brunekreef B. A joint ERS/ATS policy statement: what constitutes an adverse health effect of air pollution? An analytical framework. Eur Respir J 2017; 49:1600419.

EXHIBIT B

Studies excluded from the present review and the reasons for exclusion

Brown et al, "Pesticide exposures and multiple myeloma in Iowa men."[1]	Only provided results for multiple myeloma.
Fritschi et al, "Occupational exposure to pesticides and risk of non-Hodgkin's lymphoma." [2]	This paper did not report an effect estimate specific to glyphosate
Flower et al, "Cancer risk and parental pesticide application in children of Agricultural health study participants."[3]	Study took place in children; no specific glyphosate- lymphoma associations were reported.
Hoar et al, "Agricultural herbicide use and risk of lymphoma and self-tissue sarcoma."[4]	Results specific to glyphosate were not reported.
Kachuri et al, "Multiple pesticide exposures and the risk of multiple myeloma in Canadian men."[5]	Results only reported for multiple myeloma.
Landgren et al, "Pesticide exposure and risk of monoclonal gammopathy of undetermined significance in the Agricultural Health Study."[6]	Monoclonal gammopathy of undetermined Significance (MGUS) is a precursor condition to multiple myeloma.
Sorahan, "Multiple Myeloma and Glyphosate Use: A Re-Analysis of US Agricultural Health Study (AHS) Data."[7]	Only provided results for multiple myeloma.
Waddell et al, "Agricultural use of organophosphate pesticides and the risk of non-Hodgkin's lymphoma among male farmers (United States)."[8]	This study did not report on glyphosate.
Zhang et al, 2016, "Health effect of agricultural pesticide use in China: implications for the development of GM crops."[9]	This article examined blood chemistry measures in relation to glyphosate, (markers for renal and hepatic function such as electrolytes, B vitamins, serum glucose, C-reactive protein, and peripheral nerve conduction). Not directly relevant for NHL

References

1. Brown LM, Burmeister LF, Everett GD, Blair A. Pesticide exposures and multiple myeloma in Iowa men. *Cancer Causes Control.* 1993;4(2):153-156.
2. Fritschi L, Benke G, Hughes AM, et al. Occupational exposure to pesticides and risk of non-Hodgkin's lymphoma. *Am J Epidemiol.* 2005;162(9):849-857.
3. Flower KB, Hoppin JA, Lynch CF, et al. Cancer risk and parental pesticide application in children of Agricultural Health Study participants. *Environ Health Perspect.* 2004;112(5):631-635.
4. Hoar SK, Blair A, Holmes FF, et al. Agricultural herbicide use and risk of lymphoma and soft-tissue sarcoma. *JAMA.* 1986;256(9):1141-1147.
5. Kachuri L, Demers PA, Blair A, et al. Multiple pesticide exposures and the risk of multiple myeloma in Canadian men. *Int J Cancer.* 2013;133(8):1846-1858.
6. Landgren O, Kyle RA, Hoppin JA, et al. Pesticide exposure and risk of monoclonal gammopathy of undetermined significance in the Agricultural Health Study. *Blood.* 2009;113(25):6386-6391.
7. Sorahan T. Multiple myeloma and glyphosate use: a re-analysis of US Agricultural Health Study (AHS) data. *Int J Environ Res Public Health.* 2015;12(2):1548-1559.
8. Waddell BL, Zahm SH, Baris D, et al. Agricultural use of organophosphate pesticides and the risk of non-Hodgkin's lymphoma among male farmers (United States). *Cancer causes & control : CCC.* 2001;12(6):509-517.
9. Zhang C, Hu R, Huang J, et al. Health effect of agricultural pesticide use in China: implications for the development of GM crops. *Sci Rep.* 2016;6:34918.

Other Materials

1. Bolognesi C, Holland N. The use of lymphocyte cytokinesis-block micronucleus assay for monitoring pesticide-exposed populations. *Mutation Research.* 770 (2016) 183-203.
2. Deposition Transcripts and Exhibits of Dr. John Acquavella, Ph.D., taken on April 7-8, 2017.
3. Deposition Transcript and Exhibits of Dr. Aaron Blair, Ph.D., taken on March 20, 2017.
4. Deposition Transcripts and Exhibits of Dr. Donna Farmer, Ph.D., taken on January 11-12, 2017.
5. Deposition Transcript and Exhibits of Dr. Daniel Goldstein, M.D. taken on January 18, 2017.
6. Deposition Transcripts and Exhibits of Dr. William Heydens, Ph.D, taken on January 23-24, 2017.
7. Deposition Transcript and Exhibits of Dr. Mark Martens, Ph.D., taken on April 7, 2017.
8. Deposition Transcripts and Exhibits of Dr. David Saltmiras, Ph.D., taken on January 31 and February 1, 2017.
9. EPA. (1980a). Glyphosate; Submission of rat teratology, rabbit teratology, dominant lethal mutagenicity assay in mice. Retrieved from Washington (DC): http://www.epa.gov/pesticides/chemicalsearch/chemical/foia/cleared-reviews/reviews/103601/103601-090.pdf
10. EPA. (1985a). Glyphosate; EPA Reg.#: 524-308; Mouse oncogenicity study. Document No. 004370. Retrieved from Washington (DC): http://www.epa.gov/pesticides/chemicalsearch/chemical/foia/clearedreviews/reviews/103601/103601-183.pdf

11. EPA. (1985b). EPA Reg.#: 524–308; Roundup; glyphosate; pathology report on additional kidney sections. Document No. 004855. Retrieved from Washington (DC): http://www.epa.gov/pesticides/chemicalsearch/chemical/foia/clearedreviews/reviews/103601/103601-183.pdf
12. EPA. (1986). Glyphosate; EPA Registration No. 524–308; Roundup; additional histopathological evaluations of kidneys in the chronic feeding study of glyphosate in mice. Document No. 005590. Retrieved from Washington (DC): http://www.epa.gov/pesticides/chemicalsearch/chemical/foia/clearedreviews/reviews/103601/103601-211.pdf
13. EPA. (1991a). Second peer review of glyphosate. Retrieved from Washington (DC): http://www.epa.gov/pesticides/chemicalsearch/chemical/foia/clearedreviews/reviews/103601/103601-265.pdf
14. EPA. (1991b). Glyphosate; 2-year combined chronic toxicity/carcinogenicity study in Sprague-Dawley rats - List A pesticide for reregistration. Document No. 008390. Retrieved from Washington (DC): http://www.epa.gov/pesticides/chemicalsearch/chemical/foia/clearedreviews/reviews/103601/103601-263.pdf
15. EPA. (1991c). Peer review on glyphosate. Document No. 008527.
16. EPA. (1991d). Glyphosate – EPA registration No. 524–308 – 2-year chronic feeding/oncogenicity study in rats with technical glyphosate. Document No. 008897. Retrieved from Washington (DC): http://www.epa.gov/pesticides/chemicalsearch/chemical/foia/clearedreviews/reviews/103601/103601-268.pdf
17. EPA. (1993a). Reregistration Eligibility Decision (RED): Glyphosate. EPA 738-R-93-014. Washington (DC): Office of Prevention, Pesticides and Toxic Substances, Office of Pesticide Programs.
18. EPA. (1993b). RED facts: Glyphosate. EPA-738-F-93-011. Washington (DC): Office of Prevention, Pesticides, and Toxic Substances.
19. EPA. (1997). Pesticides industry sales and usage – 1994 and 1995 market estimates. Washington (DC): Biological and Economic Analysis Division, Office of Pesticide Programs, Office of Prevention, Pesticides And Toxic Substances.
20. EPA. (2011). Pesticides industry sales and usage – 2006 and 2007 market estimates. Washington (DC): Biological and Economic Analysis Division, Office of Pesticide Programs, Office of Prevention, Pesticides And Toxic Substances.
21. EPA. (2015) Glyphosate: Report of the Cancer Assessment Review Committee. EPA's Office of Pesticide Programs, Health Effects Division. October 1, 2015.
22. EPA. (2016) Glyphosate Issue Paper: Evaluation of Carcinogenic Potential. EPA's Office of Pesticide Programs. September 12, 2016.
23. European Food Safety Authority. Conclusion on the peer review of the pesticide risk assessment of the active substance glyphosate. EFSA J 2015;13:4302
24. JMPR. (2006). *Glyphosate. In: Joint FAO/WHO Meeting on Pesticide Residues. Pesticide residues in food – 2004: toxicological evaluations.* Report No. WHO/PCS/06.1.

25. Lan Q, Zheng T, Shen M, Zhang Y, Wang S, Zahm S, Holford T, Leaderer B, Boyle P, Chanock S. Genetic polymorphisms in the oxidative stress pathway and susceptibility to non-Hodgkin lymphoma. *Hum Genet*. 2017;121:161-168.
26. Lioi M, Scarfi M, Santoro A, Barbieri R, Zeni O, Salvemini F, Berardino D, Ursini M. Cytogenetic Damage and Induction of Pro-Oxidant State in Human Lymphocytes Exposed In Vitro to Gliphosate, Vinclozolin, Atrazine, and DPX-E9636. *Environmental and Molecular Mutagenesis*. 32:39-46 (1998).
27. Luo L, Wang F, Zeng M, Zhong C, Xiao F. In vitro cytotoxicity assessment of roundup (glyphosate) in L-02 hepatocytes. *Journal of Environmental Science and Health, Part B*. 2017, Vol. 0, No. 0, 1-8.
28. Pahwa M, Spinelli J, Freeman L, Demers P, Blair A, Pahwa P, Dosman J, McLaughlin J, Zahm S, Cantor K, Weisenburger D, Harris S. An Evaluation of Glyphosate Use and the Risks of Non-Hodgkin Lymphoma Major Histological Subtypes in the North American Pooled Project (NAPP). 27th Conference of the International Society for Environmental Epidemiology.
29. Townsend M, Peck C, Meng W, Heaton M, Robison R, O'Neill K. Evaluation of various glyphosate concentrations on DNA damage in human Raji cells and its impact on cytotoxicity. *Regulatory Toxicology and Pharmacology* (2017), doi: 10.1016/j.yrtph.2017.02.002
30. Wang S, David S, Cerhan J, Hartge P, Severson R, Cozen W, Lan Q, Welch R, Chanock S, Rothman N. Polymorphisms in oxidative stress genes and risk for non-Hodgkin lymphoma. *Carcinogenesis*. Vol. 27, No. 9, pp. 1828-1834, 2006.

EXHIBIT C

Compensation

My rates for expert work are $550.00/hour and $5,000.00/day for deposition and trial testimony.

Prior Testimony

I have not given a deposition or trial testimony in the last four years.

Low P-Values or Narrow Confidence Intervals: Which Are More Durable?

Charles Poole

What should be the role of *P*-values and confidence intervals in the interpretation of scientific results? This question is not new[1] and our field of epidemiology is far from alone in struggling with it.[2,3] I have four suggestions for authors and readers. The first is quite broad, so I offer that one before describing current practices. I then turn to the other three. My remarks are confined to settings in which *P*-values and confidence intervals accompany estimates of effect measures, such as the relative risk.

Briefly, here are my suggestions. One, we should work harder than ever to avoid strict or exact interpretations of *P*-values and confidence intervals in observational research, where these statistics lack a theoretical basis. Two, we should stop interpreting *P*-values and confidence intervals as though they measure the probability of hypotheses. Three, when we want to know the probability of hypotheses, we should use Bayesian methods, which are designed expressly for that purpose. Four, we should get serious about precision and look for narrow confidence intervals instead of low *P*-values to identify results that are least influenced by random error.

Real Life Is Not Randomized

When treatment or exposure is randomized, we have a solid theoretical basis, testable in simulations, for the probability models from which *P*-values, confidence intervals, and likelihoods are deduced. In observational research, all we can do is hope that the social, behavioral, and physical processes by which people become exposed to risk factors in the unrandomized real world do not differ too greatly from randomization.[4] Unfortunately, each time we find that risk factors are associated with each other in observational studies, we find evidence against that hope. We cannot remind ourselves too often of this fundamental problem. At the very least, it should cause us to avoid hairsplitting interpretations of probabilistic statistics in observational research, where they are intrinsically fuzzy.

Contemporary Uses of *P*-Values and Confidence Intervals

Significance testing unquestionably dominates epidemiology today. In attempting to refrain from this practice over the past 17 years,[5] I have often been expected, assumed, encouraged, and sometimes even forced to engage in it by editors, reviewers, colleagues, professors, students, funding sources, regulators, attorneys, and journalists. It is not easy to be a non-tester in a testing world.

After Rothman's highly influential 1978 essay, "A Show of Confidence,"[6] an immense and easily documented shift in reporting style took place.[7] Whereas *P*-values or "S" (significant) and "NS" (not significant) once were reported exclusively, the reporting of confidence intervals has now become accepted practice, with or without *P*-value accompaniment. Confidence intervals have a survival advantage for the tiny non-testing minority to which I belong. They enable us to gauge the precision of estimates easily, but without depriving the established majority of its beloved tests.

Epidemiologists who see no purpose to a confidence interval other than its use in significance testing sometimes wonder why this shift in reporting practice has occurred. The *P*-value provides the information they desire more efficiently and exactly. Some are vaguely aware that confidence intervals supposedly convey information that *P*-values do not, but are unsure what that extra information is and even less sure how it might be useful. The word "precision" seems to be used with increasing regularity nowadays, and confidence intervals are occasionally described as "wide," but "wide" and "imprecise" often seem nothing more than code words for "includes the null value" and hence for "not statistically significant."

Improbable Observations Do Not Imply Improbable Hypotheses

When we estimate a parameter such as the relative risk, each possible value of that parameter is the expected value under some hypothesis, and each hypothesis has a *P*-value.[3,4] What we call "the" *P*-value is the *P*-value for the null hypothesis. Approximately, each *P*-value is the probability of obtaining an estimate at least as far from a specified value as the estimate we have

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Submitted and accepted January 19, 2001.

obtained, if that specified value were the true value. It follows that no *P*-value, for the null hypothesis or any other, is the probability that the specified hypothesis is true. As an obvious example, the hypothesis corresponding to the point estimate has a (two-sided) *P*-value of 1.0. However, we do not treat our point estimates as absolutely certain to be true. Neither is the point estimate, in general, the most probable value.

For a given estimate, the 95% confidence interval is the set of all parameter values for which $P \geq 0.05$. For the value at each limit of a 95% confidence interval, $P = 0.05$ (two-sided). Thus, if either of the 95% confidence limits for a relative risk estimate equals 1.0 (the null value of this parameter), we can infer that the null *P*-value is 0.05. From this link between confidence intervals and *P*-values, it follows that a 95% confidence interval is *not* a range of values within which the unknown true value lies with 95% probability.

The well-known "coverage probability" of confidence intervals pertains to a parameter value that is known to be true and the probability that an as yet unknown confidence interval will contain it. Coverage probability does *not* pertain to a known confidence interval and an unknown true value. To interpret a given 95% confidence interval as having a 95% probability of including the unknown true value is to mistake a frequentist confidence interval for a Bayesian probability interval.[5] This error is merely an extension of the logical fallacy of mistaking the null *P*-value for the probability that the null hypothesis is true.

Why do we turn probability logic on its head in this way? We very much want to know the probabilities of hypotheses, which require Bayesian methods to determine, but our biostatistical teachers give us the *P*-values and confidence intervals of frequentist statistics. We are thus led into a basic fallacy, by which the probability of A given B is mistaken for the probability of B given A.[5] A *P*-value of 0.04 tells us that, if the null hypothesis were true, an association at least as strong as the one we observed would occur with a probability of 4%. We find it quite natural to reverse the terms, and conclude mistakenly that the probability of the null hypothesis is 4%, given the association we observed.

The null hypothesis or any other hypothesis can be highly probable even though its *P*-value is less than 0.05. The null hypothesis or any other hypothesis can have a low probability even though its *P*-value is greater than 0.05. A relative risk can be highly probable even though it lies outside a 95% confidence interval. A relative risk can be highly improbable even though it lies inside a 95% confidence interval.

The indispensable role of hypotheses in the computation of *P*-values and confidence intervals, with each hypothesis assigning a probability to each estimate we might possibly obtain, means that these measures are not the descriptive statistics they are sometimes said to be.[3] *P*-values and confidence intervals are inferential statistics, but the flow of the inference is a deductive flow, in which hypotheses confer probability "down" to estimates.[7,8,9] Inductive statistical inference, in which the direction of the probability flow is from estimates back "up" to hypotheses, properly takes place only when prior probabilities are updated with new data, by means of Bayes's theorem, to form posterior probabilities.[10,11]

The only way we can determine the probability of the null hypothesis, or a range of values within which the true value lies with a given level of probability, is by using Bayesian methods.[10,11,12] Bayesian methods cannot be employed without the specification of prior probabilities for the hypothetical values of interest (eg, all possible values of relative risk, from zero to infinity). Since we do not specify prior probability distributions when we compute conventional (frequentist) confidence intervals, those intervals have no generally valid interpretation as Bayesian probability intervals.

Many familiar expressions - some employing probabilistic language, others avoiding it - have the effect of leading us into this misinterpretation. It has been said that being located inside a 95% confidence interval makes values plausible, probable, likely, reasonably included by the data, or even possible. Values exterior to 95% confidence intervals have been said to be implausible, improbable, unlikely, reasonably excluded by the data, or even ruled out. None of these variations on a rhetorical theme can change a simple fact of statistical life: If we want to know which values are more and less likely, more and less plausible, etc., we must specify prior probabilities for those values and use Bayes's theorem to update those probabilities when new data are in hand.

It has become increasingly clear that the null *P*-value (hereafter called "the" *P*-value) does not do a very good job of the task for which it was originally intended: to quantify the statistical evidence against the null hypothesis. The reason is simple. The familiar Type I and Type II error rates upon which Neyman and Pearson taught us to focus[6,7] beg vitally important questions.

One minus the Type I error rate is the specificity of a significance test: the probability of not declaring "significance" when the null hypothesis is true. One minus the Type II error rate is the test's power or sensitivity: the probability of declaring "significance" when the alternative hypothesis is true. No informed patient would be satisfied with a diagnostic test result knowing only the test's specificity and sensitivity. That patient would want to know the test's predictive value (positive or negative, depending on the result).

Significance tests are no different. In the same frequency terms that Neyman and Pearson used,[6,7] the researcher who wishes to be fully informed should be interested in questions such as the following: How often is the null hypothesis true when we fail to reject it? When we do reject the null hypothesis, how often is the alternative hypothesis true? These are the probabilities of ultimate concern in significance testing – the predictive values of "NS" and "S." There is no way to determine them without postulating (stated again in frequency terms) how often the null and alternative hypotheses are true.

The interest many epidemiologists express in how low the *P*-value is, if it is lower than 0.05,[5] raises still other questions. How much evidence against the null hypothesis do we have when $P = 0.04$, or when $P = 0.001$? To answer these questions, we need to consider the probabilities under the null and alternative hypotheses of obtaining these particular *P*-values, not just the probabilities of obtaining $P < 0.05$.

Statisticians who have examined these questions in detail[17–26] have found, under widely ranging conditions, that *P*-values on the order of 0.05, 0.01, and even lower provide much less evidence against the null hypothesis than they appear to provide at face value. As a general matter, *P*-values in the vicinity of 0.05 provide almost no evidence against the null hypothesis at all. $P = 0.04$, for instance, is typically found to be almost equally probable under the null and alternative hypotheses.

One upshot of this work has been a statistical research program devoted to calibrating, standardizing, conditioning, or adjusting low *P*-values to make them higher, so that they reflect more realistically the limited statistical evidence they provide against the null hypothesis.[20–26] Now that Bayesian methods are computationally feasible, one wonders whether these efforts to patch up *P*-values will ultimately be viewed a transitional stopgap.

Taking Precision Seriously

Transitional stopgaps should not be dismissed lightly, especially when the transitions in question take decades to unfold. Stopgaps can be particularly valuable when it seems that the only alternative is to cry in the (frequentist) wilderness for a (Bayesian) revolution. In epidemiology, the advent of confidence intervals creates an opportunity to take another small step toward more widespread use of Bayesian methods, while at the same time improving overall interpretation. This step is merely to take precision seriously.

Epidemiologists have many reasons to emphasize certain results over others. Some results may pertain to particularly topical research questions. Some may be more valid than others. And some may be less influenced by random error. This last consideration seems to be an important one to many epidemiologists, who regularly use *P*-values to determine the degree to which chance influences their results. They believe that the lower the *P*-value, the less the influence of chance. Unfortunately, this extremely common use of the *P*-value is a misuse and an abuse of that statistic. The estimates least influenced by chance are not those with low *P*-values, but those with narrow confidence intervals.

Consider the four hypothetical relative risk estimates in Table 1. The ratio of the upper to lower 95% confidence limits (CLR) is a handy measure of confidence interval width, and thus of precision. (For a difference measure such as the risk difference, the difference between the upper and lower confidence limits would serve the same purpose.) The example was devised to dramatize four clear-cut combinations of statistical "significance" and precision.

TABLE 1. Results from a Hypothetical Study of a Single Binary Exposure and Four Diseases or of a Single Disease and Four Binary Exposures

Exposure or Disease	RR (95% CI)	P	95% CLR
A	2.5 (0.80–8.0)	0.1	10
B	1.7 (1.2–2.4)	0.003	2
C	4.1 (1.2–14)	0.02	12
D	1.4 (0.80–2.4)	0.2	3

Abbreviations: RR = relative risk; CI = confidence interval; P = two-sided null *P*-value; CLR = upper-to-lower confidence limit ratio.

To the extent that the role of chance would be taken into account in deciding which of these results to emphasize, the conventional choices would be the statistically "significant" estimates B and C. These would be the "associations unlikely to be due to chance alone." But one of them, estimate C, is very unstable. That estimate is influenced much more by random error, and from that standpoint is much less dependable, than estimate B.

Of equal importance, when C is compared with D, estimate C is influenced much more by chance and in that regard is much less trustworthy, even though estimate C is statistically "significant" and estimate D is not. Estimates B and D – not B and C – are this study's most precise estimates. Estimates B and D stand the best chance of holding up, conditional on their validity, in the context of existing and future research. Estimates B and D would weigh more heavily into meta-analyses and would exert stronger influences on probability distributions in properly conducted Bayesian analyses. Estimates B and D are the results that should be put forth for emphasis as the most statistically stable results this study has to offer.

It is sometimes said that confidence intervals are especially valuable, and that increases in sample size and statistical efficiency are particularly needed, when statistical "significance" has not been attained. To the contrary, an estimate that has a wide confidence interval is imprecise and unstable no matter how low its *P*-value. Based solely on the results in Table 1, larger sample sizes, special study populations and statistically more efficient designs would be particularly desirable for A and C, regardless of the fact that one of these estimates is statistically "significant" and the other is not.

Some epidemiologists wonder what all the fuss over *P*-values and confidence intervals is about. This hypothetical example shows how an emphasis on precision rather than statistical "significance" can affect which results we may choose to highlight. I invite the reader to examine published research reports in which the estimates with the lowest *P*-values have been singled out for emphasis, and to imagine how differently those papers would read if the estimates with the narrowest confidence intervals had been highlighted instead.

CONCLUSION

Our results that deserve the greatest reliance are those that are most stable and trustworthy. With regard to random error, a very poor way of identifying dependable results is to select associations with impressively low

P-values. Inference and decision-making would be far better served by choosing estimates with narrow confidence intervals, which are least vulnerable to the play of chance. These are the results for which, by virtue of intentional or accidental features of our research methods, our studies provide the most evidence (as distinguished from the most *valid* evidence).

By taking precision seriously, we can easily identify those research questions on which our studies provide the greatest quantity of statistical evidence, and those questions for which larger and more statistically efficient studies are needed. In terms of resistance to random error, our most durable results are our most precise estimates - however unspectacular, unsensational, and "non-significant" many of those estimates might be.

References

1. Berkson J. Some difficulties of interpretation encountered in the application of the chi-squared test. J Am Stat Assoc 1938;33:526–536.
2. Anderson DR, Burnham KP, Thompson WL. Null hypothesis testing: problems, prevalence, and an alternative. J Wildlife Management 2000;64:912–923.
3. Walter SD. Methods of reporting statistical results from medical research studies. Am J Epidemiol 1995;141:896–906.
4. Greenland S. Randomization, statistics, and causal inference. Epidemiology 1990;1:421–429.
5. Poole C, Lanes SL, Rothman KJ. Analyzing data from ordered categories (letter). New Engl J Med 1984;311:1382.
6. Rothman KJ. A show of confidence. N Engl J Med 1978;299:1362–1363.
7. Savitz D, Tolo K-A, Poole C. Statistical significance testing in the American Journal of Epidemiology 1970 to 1990. Am J Epidemiol 1994;139:1047–1052.
8. Poole C. Beyond the confidence interval. Am J Public Health 1987;77:195–199.
9. Poole C. Confidence intervals exclude nothing. Am J Public Health 1987;77:492–493.
10. Lindley DV. The philosophy of statistics (with discussion). The Statistician 2000;49:293–337.
11. Savitz DA, Olshan AF. Describing data requires no adjustment for multiple comparisons: a reply from Savitz and Olshan. Am J Epidemiol 1998;147:813–814.
12. Poole C. Induction does not exist in epidemiology, either. In: Rothman KJ (ed). Causal Inference. Chestnut Hill, MA: Epidemiology Resources Inc., 1988:153–162.
13. Greenland S. Probability logic and probabilistic induction. Epidemiology 1998;9:322–332.
14. Gelman AB, Carlin JS, Stern HS, Rubin DB. Bayesian data analysis. Boca Raton, FL: Chapman & Hall/CRC 1995:42–45.
15. Berry DA. Statistics: a Bayesian perspective. Belmont, CA: Duxbury Press 1996:147–161.
16. Neyman J, Pearson E. On the use and interpretation of certain test criteria for purposes of statistical inference. Biometrika 1928;20:175–240.
17. Neyman J, Pearson E. On the problem of the most efficient tests of statistical hypotheses. Philos Trans R Soc Lond A 1933;231:289–337.
18. Goodman SN. *p* values, hypothesis tests, and likelihood: implications for epidemiology of a neglected historical debate (with discussion). Am J Epidemiol 1993;137:485–501.
19. Casella G, Berger R. Reconciling Bayesian and frequentist evidence in the one-sided testing problem (with discussion). J Am Stat Assoc 1987;82:106–111.
20. Berger JO, Selke T. Testing a point null hypothesis: the irreconcilability of *P*-values and evidence. J Am Stat Assoc 1987;82:112–122.
21. Berger JO, Delampady M. Testing precise hypotheses (with discussion). Stat Sci 1987;3:317–352.
22. Delampady M, Berger JO. Lower bounds on Bayes factors for the multinomial distribution, with application to chi-squared tests of fit. Ann Stat 1990;18:1295–1316.
23. Berger J, Boukai B, Wang Y. Unified frequentist and Bayesian testing of a precise hypothesis (with discussion). Stat Sci 1997;12:133–160.
24. Selke T, Bayarri MJ, Berger J. Calibration of P values for testing precise null hypotheses. Am Stat 2001;55:62–71.
25. Goodman SN. Towards evidence-based medical statistics. I. The *P*-value fallacy. Ann Intern Med 1999;130:995–1004.
26. Goodman SN. Towards evidence-based medical statistics. II. The Bayes factor. Ann Intern Med 1999;130:1005–1213.

Review: Causal Inference in Epidemiology

Confounding

Beate Ritz, MD, Ph.D.

EPI 200B

Winter 2010

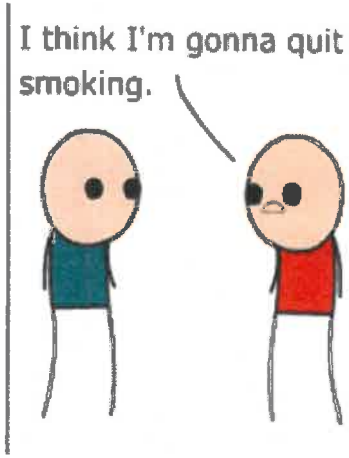
NOTE: Many of the following slides are based on the lectures notes provided by Dr. Hal Morgenstern (Epi Methods I and II)

Major Methodologic Concerns in Epidemiologic (Observational) Population Research

Three biases we try to avoid or control for:

- **Information Bias** – measurement error of exposure or disease
- **Selection bias** – does selection of the control/reference group depend on outcom and the exposure of interest
- **Confounding Bias** - lack of comparability (lack of exchangeability) between exposed and unexposed populations

- In addition, we try to assess differences of effect estimates in subgroups e.g. men *vs.* women (***statistical interactions or effect measure modification***)



Counterfactual Causality

"What would have happened to the *same fixed individual* at the *same fixed time* under one ('exposed') versus another ('unexposed') condition"

Counterfactual causal thinking

- provides a useful concept of causation
- allows to draw probabilistic causal inferences in observational studies
  - provides framework for statistical procedures to estimate causal effects
  - demonstrates the limitations of observational data

See Hoefler. Causal inference based on counterfactuals BMC Med Research Meth. 5:28, 2005

Exploring Causes of Disease in Human Populations: Use of Counterfactual Causality

In counterfactual causal thinking we imagine the consequences of changing the value of a single factor in a comprehensive (complex) causal system

The **counterfactual** is by definition ***unobservable.*** Instead, we identify a valid comparison group, i.e. similar in every aspect except for exposure.

"Causal Models" (but NOT a causal pathway diagram (DAG)!):

From: Marbury MC, Maldonado G, Waller L. The indoor air and children's health study: methods and incidence rates. Epidemiology. 1996 Mar;7(2):166-74.

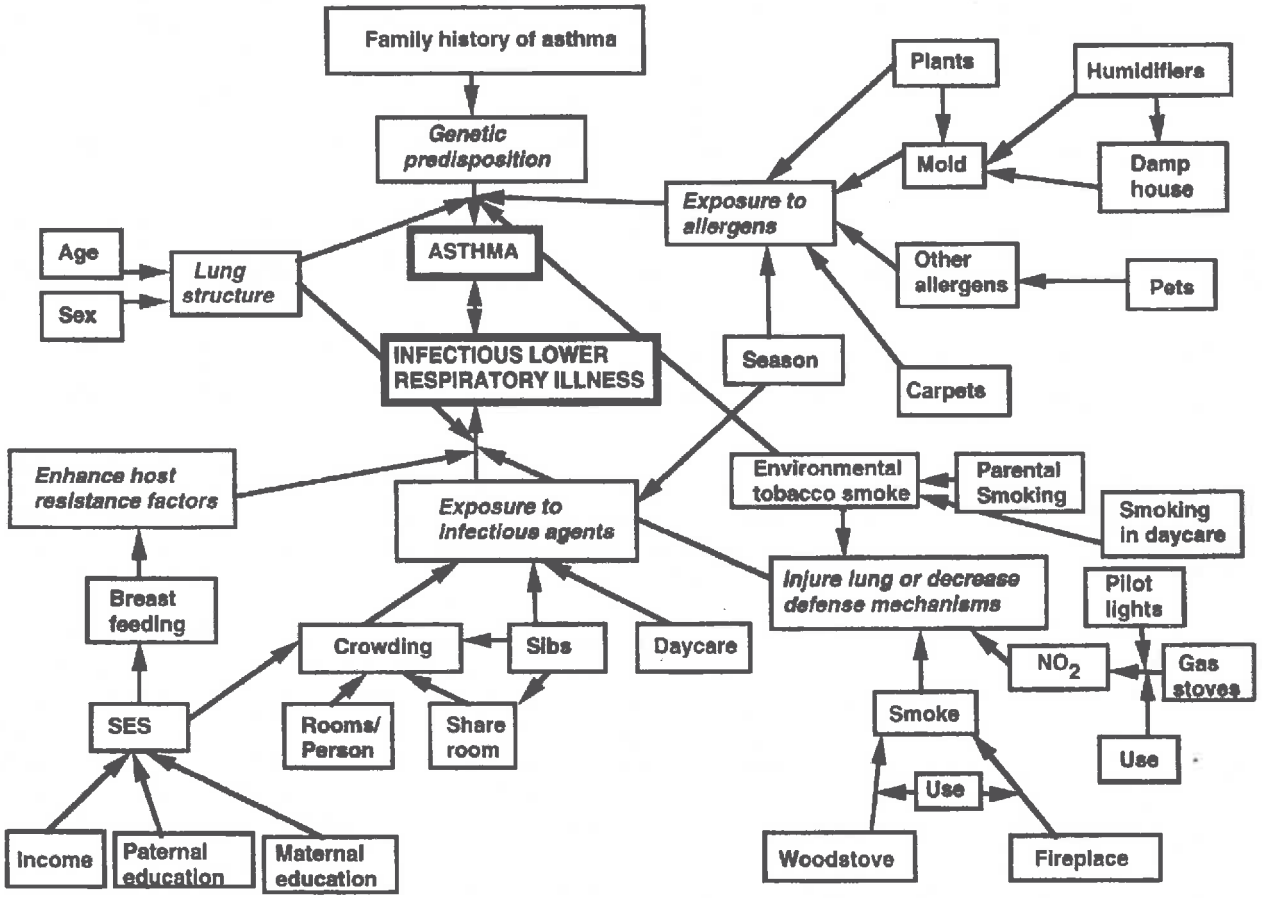


FIGURE 1. Conceptual model of the relation between risk factors and outcomes.

Causal Inference: Rothman's sufficient-component-cause model of causation

Builds a conceptual model for inferential considerations as a bridge between meta-physics and epi studies

Similar to but finer than the counterfactual model

Entities in this model are not individuals but mechanisms of causation

A mechanism is defined as a combination of events/factors that are jointly sufficient to induce a binary outcome event (diseased / non-diseased)

Rothman's sufficient-component-cause model

A **cause of a disease** is an **event, condition, or characteristic** that plays an essential role in producing an occurrence of the disease

Sufficient and component causes

- A causal mechanism consists of a constellation of **components** that act in concert
- A "**sufficient**" cause may be defined as a set of minimal conditions and events that inevitably produce disease
- "**Minimal**" implies that none of the conditions or events are superfluous
- The completion of a sufficient cause may be considered equivalent to the onset of disease
- A factor present in every sufficient cause constellation/mechanism constitutes a **necessary** component cause

Rothman's model of causation

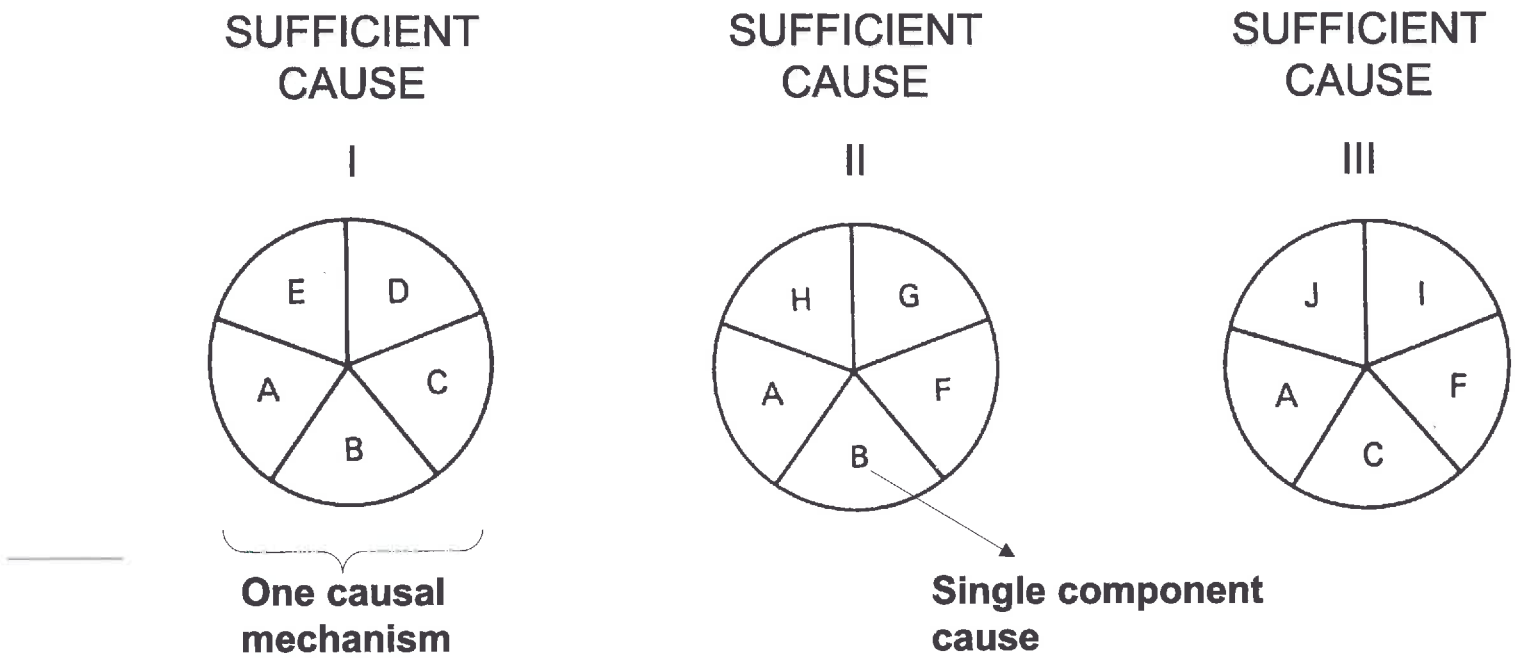
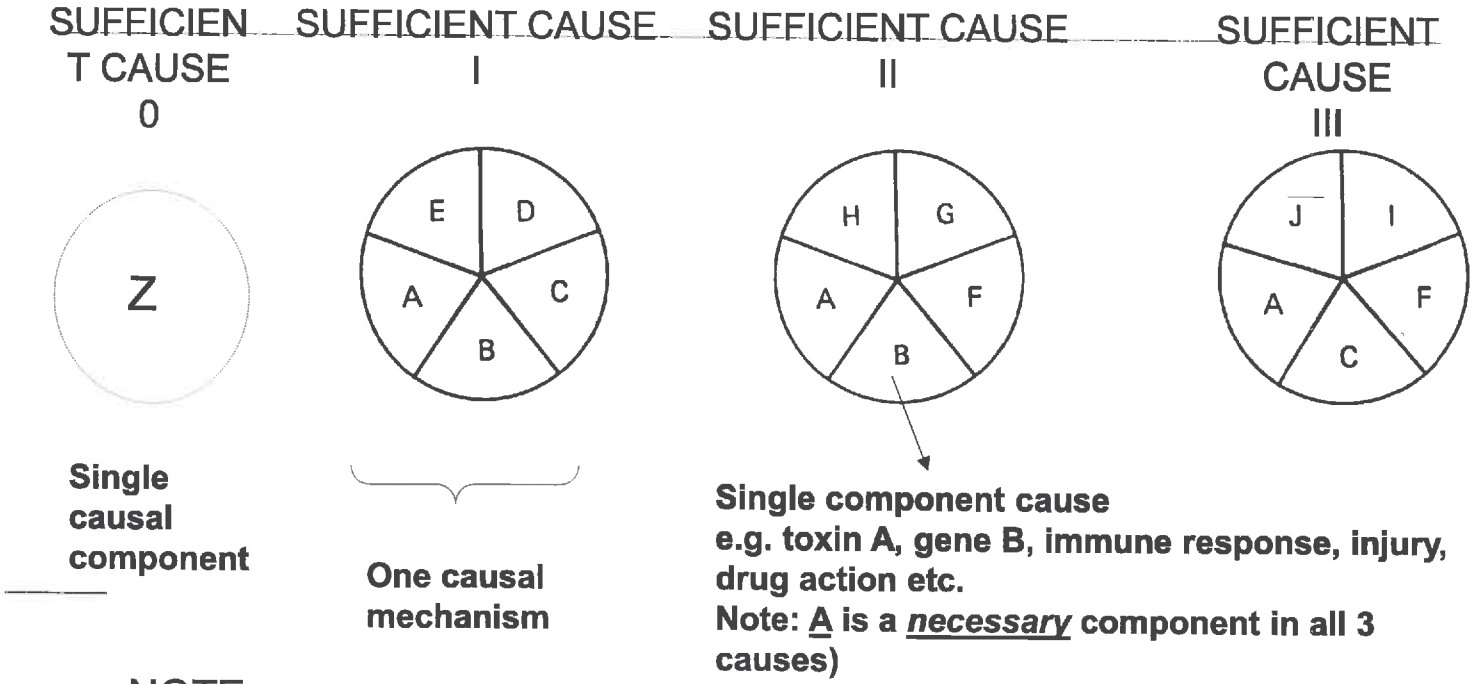


Fig. 2-1. Conceptual schematization of three sufficient causes for a disease [Rothman, 1976].

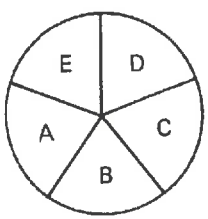
Causes of Complex Diseases in Populations
Rothman's model of causation

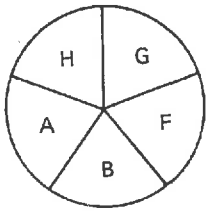


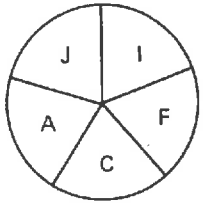
NOTE:

- For biologic systems, most and sometimes all of the components of a sufficient cause are unknown
- Generally, there is more than one sufficient cause for a disease

Conceptual schematization of three sufficient causes for a disease [Rothman, 1976].

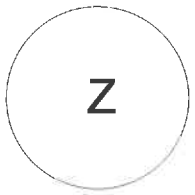






Examples

1. Suppose component causes A, B, C, in sufficient causes I-III are all factors commonly present or experienced by people and E is rare. Although all factors are causes, E would appear to be a stronger determinant of disease because those with E differ greatly in risk from those without E. Thus, the strength of a cause is determined by the relative prevalence of component causes.
2. G is a substance created and confined to in a laboratory. Thus, any causal pie that includes G will not cause disease until G is released in the environment.
3. A is a necessary but not a sufficient cause. What proportion of disease is caused by A? *Note:*
   - No disease is caused solely by A, since A is not a sufficient cause.
   - A single cause or category of causes that is present in every sufficient cause will have an attributable fraction of 100%
   - What if component C in cause III was a B instead?



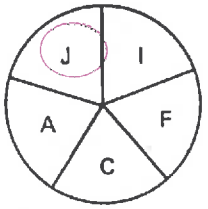
Rothman's sufficient-component-cause model

NOTE:

For biologic effects, most and sometimes all of the components of a sufficient cause are unknown

Generally, there is **more than one** sufficient cause for a disease

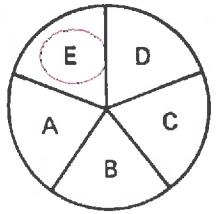
Example: Breast cancer causes



BRCAI and BRCAII = J

Early age at menarche = E

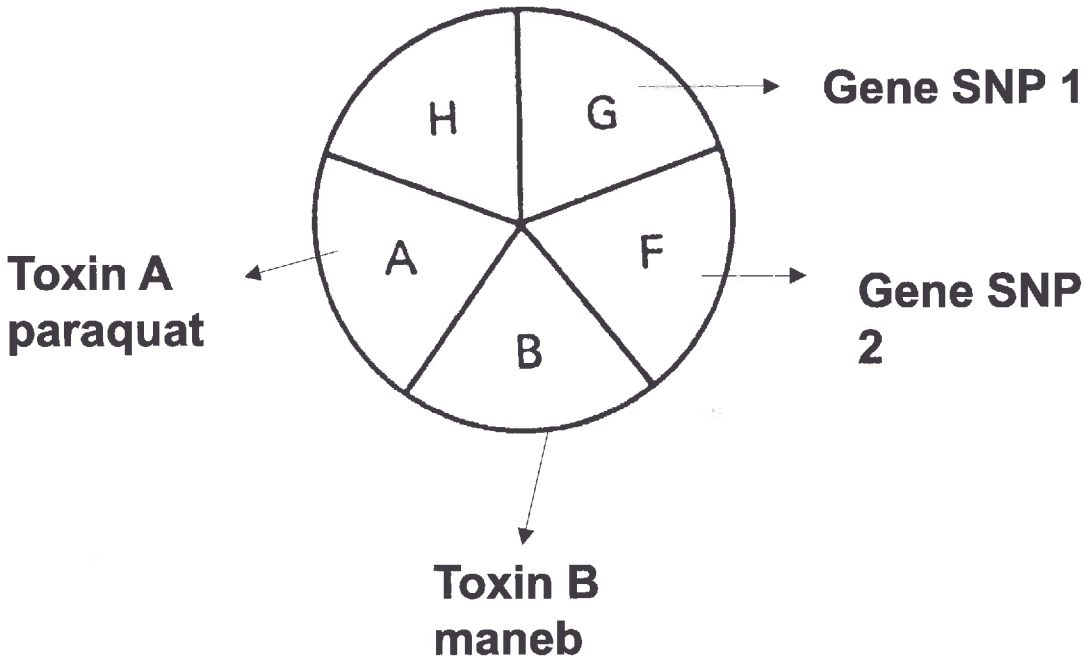
Late age at first pregnancy etc.....



Sufficient Cause Models

SUFFICIENT CAUSE

Several toxins and genes as component causes



Point-Counterpoint Commentary: Positivized epidemiology and the model of sufficient and component causes

Charles Poole *International Journal of Epidemiology* 2001;30:707-709

The Rothman model of sufficient and component causes (SCC) gives epidemiologists engaged in etiological research on any disease a clear choice between two options at any point in time:

1. Consider all remaining variability in the disease's occurrence, conditional on its known determinants, to be due to chance or some other source of irreducible stochastic uncertainty, and **close up shop** (Peto)
2. Keep searching for additional determinants

One authority (Colditz) on cancer epidemiology very recently declared the search for cancer risk factors to be over.

For health outcome, a way of emphasizing a working agreement on option 2 is to include unlabelled slices in pie-chart depictions of sufficient causes.

1 Peto R. Cancer risk. *New Scientist* 1977;**73:480–81.**
2 Colditz G. Cancer culture: Epidemics, human behavior, and the dubious search for new risk factors. *Am J Public Health* 2001; **91:357–64**

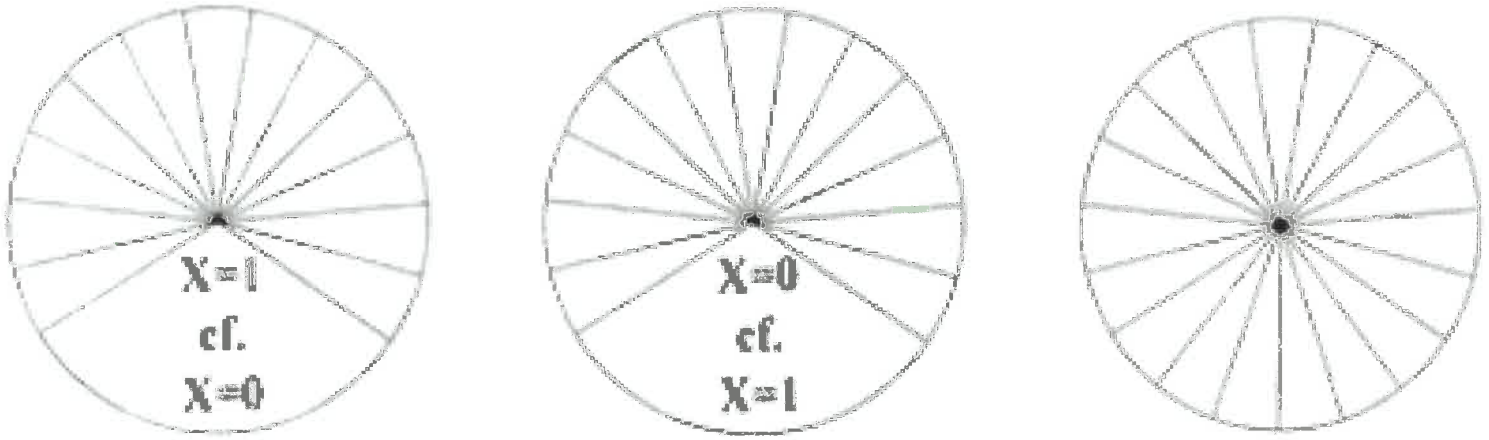


Figure 1. Modified pie-chart depiction of all hypothetically possible classes of sufficient causes (etiologic mechanisms) of an outcome with regard to a well-specified index condition (X = 1) and reference condition (X = 0). Each label states the specific causal contrast postulated by the hypothetical class of sufficient causes. Unlabelled slices represent known or hypothesized component causes that are unspecified in this particular analysis, as well as unknown component causes that might be discovered in future research.

Example:

If X = 1 is the presence of an air bag, X = 0 is its absence, and the outcome is death in an automobile collision, the first pie chart represents mechanisms in which 'air bags kill', the second represents mechanisms in which 'air bags save lives', and the third represents fatal etiologies in which air bags, by their presence or absence, play no role

Bradford Hill. The environment and disease: association or causation?

Proc R Soc Med 1965;58:295-300.

The seldom quoted bottom-line of the so-called "Hill criteria" (which he called '**viewpoints**') **and** fundamental question is:

"Is there any other way of explaining the set of facts before us, is there any other answer equally, or more, likely than cause and effect?"

Confounding - definition

Confounding is bias in the estimation of the effect of exposure on disease occurrence, due to a *lack of comparability (lack of exchangeability)* between exposed and unexposed populations;

thus, disease risks would be different even if the exposure were absent in both populations.

Note: a confounded estimate of effect is not expected to equal the causal parameter of interest in the source population.

Confounding

To quantify the exposure effect, we compare

the # of new cases *occurring* in the exposed population

with

the # cases that *would have occurred* in the absence of exposure (a causal parameter).

Thus, confounding occurs when the exchangeability assumption (= reference or unexposed population exhibits the risk the exposed population would have experienced, if exposure had been absent) is not met

Note: this counterfactual contrast can never be made directly i.e. the **same population** is never both exposed and unexposed at the **same time**

Confounding

In practice we compare a group of *exposed* subjects with another group of *unexposed* subjects.

Thus, the validity of this comparison depends on the *assumption* that the risk of disease in the *unexposed* group is equal to the risk that *would have occurred in the exposed group in the absence of exposure*.

When this assumption is not true, the observed comparison between exposure groups is confounded.

Confounding in experiments

Confounding may occur in any type of study, including experiments.

Randomized experiments:

Randomization **tends** to make assigned (treatment) groups exchangeable (comparable), thus confounding is usually not a major source of bias in well-conducted experiments, provided the sample size is not too small

Group 1: 

Group 2: 

Confounding in experiments

Furthermore, randomization yields known treatment probabilities, thus, confidence intervals (CI) in randomized studies actually reflect possible confounding, which might have occurred in either direction;

Note: the amount of possible bias and the CI width become smaller as the sample size increases.

Thus, the interpretation of CIs in observational studies requires the assumption of no bias, whereas in randomized studies, CIs reflect possible confounding (which in randomized studies becomes part of the random error), although they do not reflect other biases (such as measurement error or differential loss to follow up).

Causal types

We could determine whether confounding exists if we knew the counterfactual risk of disease in the exposed group in the absence of exposure ($\mathcal{R}_1$).

To determine the counterfactual risk, we need to know the distribution of 4 "causal types" (i.e. doomed, causative, preventive, immune).

Table 4-1 p 60 ME2 (Rothman and Greenland). An elementary model of causal types and their distribution in two distinct cohorts

1=gets disease, 0=does not get disease

Causal Type	Response under Exposure	Response under Non-exposure	Cohort 1 (Exposed)
1) Doomed	1	1	p1
2) Causative	1	0	p2
3) Preventive	0	1	p3
4) Immune	0	0	p4

Causal risk difference in cohort 1: $(p1+p2) - (p1+p3) = p2 - p3$

get disease among exposed *get disease if unexposed*

Causal risk ratio in cohort 1: $\frac{(p1+p2)}{(p1+p3)}$

Causal odds ratio in cohort 1: $\frac{(p1+p2) / (p3+p4)}{(p1+p3) / (p2+p4)}$

NOTE: if p2 - p3 = 0 then causal risk and odds ratio = 1 ➡ balance between causative and preventative effects

Table 4-1 p 60 ME2 (Rothman and Greenland). An elementary model of causal types and their distribution in two distinct cohorts

1=gets disease, 0=does not get disease

Causal Type	Response under Exposure	Response under Non-exposure	Cohort 1 (Exposed)	Cohort 0 (Unexposed)
1) Doomed	1	1	p1	q1
2) Causative	1	0	p2	q2
3) Preventive	0	1	p3	q3
4) Immune	0	0	p4	q4

Causal risk difference: $(p1+p2) - (q1+q3)$

get disease in cohort 1(=exposed) — *get disease in cohort 0 (=unexposed)*

Causal risk ratio: $\frac{(p1+p2)}{(q1+q3)}$

Causal odds ratio: $\frac{(p1+p2) / (p3+p4)}{(q1+q3) / (q2+q4)}$

NOTE: if $q1 + q3 \neq p1 + p3$ then $q1+q3$ cannot be exchanged or substituted for $p1+p3$

→ the association measure (risk comparisons) are confounded by the discrepancy between these two quantities

Causal types (example from Morgenstern)

Example: Frequency distribution (in %) of 4 causal types, by exposure Status (E vs. Ē), in 3 closed cohorts; $\mathcal{R}_0$= counterfactual risk in the unexposed group of everyone were exposed.

	Cohort 1		Cohort 2		Cohort 3	
Causal Type	E	Ē	E	Ē	E	Ē
1) Doomed	20	10	20	20	10	20
2) Causative	0	0	20	0	30	20
3) Preventive	0	0	0	0	10	0
4) Immune	80	90	60	80	50	60
Expected Risk (R_1; R_0)	0.2	0.1	0.4	0.2	0.4	0.2
Counterfactual Risk ($\mathcal{R}_1$; $\mathcal{R}_0$)	0.2	0.1	0.2	0.2	0.2	0.4
Expected RR (R_1/R_0 = RR)	2		2		2	
Causal RR ($\mathcal{RR}$) ($R_1/\mathcal{R}_1$; $\mathcal{R}_0/R_0$)	1	1	2	1	2	2

Confounding

In all three cohorts, we would expect to observe a risk ratio (RR) of 2.

In Cohort 1, this expected RR is biased (confounded) because the exchangeability assumption is not met – i.e., R_0 does not equal $\mathcal{R}_1$. Thus, the expected RR = 2 does not equal the causal risk ratio in the *exposed* group ($\mathcal{RR}_1 = 1$).

In Cohorts 2 and 3, however, the expected RRs are not biased because the exchangeability assumption is met – i.e., $R_0 = \mathcal{R}_1$. Thus, the expected RR is equal to the causal risk ratio in the *exposed* group ($\mathcal{RR}_1 = 2$).

Comments: When focusing on causal parameters in an ***exposed*** source population (e.g., $\mathcal{RR}_1 = R_1/\mathcal{R}_1 = a/a_0$), there is no confounding if the total proportion of Type 1 and Type 3 individuals is the same in exposed and unexposed groups.

In this situation, the risk of disease in the unexposed group (R_0) is equal to what the risk would have been in the exposed group in the absence of exposure ($\mathcal{R}_1$).

NOTE: this condition is met in Cohorts 2 and 3, but not Cohort 1. This is the usual (often implied) meaning of confounding in epidemiology.

	Cohort 1		Cohort 2		Cohort 3	
Causal Type	E	$\bar{E}$	E	$\bar{E}$	E	$\bar{E}$
1) Doomed	20	10	20	20	10	20
2) Causative	0	0	20	0	30	20
3) Preventive	0	0	0	0	10	0
4) Immune	80	90	60	80	50	60
Expected Risk (R_1; R_0)	0.2	0.1	0.4	0.2	0.4	0.2
Counterfactual Risk ($\mathcal{R}_1$; $\mathcal{R}_0$)	0.2	0.1	0.2	0.2	0.2	0.4
Expected RR ($R_1/R_0 = RR$)	2		2		2	
Causal RR (RR_i) ($R_1/\mathcal{R}_1$; $\mathcal{R}_0/R_0$)	1	1	2	1	2	2

If we were interested in what the risk would have been in the ***unexposed*** source population had they been exposed (i.e., focusing on causal parameters in the unexposed source population, e.g., $\mathcal{RR}_0 = \mathcal{R}_0/R_0 = c_1/c$), no confounding would mean that the total proportion of Type 1 and Type 2 individuals is the same in exposed and unexposed groups.

In this situation, the risk of disease in the exposed group (R_1) is equal to what the risk would have been in the unexposed group in the presence of exposure ($\mathcal{R}_0$).

This condition is met in Cohort 3, but not Cohorts 1 and 2. Note that the causal risk ratio in Cohort 2 is different in the exposed and unexposed groups.

	Cohort 1		Cohort 2		Cohort 3	
Causal Type	E	$\bar{E}$	E	$\bar{E}$	E	$\bar{E}$
1) Doomed	20	10	20	20	10	20
2) Causative	0	0	20	0	30	20
3) Preventive	0	0	0	0	10	0
4) Immune	80	90	60	80	50	60
Expected Risk (R_1; R_0)	0.2	0.1	0.4	0.2	0.4	0.2
Counterfactual Risk ($\mathcal{R}_1$; $\mathcal{R}_0$)	0.2	0.1	0.2	0.2	0.2	0.4
Expected RR (R_1/R_0 = RR)	2		2		2	
Causal RR (RR_i) ($R_1/\mathcal{R}_1$; $\mathcal{R}_0/R_0$)	1	1	2	1	2	2

Confounding

If we were interested in estimating causal parameters for the *total* source population, no confounding would mean that both conditions described above would hold.

> That is, the two exposure groups would be completely exchangeable: The same exposure-risk relation would exist if the two exposure states were exchanged (i.e., if the exposed became unexposed and the unexposed become exposed).

Note that complete exchangeability does not necessarily require that the total distribution of causal types be the same in exposed and unexposed populations (e.g., see Cohort 3; if exposure groups were reversed, RR would still be 2).

Conclusion: In practice, we do not know the distribution of the 4 causal types. Thus, we cannot measure confounding without introducing untestable assumptions!

Confounders

In practice, there is no empirical method for directly examining the ***correctness*** of the **comparability (exchangeability) assumption** that defines "no confounding".

What we do instead is

- attempt to identify and control for empirical sources of confounding.
- search for differences between exposure groups in the distribution of extraneous risk factors for the disease.
  - such differences could produce a violation of the exchangeability assumption, which would bias (confound) the exposure effect estimator

Extraneous risk factors responsible for confounding are called confounders or confounding variables, and they serve as a means for the identification and control of confounding.

Confounders - example

Suppose age is a risk factor for the disease in the source population.

If exposed persons are older than unexposed persons, how do we know whether the estimated exposure effect (e.g, $\widehat{RR} > 1$) is actually due to the effect of the exposure or to being older?

Thus, age is a confounder in this population; the two exposure groups are probably not exchangeable because of the age difference.

Confounders

If we have adequately measured confounders in all subjects, we can control or adjust for their distorting effect in the analysis.

Analytic control is achieved by examining the desired association within categories (or strata) of the confounders (i.e, stratified analysis).

Within strata (defined by the cross-classification of a sufficient set of accurately measured confounders), the exposure groups are exchangeable, and our causal effect estimator is not confounded.

Confounders

Although we cannot observe what the frequency of disease would have been in the exposed group in the absence of exposure, we can identify predictors of the disease in the unexposed group.

When we adjust the effect estimate for differences in these predictors between exposure groups, we are attempting to remove that portion of confounding produced by these differences.

Thus, a confounder is defined as a variable that, when properly controlled, produces an expected estimate of effect that is closer to the unknown effect parameter in the source population than when it is not controlled–i.e., bias is reduced.

Properties of a confounder

In general, a necessary (but not sufficient) characteristic of a confounder is that it be associated with both exposure status and disease occurrence.

It is difficult to assess this criterion from data, however, because data associations are influenced:

1. by effects of other variables on the association between the suspected confounder, the exposure, and the disease in the source population;
2. the manner in which subjects are selected, e.g., via restrictions;
3. flaws in data collection, subject classification, and data analysis.

Properties of a confounder

Consequently, the assessment of confounding for a given effect in a particular study involves:

1. Prior (external) information of effects in the source population
2. evaluation of study design and conduct
3. statistical analysis of relevant associations in the data

Study-design issues relevant to the assessment of confounding include

- randomization
- various selection procedures (such as restriction and matching)
- identification of the source population

Properties of a confounder

The direction of the bias due to a particular confounder will be

- positive if the confounder-exposure (C-E) association and the confounder-disease (C-D) association are in the same direction
- negative if the C-E and C-D associations are in opposite directions

NOTE: Confounding is defined in terms of the source population

Recall that in a follow-up design (cohort study or experiment, but not case-control study), the source population is the baseline study cohort (and not the person-time at risk).

Thus, we at least partially observe all members of the source population in a cohort study, whereas in a case-control study we do not.

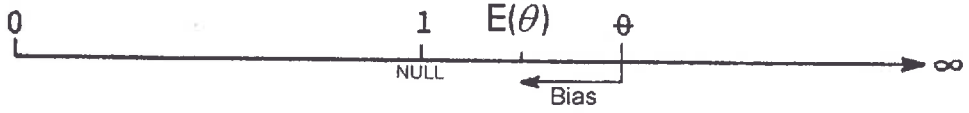
This difference has important implications to the identification and control of confounders in observational studies.

Direction of Bias

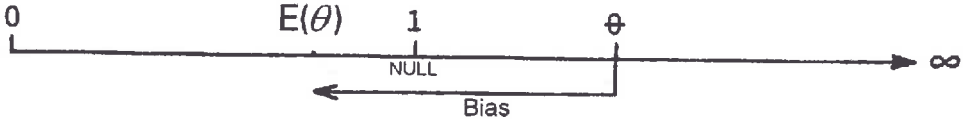
θ is a difference or log ratio effect measure in a source population and $E(\hat{\theta})$ is the expected value of the estimator of θ

Example 1: Positive bias away from the null

Example 2: Negative bias toward the null



Example 3: Negative bias beyond the null



Example 4: Positive bias toward the null

Confounding

Example 1: Oral contraceptive use, SES and Breast cancer

Hypothesis and design: Consider a case-control study designed to estimate the possible effect of oral contraceptive (OC) use on breast cancer.

Potential confounder: Since socioeconomic status (SES) is a known risk factor for the disease and since it is probably related to OC use, we will control for SES as a confounder, using stratified analysis.

Hypothetical results: Expected number of breast cancer cases (D) and controls ($\overline{D}$) by OC use and SES.

Confounding

Example 1: Oral contraceptive use, SES and Breast cancer

SES	OC Users (E)		Nonusers ($\bar{E}$)		
Stratum	D	$\bar{D}$	D	$\bar{D}$	$\widehat{OR}$
Low	25	50	75	150	1.00
Middle	50	50	50	50	1.00
High	120	40	30	10	1.00
Total	195	140	155	210	1.89

Conclusion: Because the **crude** (***marginal or unadjusted***) $\widehat{OR}$ (1.89), ignoring SES, is larger than the stratum-specific $\widehat{OR}$s (1.00), SES appears to positively confound the estimated effect of OC use on breast cancer.

Thus, the crude (marginal) $\widehat{OR}$ appears to be confounded by SES, and we would generally infer from the stratum-specific $\widehat{OR}$s that OC use does not appear to be a risk factor for this disease in this source population (Note: We should also consider other possible sources of bias and the precision of these estimates by estimating confidence intervals)

Confounding

Example 1: Oral contraceptive use, SES and Breast cancer

SES	OC Users (E)		Nonusers ($\bar{E}$)		
Stratum	D	$\bar{D}$	D	$\bar{D}$	$\widehat{OR}$
Low	25	50	75	150	1.00
Middle	50	50	50	50	1.00
High	120	40	30	10	1.00
Total	195	140	155	210	1.89

Comment: SES appears to be a confounder because SES is positively associated with

- exposure status (among noncases, who represent the source population): *[(50x150)/(50x50)=3 and (40x150)/(50x10)=12]*

and

- disease status (among nonusers): *[(50x150)/(75x50)=2 and (30x150)/(75x10)=6]*

presumable because it affects both.

The fact that the direction of these two associations was the same made the bias is positive –i.e., the crude $\widehat{OR}$ is larger than the stratum-specific $\widehat{OR}$s.

Confounding

Example 2: Wood dust, respiratory disease and smoking

Hypothesis and design: Suppose that we conduct a fixed cohort study to estimate the effect of exposure to wood dust on the occurrence of chronic respiratory disease (CRD) in middle-aged, male furniture workers.

Potential confounder: Since cigarette smoking is a known cause of the disease, we will control for smoking as a confounder, using stratified analysis.

Hypothetical results: Expected numbers of subjects at risk (N), new CRD cases (D), and risk (R), by wood-dust exposure and smoking

Confounding

Example 2: Wood dust, respiratory disease and smoking

Smoking Status	Exposed			Unexposed			
	D	N	$\hat{R}_1$	D	N	$\hat{R}_0$	$\widehat{RR}$
Smoker	168	400	0.420	152	600	0.253	1.66
Nonsmoker	57	600	0.095	23	400	0.058	1.65
Total	225	1000	0.225	175	1000	0.175	1.29

Conclusion: Crude (unadjusted) $\widehat{RR}$ (1.29) is less than the stratum-specific estimates (1.65-1.66), thus smoking appears to negatively confound the estimated effect of wood-dust exposure on CRD.

Thus, the crude $\widehat{RR}$ is biased for the effect, and we would infer from the stratum-specific RRs that exposed workers in this source population are about 65% more likely to develop the disease than are unexposed workers–assuming no further confounding or other bias is present.

Confounding

Example 2: Wood dust, respiratory disease and smoking

Smoking Status	Exposed			Unexposed			
	D	N	$\hat{R}_1$	D	N	$\hat{R}_0$	$\widehat{RR}$
Smoker	168	400	0.420	152	600	0.253	1.66
Nonsmoker	57	600	0.095	23	400	0.058	1.65
Total	225	1000	0.225	175	1000	0.175	1.29

Comment: Confounding appears to have occurred in this study because smoking is positively associated with CRD risk (among the unexposed) and inversely associated with wood-dust exposure (in the source population).

The latter association may be due to the fact that smokers elect or are selected to work in dust-free jobs where they can more easily and safely smoke.

Confounding

Example 3: Physical activity, coronary heart disease (CHD), and age and gender

Hypothesis and design: Suppose that we conduct a cohort study to estimate the effect of physical activity level on the occurrence of CHD in a population of adults, aged 50-69.

Potential confounders: Since age and sex are known risk factors for CHD, we will control for these variables as confounders, using stratified analysis. The different strata are formed from the cross-classification of both variables (covariates)–i.e., younger men, older men, younger women, and older women.

Hypothetical results: Expected number of new CHD cases (D) over 10 years, by sex, age, and physical activity level at baseline (active vs. sedentary), in the absence of loss-to-follow-up:

Confounding

Example 3: Physical activity, coronary heart disease (CHD), and age and gender

		Active (E)		Sedentary ($\bar{E}$)		
Sex	Age	D	Persons	D	Persons	$\widehat{RR}$
Male	50-59	70	9,500	386	28,500	0.54
	60-69	66	6,000	364	18,000	0.54
Female	50-59	15	10,000	83	30,000	0.54
	60-69	41	7,500	226	22,500	0.54
Total		192	33,000	1059	99,000	0.54

Conclusion: Because the crude $\widehat{RR}$ (0.54) is equal to the stratum-specific estimates, age and sex do not appear to confound the estimated effect of physical activity level on CHD.

Thus, the crude $\widehat{RR}$ would be unconfounded (but may be confounded by other factors) and we would infer that the rate in active adults is nearly half the rate in sedentary adults (assuming no other confounding occurred).

Confounding

Example 3: Physical activity, coronary heart disease (CHD), and age and gender

		Active (E)		Sedentary ($\bar{E}$)		
Sex	Age	D	Persons	D	Persons	RR
Male	50-59	70	9,500	386	28,500	0.54
	60-69	66	6,000	364	18,000	0.54
Female	50-59	15	10,000	83	30,000	0.54
	60-69	41	7,500	226	22,500	0.54
Total		192	33,000	1059	99,000	0.54

Comment: Confounding did not appear to occur in this study because activity level was not associated with age and sex (in the source population)–even though both age and sex were predictors of CHD (in the sedentary group). Thus, the two exposure groups appear comparable–at least with respect to age and sex.

NOTE: it would be technically incorrect (although rarely an important error) to use person time and rates instead of persons to do this evaluation – if loss of follow-up occurred, one should estimate the risks using methods for censored data and base the evaluation on those *risk ratio* estimates.

Confounding

Example 4: Social Support, hypertension, and race/ethnicity

Hypothesis and design: Suppose that we conduct a cross-sectional study to estimate the effect of social-support level on the presence of hypertension (elevated BP and/or maintained on antihypertensive medication) in a rural adult population.

Potential confounder: Since race is a known risk factor for hypertension, we will control for race as a confounder, using stratified analysis.

Hypothetical results: Expected number of subjects, by disease status, social-support level, and race.

Confounding

Example 4: Social Support, hypertension, and race/ethnicity

	Low support (E)		Adequate support ($\bar{E}$)		
Race	D	$\bar{D}$	D	$\bar{D}$	$\widehat{OR}$
White	73	270	167	690	1.12
Black	111	151	153	385	1.85
Total	184	421	320	1075	1.47

Conclusion: Although the crude $\widehat{OR}$ (1.47) differs from both stratum-specific $\widehat{OR}$s(1.12 and 1.85), the latter two $\widehat{OR}$s differ from each other. In this situation, we assess possible confounding by comparing the crude (marginal) measure to a summary measure that has been properly adjusted (standardized) for the covariates. Since, in this example, that summary $\widehat{OR}$ (not shown) is almost identical to the crude $\widehat{OR}$ race does not appear to be a confounder.

Confounding

Example 4: Social Support, hypertension, and race/ethnicity

	Low support (E)		Adequate support ($\bar{E}$)		
Race	D	$\bar{D}$	D	$\bar{D}$	$\widehat{OR}$
White	73	270	167	690	1.12
Black	111	151	153	385	1.85
Total	184	421	320	1075	1.47

Comment: Confounding by race appears to be absent in these data because race was not associated with social-support level (among noncases [(270x385)/(690x151)=1].

It appears, however, that race modifies the effect of social support on hypertension–i.e., the magnitude of the estimated social-support $\widehat{OR}$ is different for whites and blacks (effect measure modification).

Example 5: Confounding *vs.* Noncollapsibility

To show one problem with the change-in-estimate criterion for identifying confounders, consider the results of this hypothetical fixed cohort study in which the **covariate is known** to be a **risk factor** for the disease. The table below shows the number of subjects (N) at baseline, the estimated disease risk $\hat{R}$ and 4 estimated measures of association, by covariate status (C vs. $\bar{C}$).

Example 5: Confounding *vs.* Noncollapsibility

Covariate Status	Exposed N	Exposed $\hat{R}$	Unexposed N	Unexposed $\hat{R}$	Measure of Association $\hat{RR}$	$\hat{RD}$	$\hat{IOR}$	$\hat{corr}$
C	100	0.95	100	0.75	1.27	0.20	6.33	0.28
$\bar{C}$	100	0.25	100	0.05	5.00	0.20	6.33	0.28
Total	200	0.60	200	0.40	1.50	0.20	2.25	0.20

Conclusion: Although C is a risk factor for D (reflected in the data), it is not associated with exposure status in the total sample (source population). Thus, C is not a confounder– a fact that is properly conveyed by comparing the crude and stratum-specific RD or RR estimates. (Since the RR estimates differ between strata, we must compare the crude (marginal) RR with a properly standardized estimate; they are equal).

Example 5: Confounding *vs.* Noncollapsibility

On the other hand, the crude (marginal) and stratum-specific incidence odds ratios ($\widehat{IOR}$s) and the correlation coefficients (corr) are not equal, incorrectly suggesting presence of confounding.

One reason is that the $\widehat{OR}$ need not be collapsible across strata (stratum specific $\widehat{OR}$ can differ from marginal $\widehat{OR}$) even when there is no confounding.

A correlation coefficient never reflects the exposure effects alone, since its value depends on non-causal parameters (the ratio of sample variances)

{IOR does not approximate the RR (or RR) in a cohort study when the disease is not rare–even when exposure groups are comparable}.

Example 6: Confounding and Random Error [1]

In a double-blind clinical trial involving about 10,000 subjects followed for three years, the efficacy of a certain drug was tested for its ability to prevent first occurrence of a disease (D). Subjects were randomized into treated and placebo groups so that each subject had a 50 percent chance of getting the test drug. The results showed that the drug substantially lowered the risk of the disease.

At the end of the trial, the investigators were told of a new hypothesis linking another exposure with the same disease. To examine this hypothesis in their population, the investigators conducted **a nested case-control study**, comparing all ***66 observed cases*** of D with an equal number of ***noncases randomly sampled from the total cohort***. Exposure histories were obtained from all 132 subjects, and the results of this study are given in the table below, stratified by assigned treatment group (the covariate, C).

Example 6: Confounding and Random Error [1]

Treatment Group (C)	Exposed D	Exposed $\bar{D}$	Unexposed D	Unexposed $\bar{D}$	$\widehat{OR}$	95% CL
Test Drug	5	17	10	34	1.00	(0.29, 3.39)
Placebo	34	10	17	5	1.00	(0.29, 3.39)
Total	39	27	27	39	2.09	(1.04, 4.18)

Conclusion: Even though the crude (marginal) and stratum-specific estimates of effect differ substantially (i.e., there is a change in the estimate when stratifying), treatment group is not a confounder in this study since it is very unlikely to be associated with exposure status in the source population of 10,000. We know this (*a priori*) because subjects were ***assigned randomly to two very large treatment groups***. Thus, the marginal odds ratio (= 2.09) will likely be closer to the true population odds ratio than would be the stratified.

Example 6: Confounding and Random Error [1]

Treatment Group (C)	Exposed D	Exposed $\bar{D}$	Unexposed D	Unexposed $\bar{D}$	$\widehat{OR}$	95% CL
Test Drug	5	17	10	34	1.00	(0.29, 3.39)
Placebo	34	10	17	5	1.00	(0.29, 3.39)
Total	39	27	27	39	2.09	(1.04, 4.18)

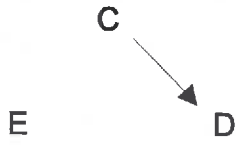
Comment: As illustrated in this example, the change-in-estimate criterion for identifying confounders (i.e., observing a change in effect estimate when stratifying on a covariate) may also go astray due to random error. In this example there is prior information to indicate that the C-E association observed in the data suffers from large random error.

Example 6: Confounding and Random Error [1]

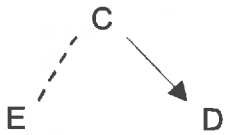
In this example, we knew with very high probability (due to the randomization in a large cohort) that there was no association between exposure status and treatment group (C) in the source population of 10,000

But, we observed a strong association in the (small) control group of 66 subjects ($\widehat{OR} = 0.25$), which was probably due to sampling error or unknown selection bias.

Prior knowledge



Observed



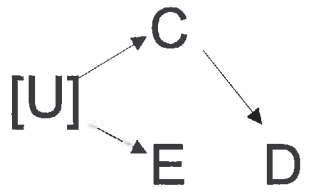
It was this observed E-C association (along with the treatment effect on disease) that made the marginal estimate of effect ($\widehat{OR} = 2.09$) different from the stratum-specific estimates ($\widehat{OR} = 1$).

Thus, because the observed exposure-treatment association does not represent the actual E-C association in the source population, the stratum-specific estimates of effect are almost certainly way off the truth.

Example 6: Confounding and Random Error [2]

Suppose that smoking (C) is known to be a risk factor for the disease and is associated with exposure status in the source population (via an unmeasured factor U). The results of a hypothetical case-control study of this possible exposure-disease relation are shown in the table below.

Prior knowledge:



Example 6: Confounding and Random Error [2]

	Exposed		Unexposed			
Smoker?	D	$\bar{D}$	D	$\bar{D}$	$\hat{OR}$	(95% CL)
Yes	20	10	1	2	4.00	(0.32, 49.6)
No	2	1	10	20	4.00	(0.32, 49.6)
Total	22	11	11	22	4.00	(1.44, 11.1)
Internally standardized for smoking ($s\hat{OR}$):					4.00	(0.40, 39.9)

Conclusion: Although the crude (marginal) and stratum-specific point estimates of effect are equal, the 95% confidence intervals are very different. Note the discrepancy between our prior knowledge that smoking is a risk factor for the disease and our observation of no C-D association in the 33 unexposed subjects. We would probably conclude from our prior knowledge that the lack of smoking association with D in the data is due to random error or bias, and hence that smoking ***is*** a confounder, even though the crude (marginal) and stratum-specific point estimates of effect are the same. Therefore, we would infer that both the crude and stratum-specific estimates (4.00) are probably biased.

Example 6: Confounding and Random Error [2]

The less precise stratified result $\widehat{sOR}$ provides a more accurate measure of uncertainty than does the marginal results, because it correctly reflects our inability to separate the two effects statistically.

That is, the study provides evidence that at least one of the factors, exposure and/or smoking has an effect on D, but we cannot rule out either possibility without additional information.

This problem is often called a collinearity problem because, the stronger the C-E association, the more difficult it is to separate their effects statistically (that is based on the data).

Confounders : C-D

To be a confounder for estimating the effect in the exposed,

- a covariate (C) must be a risk factor for the disease (D) in the *unexposed source population*,

To be a proxy for a confounder

- it must be a marker (proxy) for another (usually unmeasured) risk factor.

Directed Acyclic Graph (DAG)

Path = nodes (variables) connected by arrows

Causal path = directed path going along the arrow

Backdoor path = going against the arrow

X on C direct effect

X on Y indirect effect

Acyclic = no feedback loops

Collider = variable in path that has arrowhead going into it in an inverted fork X → C ← Y (if a path has one or more colliders it is blocked, otherwise unblocked, open)

Unassociated variables = have no (unblocked) causal or backdoor path between them (AKA marginally independent)

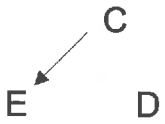
Causal DAG = causal path with directed arrows from one variable to another (can be direct or indirect)

Simple Causal Diagrams: No Confounding

Selected relations among 3 or 4 variables: an exposure (E), a disease (D), and one or two covariates (C and C*). Each arrow in the figures represents a direct causal effect in the source population

---

1) C affects E, but is ***not*** a risk factor for D in the unexposed source population



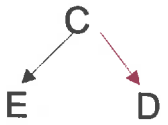
E =lead exposure in children
C= poverty
D= neuropsychologic development

Again, there is ***no*** open backdoor paths from E to D, so C is ***not*** a confounder and should not be controlled for in the analysis.

Matching on C in a case-control study (but not in a cohort study) is likely to reduce statistically efficiency – due to overmatching.

Note: if there were a direct effect of E on D, then C affects D (indirectly through E) but is not a risk factor among the unexposed, thus C is still not a confounder.

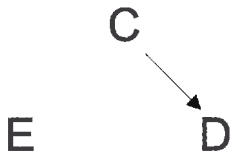
Suppose, however, that poverty does affect neuropsychological impairment independent of lead exposure, then there would be an arrow from C to D and poverty would be a confounder.



Simple Causal Diagrams: No Confounding

Selected relations among 3 or 4 variables: an exposure (E), a disease (D), and one or two covariates (C and C*). Each arrow in the figures represents a direct causal effect in the source population

2) C affects D, but is ***not*** associated with E in the source population



E =blood type O
C=gender
D= coronary heart disease

There is ***no*** open backdoor paths from E to C, so C is ***not*** a confounder in this example. C need not be controlled for in the analysis (except perhaps in a cohort study to increase precision).

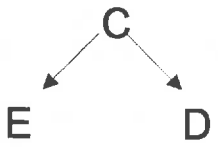
Note: the lack of an E-C association in the source population can be observed in a cohort study (cohort is the source population) but only estimated in a case control study.

If subjects were selected in a cohort study so as to create an E-C association, C would become a confounder.

Simple Causal Diagrams: Confounding

Selected relations among 3 or 4 variables: an exposure (E), a disease (D), and one or two covariates (C and C*). Each arrow in the figures represents a direct causal effect in the source population

3) C is a risk factor for both E and D



E =high blood pressure
C= age
D= breast cancer

There **is** an open backdoor paths from E to D (E-C-D),

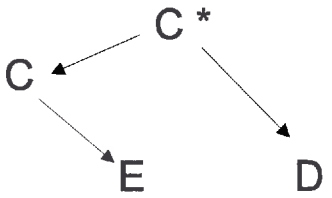
Thus, C **is** a confounder and should be controlled for
in the analysis and/or
by restriction of eligible subjects (complete restriction or matching)

By conditioning on C, we block the open backdoor path and, thus, control for confounding by C

Simple Causal Diagrams: Confounding (2 risk factors in path)

Selected relations among 3 or 4 variables: an exposure (E), a disease (D), and one or two covariates (C and C*). Each arrow in the figures represents a direct causal effect in the source population

4) C is a risk factor for E in the source population, and C is affected by an unmeasured risk factor (C*) for D



E =coffee consumption
C= social stress,
C*=gastrointestinal symptoms
D= depression

Either C or C* alone is sufficient for control of confounding via the backdoor path E-C-C*-D.

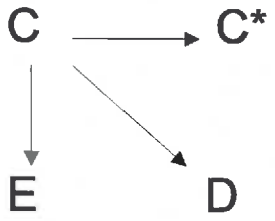
Because we need only control for C or C*, if we can measure both without error, we should control for the covariate that can be measured with the lowest cost.

Otherwise we would also consider accuracy of measurement.

Simple Causal Diagrams: Confounding (*proxy*)

Selected relations among 3 or 4 variables: an exposure (E), a disease (D), and one or two covariates (C and C*). Each arrow in the figures represents a direct causal effect in the source population

5) C* is a direct effect of an unmeasured confounder (C), but it is not in a causal pathway between C and either E or D



E =peridontitis
C= genetic susceptibility to CHD
C*=parental history of CHD
D= Coronary heart disease (CHD)

C* is a *proxy* for the confounder C.

Unless C and C* are perfectly correlated, controlling for C* will remove some, but not all of the confounding by C.

This is equivalent to measuring C with some error.

Causal and Proxy Confounders

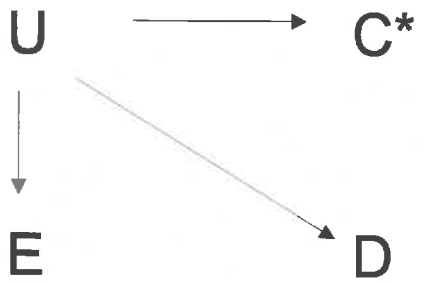
Proxy confounder (C* proxy for U): U is a causal (but unknown – unmeasured) confounder (open backdoor path), C* is associated with U (open path between U and C) and not affected by E or D; but C* is not on every open backdoor path that contains U. Therefore, U is still a confounder when controlling for C*; after controlling for C*, U is still on at least one backdoor path between E and D.

As shown in the above DAGs, controlling for U eliminates the bias, but controlling for C* alone does not control for confounding due to U.

Thus, controlling for C* is similar to controlling for a misclassified measure of U.

Causal and Proxy Confounders

Example 1:



E=blue eye color,

C=family history of CHD

U=genotype

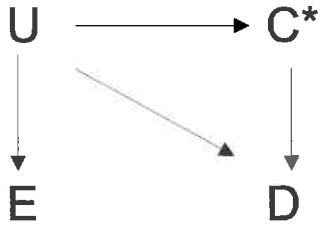
D=Coronary Heart Disease

This illustrates that we cannot usually eliminate confounding due to genetic factors (genotype U) by controlling for family history of the disease (phenotype, C).

Causal and Proxy Confounders

Example 2:

Controlling U eliminates the confounding, but controlling C* alone would increase or decrease bias, depending on the direction of the direct and indirect effects of U on D. If the direct (U-D) and indirect (U-C*-D) effects were in the same direction (both positive or inverse), controlling for C alone would decrease the bias (but not eliminate it, because U is still a confounder). On the other hand, if the direct and indirect effects of U on D were in the opposite directions, controlling for C could actually increase the bias



E=body mass index (obesity)
C*=HDL cholesterol
U= physical activity
D=Coronary Heart Disease

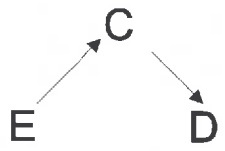
Since the direct and the indirect effects of more physical activity on CHD risk are the same direction (to lower risk), controlling for C alone would reduce , but not eliminate, confounding by U

Simple Causal Diagrams: Intermediate

Selected relations among 3 or 4 variables: an exposure (E), a disease (D), and one or two covariates (C and C*). Each arrow in the figures represents a direct causal effect in the source population

---

6) C is affected by E, and it is a direct cause of D

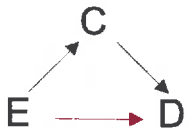


E =physical activity
C= high HDL level
D= coronary heart disease

C is an ***intermediate*** variable; thus it should not be matched on or controlled for in the analysis.The bias produced by matching on an intermediate ordinarily cannot be eliminated in the analysis.

Note that E might also have a residual ("direct") effect on D that is independent on C, i.e. an effect not mediated by C but by another biological mechanism such as decrease in platelet aggregation – which would be represented by an arrow between E and D.

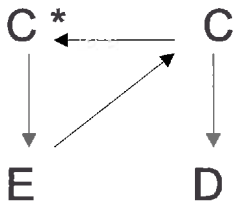
Unfortunately, we usually cannot estimate the direct effect by controlling for C using conventional methods



Simple Causal Diagrams: Confounder and Intermediate

Selected relations among 3 or 4 variables: an exposure (E), a disease (D), and one or two covariates (C and C*). Each arrow in the figures represents a direct causal effect in the source population

7) C is affected by E, and it is a risk factor for both E and D



E =cumulative exposure to occ. Toxin
C= respiratory symptoms
C*=early job termination
D= death from respiratory disease

C is **both a confounder and an intermediate**; C* is a *proxy* confounder and a *proxy* intermediate.

Thus, conventional methods for controlling for C and C* will be biased.

To validly control for confounding by C, we must treat both E and C (or C*) as time-dependent covariates and use a special type of analysis (stratify on time and the covariates; use structural nested models (using G-estimation) or marginal structural models (using inverse probability of treatment weighting).

NOTE: the **diagram has a cycle** (feedback loop, E-C-C*-E) and therefore is **not a DAG**

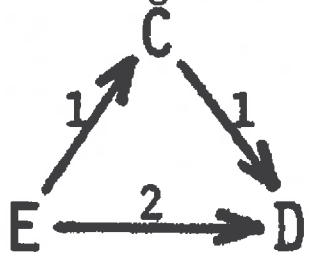
Confounders and Intermediates

When C is an intermediate variable, we would not control for C to reduce bias; in fact, conventional methods for controlling for an intermediate variable introduces bias in effect estimation.

Part of the exposure effect on D is due to the mediating effect of C– i.e., the "indirect" effect of E (path 1 in the figure below); but there may also be a residual ("direct") effect due to other causal mechanisms (path 2).

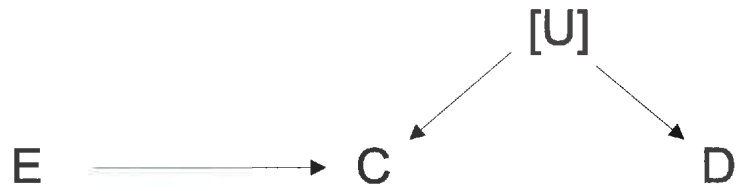
Unfortunately, we often cannot separate these two components analytically because we may lack longitudinal data;

Even when we have those data, we usually cannot estimate the residual ("direct") effect simply by controlling for C in the same way we control for confounders.



Confounders and Intermediates

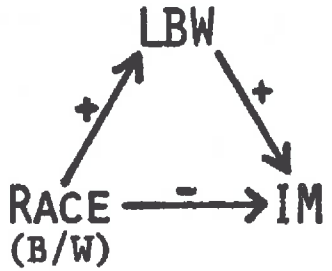
This is so, even in a randomized trial as the following diagram illustrates. Controlling for the intermediate C opens a back-door path (through U) and hence introduces confounding, even when there was no confounding to begin with



The identification of intermediates is important, i.e. to distinguish them from confounders and to explain hypothesized effects in terms of biological or behavioral mechanisms

Examples: Confounders and Intermediates

The effect of race (black vs. white) on infant mortality (IM) is probably mediated in part by low birth weight (LBW)



In this example, the indirect effect of being black (mediated by LBW) increases the risk of infant mortality, but the residual (direct) effect of being black decreases the risk (i.e., within birthweight strata). It is possible, therefore, that these two effects cancel each other, leading to approximately equal risks in blacks and whites. In most U.S. populations, however, it appears that the indirect effect is greater than the residual effect; thus, the overall risk of death is higher in black than white infants.

Example 8: Confounders and Intermediates

Hypothesis and design: Consider again the fixed cohort study of behavior type (A vs. B) and CHD in white males.

Potential confounder: Since serum cholesterol level is a known risk factor for the disease, we will control for this variable, using stratified analysis.

Hypothetical results: Numbers of subjects at risk (N), new CHD cases (D), and risk (R), by behavior type and baseline cholesterol.

Example 8: Confounders and Intermediates

Cholesterol level	Type A			Type B			
	D	N	$\widehat{R}$	D	N	$\widehat{R}$	$\widehat{RR}$
High	13	85	0.152	3	30	0.100	1.53
Low	3	58	0.052	4	109	0.037	1.41
Total	**16**	**143**	**0.112**	**7**	**139**	**0.050**	**2.22**

Conclusion: Even though the crude (marginal) $\widehat{RR}$ (2.22) is larger than both stratum-specific (conditional) estimates (1.53 and 1.41) as well as the summary adjusted estimate (1.51), cholesterol level is probably not a confounder.

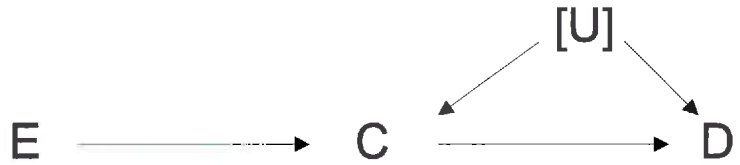
The reason, which cannot be inferred from the above results alone, is that elevated serum **cholesterol** is likely to be an **intermediate** variable in the hypothesized causal pathway between Type A behavior and CHD

Example 8: Confounders and Intermediates

From previous research, we would expect the effect of behavior type on CHD to be mediated in part via the behavior type's effect on serum cholesterol level, thus control for cholesterol would remove that part of the total effect.

Furthermore if Cholesterol level and CHD share a common, unmeasured cause [U], then conditioning on cholesterol level opens a backdoor path between Type A behavior and CHD.

Given these relations, we'd expect the marginal (crude) RR to be closer to the total effect of Type A behavior in this population than the cholesterol-adjusted RR.



Comment: On the basis of these results alone, there is no way to determine whether cholesterol level is a confounder or an intermediate variable. In both cases, the covariate will be associated with both exposure and disease occurrence in the population. If the E-C association is observed cross-sectionally, our conclusion would have been based on prior information about their causal relation (if such information exists).

Confounder vs. Intermediate

Thus, the distinction between a confounder and an intermediate may be difficult to make in practice because it requires prior information, which may be lacking or incomplete. Yet this distinction is critical to validity considerations in any type of study.

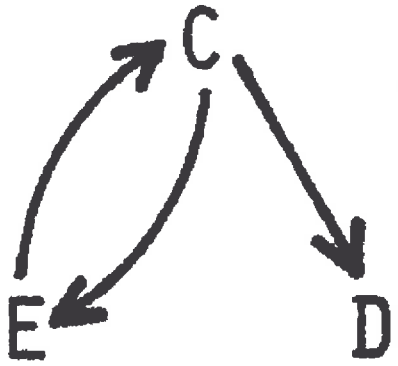
If C is an ***intermediate*** and not a confounder, controlling for C results in bias in the estimation of the E effect; this bias could be in any direction, depending on the directions of the E-C, C-D, and the residual E-D associations.

If C is a ***confounder*** and not an intermediate, controlling for C reduces confounding due to C or other causal confounders for which C is a proxy.

Confounder vs. Intermediate

Example: E = use of AZT among HIV positives,
C = CD4+ lymphocyte count
D = death from AIDS

Not a DAG!



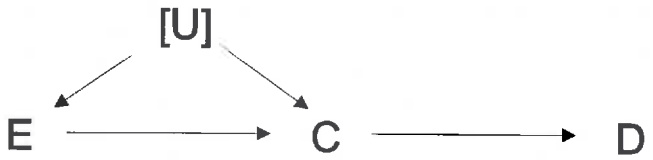
In order to properly analyze this relation in which a time-dependent variable is both a confounder and an intermediate (C=CD4+ lymphocyte count), you must use a technique for longitudinal data analysis. Here, 'GEE' would be an incorrect method of analysis , whereas G-estimation would be an appropriate analytic technique.

Confounder and Intermediate

The distinction between a confounder and intermediate gets more complicated when an intermediate (C) is also a proxy for an unmeasured confounder [U].

If C is an *intermediate* and U is a *confounder*, controlling for U eliminates confounding due to U. But, in the absence of data on U, C is also a proxy confounder (as well as an intermediate).

Using conventional statistical methods, we get a biased estimate of the E effect whether or not we control for C.



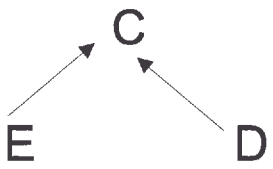
Confounder control is most problematic when the same time-dependent variable (C) is both a confounder and an intermediate of the same hypothesized relation.

In this situation, even with valid data on all variables, we would not, in general, get an unbiased estimate of the E effect by controlling or not controlling for C, using conventional statistical methods.

Simple Causal Diagrams: Selection Bias in Some Studies

Selected relations among 3 or 4 variables: an exposure (E), a disease (D), and one or two covariates (C and C*). Each arrow in the figures represents a direct causal effect in the source population

8) C is affected by both E and D



E =active life style (frequent falls likely)
C= hip fracture
D= osteoporosis

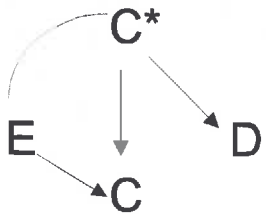
Controlling for C – or excluding potential subjects with or without C is likely to introduce bias which is a form of selection bias (AKA Berksonian bias where C=hospitalization)

The causal diagram represent a general mechanism for **selection bias** in a **case-control** or **cross sectional** study, where C reflects any selection procedure that is influenced by both E and D

Simple Causal Diagrams: Neither confounder nor intermediate

Selected relations among 3 or 4 variables: an exposure (E), a disease (D), and one or two covariates (C and C*). Each arrow in the figures represents a direct causal effect in the source population

9) C is affected by both E and by a risk factor (C*) for D



E = history of head trauma
C = cognitive impairment
C*= high blood pressure
D = stroke

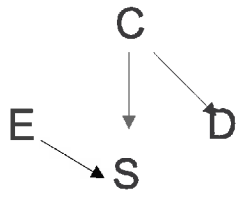
Neither C nor C* is a confounder or an intermediate; thus, we would expect the marginal (crude) effect estimate to be unbiased (assuming no other sources of bias).

Restricting eligibility on C or controlling for C in the analysis, however, is likely to introduce bias unless we also control for C*, because conditioning on C creates an E-C* association.

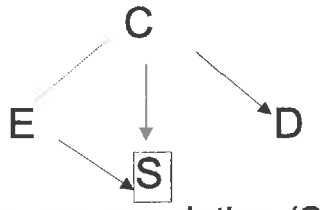
The bias applies to **cohort studies** even if C is measured at baseline. This diagram represents the general mechanism for selection bias in a cohort study, where C reflects or affects **loss to follow-up** (right censoring) and is influenced by both E and by an unmeasured risk factor for D.

Induced Confounders (by selection)

In a cohort, subjects might be selected (S represents selection) in such a way as to create an association between E and an extraneous factor (C) in the source population, making C a selection confounder even when E and C are not causally related. Subjects might also be selected to eliminate such a C-E association in the source population, preventing C from being a confounder.

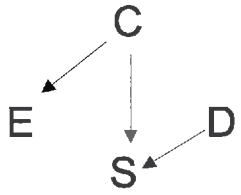


Target population

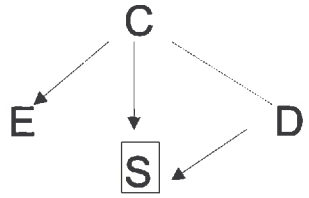


Source population (S=1)

In a case control study, matching controls to cases on a covariate (C) can make C a selection confounder, even if C is not a risk factor for the disease



Target population



Source population (S=1)

Induced Confounders (by selection)
Example

If race and sex are risk factors for the disease, we can prevent confounding by race and sex in a cohort study by restricting the entire study (source) population to black males.

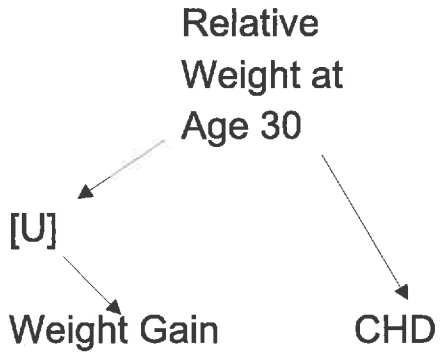
On the other hand, we would probably induce confounding by selecting mostly black males as the exposed group and white females as the unexposed group.

Furthermore, if there is no overlap in the race-sex distribution between exposed and unexposed groups (if **all** exposed subjects = black males; **all** unexposed subjects = white females), we would not be able to identify or control for these confounders by stratification in the analyses, because every stratum would contain only exposed or unexposed subjects. This situation is an example of **extreme collinearity**.

Baseline values as confounders

When the exposure involves a change in a particular variable, it may be necessary to treat the baseline level of that variable (i.e., at the start of the period during which the change is observed) as a confounder.

Example: Suppose that we want to estimate the effect of weight gain between ages 30 and 40 on the risk of CHD. Since overweight 30-year olds may be more (or less) likely to gain weight during their 30s than are non-overweight 30-year olds and since relative weight is a risk factor for CHD, we would control for relative weight at age 30 as a confounder to isolate the effect of weight gain.

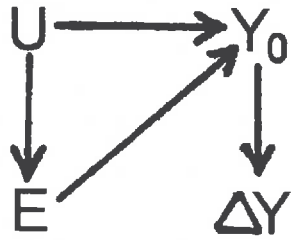


Baseline values as confounders

(cont.)

Comment: When the *outcome* involves a change in a continuous variable (ΔY), the baseline level of that variable (Y_0 , at time t_0) in an observational study may be a proxy for another unmeasured, perhaps unknown, confounder (U); *or* Y_0 may have been affected by previous levels of the exposure (E)–i.e., possibly acting as an intermediate variable).

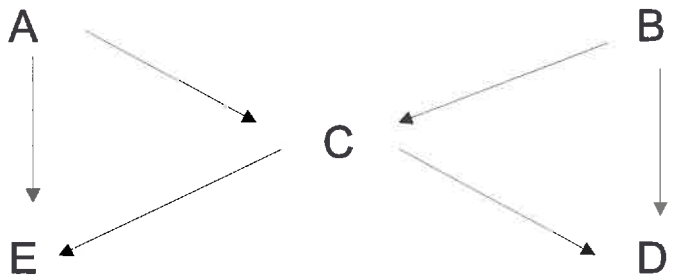
Thus, controlling for Y_0 in an observational study might still produce a biased estimate of the exposure effect because it involves over-adjustment for an intermediate. Not controlling for Y_0 however, might also results in bias due to confounding by U. In an experiment, however, Y_0 cannot be an intermediate because it occurs before the intervention (exposure).



Interdependence of Confounders

Adjustment for a confounder C removes confounding only along the paths blocked by C, but may not reduce net confounding, and may even introduce confounding (if C is the sole **collider on a backdoor path**).

Such an example is demonstrated in the 'Bowtie diagram' where conditioning upon C opens a backdoor path through A-B. Thus, in order to obtain an unbiased estimate of the E-D relationship, one **must control for both *C and A* or *C and B*** since merely controlling for C introduces confounding.



See also: Greenland S. Quantifying Biases in Causal Models: Classical confounding vs. collider stratification bias. Epidemiology 2003; 14:300-6.

Interdependence of Confounders

Thus to ensure control of confounding we would have to adjust for all potential confounders simultaneously – not one at a time.

This stipulation poses certain limitations in any non-experimental study, because

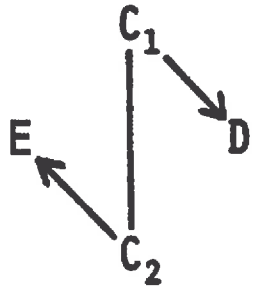
1. we cannot generally identify and measure *all* confounders; and
2. analytic methods of control (e.g., stratified analysis) cannot handle an unlimited number of covariates or strata since we never have an unlimited number of subjects.

Interdependence of Confounders

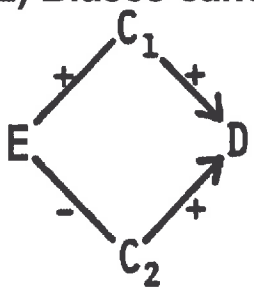
Fortunately, in practice, it is not necessary to control for *all* confounders because bias due to different confounders:

- may be redundant since one (or each) confounder is a *proxy for the other*; or
- may *cancel each other*.

1) Redundant confounders



2) Biases cancel



In the first situation, we would probably need to control for either C1 or C2–not both–to eliminate bias due to these potential confounders.

In the second situation, it might not be necessary to control for either covariate if the positive confounding due to C1 equals the negative confounding due to C2. In fact, controlling for only one covariate might increase bias (relative to no control).

Note that you must therefore control for neither C1 or C2 or both C1 and C2

Interdependence of Confounders

Comment: The implication of these issues is that the identification of confounders and their control is difficult because assessing confounding by each covariate depends on what other potential confounders are controlled.

Indeed, the identification and control of confounders is an imperfect, but necessary, method in nonexperimental studies to reduce confounding.

Identifying confounders

It is common, but erroneous, practice to identify confounders by estimating or testing several C-D or E-C associations in the data and selecting those covariates (C) for control that have the strongest or most "significant" associations with either variable. In general, this approach is inappropriate for several reasons:

1. It ignores **prior (external) information**. Associations observed in the data may conflict with our prior information of these associations or effects in the **source population**. Also, the approach ignores the important distinction between confounders and intermediates.

2. Identifying those covariates with the **strongest associations with E or D** cannot demonstrate that these covariates *are* confounders, because such covariates may not be associated with the other primary variable.
   - A strong risk factor for D will not be a confounder if it is not associated with E in the source population;
   - A strong correlate of E will not be a confounder if it is not a risk factor for D in either the exposed or unexposed source population.

Identifying confounders (cont.)

3. Unfortunately, the magnitudes of the C-D and E-C associations relevant to confounding are not the crude associations, but the **associations *conditional* on other covariate (C) being controlled**. Since the relevance of each potential confounder depends on what other covariates are being controlled, there is no definitive statistical method for identifying confounders without prior knowledge of all relevant covariates and effects.

4. **Statistical testing** of the C-D or E-C associations in the data cannot demonstrate that a particular covariate is, or is not, a confounder, because testing does not indicate the magnitude of these associations and does not properly account for uncertainty about these magnitudes. E.g., C may be a strong confounder even if it is not "significantly" associated with D (e.g., if $P > 0.05$). In fact, a small sample size is likely to produce large P values for both the E-C and C-D associations–even though there might be substantial confounding by C. Indeed, confounding is not less of a problem in small studies; the opposite is true because it is more difficult to control analytically for confounders in a small study.

Example 9: Confounders

The University Group Diabetes Program (randomized) Clinical Trial was done to estimate the possible effects of tolbutamide use (an oral hypoglycemic agent) on various health outcomes among diabetics. The table below shows the number of total deaths (D) between 1961 and 1969, the number of subjects (N), and the estimated risk R of total mortality, by treatment group and age at baseline.

	Tolbutamide			Placebo			
Age	D	N	R	D	N	R	RD
<55	8	106	0.075	5	120	0.042	0.034
>=55	22	98	0.224	16	85	0.188	0.036
Total	30	204	0.147	21	205	0.102	0.045

Source: University Group Diabetes Program Research Group. A study of the effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes: II. Mortality results. *Diabetes* 1970; 19(Suppl 2):785-830 (see Table 8).

Example 9: Confounders

It appears that tolbutamide increased the risk of dying among diabetics–an unexpected finding. Note the association between treatment status and age in the total sample (the source population):

OR=(98*120)/(106*85)=1.31 (95% CI=0.88,1.93)

X_{MH}= 1.34; P = 0.18

As indicated by the RD estimates, age (a risk factor for total mortality) appears to confound the estimated effect of tolbutamide on total mortality.

Thus, despite randomization, it appears that (by chance) age is a confounder and probably should be controlled in the analysis.

Testing the null hypothesis of no crude age-treatment association (i.e., P = 0.18 > 0.05) is not relevant to our determination of whether age is a confounder, because the association of concern is the one in the source population; not some larger population of which the cohort is a sample.

Note that in a randomized trial, a widened confidence interval may reflect the presence of residual confounding due to random covariate imbalances.

It is possible that there are other confounders as well, but if randomization was not violated within age strata, it is unlikely that the residual confounding is large.

Methods of controlling for confounders

Investigators have several options for reducing or eliminating confounding, which may be grouped into two general strategies:

Methods used in the *design and conduct* of a study to prevent confounding in the source population; and

Methods used in the *analysis of data* to adjust effect estimates.

Methods of controlling for confounders

Design and Conduct of a Study:

1) Randomization (in experiments):

- Proper randomization implies that the only baseline difference between treatment and control groups will be random including differences in unmeasured or unrecognized factors.
- Consequently, conventional confidence intervals and p values in randomized studies actually reflect possible confounding due to random covariate imbalance (in either direction) which will tend to be smaller as the sample size increases.
- Because there is no guarantee that randomization has eliminated all confounding, especially with small sample sizes, other options are also used to control for confounding (e.g., analytic methods).
- In fact, loss to follow-up ('drop-out' or censoring) and non-compliance may lead to confounding, sometimes called 'broken randomization in the context of a randomized trial'.
- Intent-to treat analysis attempts to eliminate the latter confounding by redefining 'treatment' as 'intent to treat', but the latter is usually not the exposure of biologic interest.

Methods of controlling for confounders:

Design and Conduct of a Study:

2) and 3) not likely in observational studies

2. *Select a reference population (without randomization) that is exchangeable to the index (exposed) population*. Such **natural experiments**, however, may be <u>difficult to achieve</u>

3. *Keeping the values of potential confounders the same and fixed for all subjects* (in experimental or quasi-experimental studies):

   This strategy is often used in **laboratory studies** where the investigator can control certain environmental factors (e.g., temperature) that are known to affect the outcome, but is <u>not an option</u> in observational studies.

Methods of controlling for confounders:

Design and conduct of a study:
4) Restriction and Matching

4. *Restricting the eligibility of subjects according to values of potential confounders* (in any type of study):

   This strategy is the major design option used in observational studies to control for known risk factors (i.e. known, measurable, and not likely to reduce eligible N too much).

   It could involve restricting the eligibility of all subjects (complete restriction) or comparison subjects only (partial restriction or matching).

   Except in some natural experiments, however, restriction is rarely sufficient to eliminate confounding in observational studies.

Thus, we also use analytic methods.

Methods of controlling for confounders:

Analytic methods of adjustment

Analytic methods of adjustment: We estimate the E-D association conditional on levels of measured confounders (and proxies). There are two general methods for such analytic control or adjustment:

- *Stratified analysis*: We estimate the E-D association within categories or strata of the confounders (as in the examples given previously) or/and derive a summary estimate of this association across these strata (which often assumes that the association does not vary across strata)

- *Model fitting*: We "fit" to the data a mathematical model (e.g., linear or logistic) that includes both the exposure variable and potential confounders (covariates) as predictors of the outcome variable. The estimated model coefficient (slope) for the exposure variable reflects the E-D association conditional on other predictors in the model (a summary which assumes that the model adequately fits the data).

Methods of controlling for confounders

Comments: Strictly speaking, both stratified analysis and 'model fitting', assume a mathematical model for the data.

In stratified analysis all variables must be categorized, whereas in 'model fitting' one or more of the variables can be continuous.

The flexibility to model continuous covariates is usually accompanied by stronger modeling assumptions (e.g. model fit to continuous variables often makes assumptions about the functional dependence of the outcome on the covariate, e.g. linearity or log-linearity), although the assumptions may be weaker (e.g. when splines are used).

The net results of these differences is that model fitting techniques, such as regression, may produce **more precise** (adjusted) estimates of effect sometimes at a **cost of stronger assumptions**.

Conclusions and Summary: Confounding *and* Confounder (control)

Confounding is bias in the estimation of the exposure effect, due to a lack of comparability of potential outcomes (non-exchangeability) between exposed and unexposed groups in the source population.

When the exposed group is the target population, this means that the unexposed (reference) population does not have the same risk as the exposed (index) population would have had in the absence of exposure.

The concept of confound***ing*** is more fundamental than is the concept of confound***er*** or confounder control.

Note that the definition of confounding does not depend on the designation of confounders. It follows, therefore, that the properties of a confounder do not define confounding but are derived from the non-exchangeability definition of confounding.

Conclusions and Summary: Confounding *and* Confounder (control)

A confounder can be defined as a variable that when controlled removes a source of confounding

I.e. at least partially blocks an open backdoor path between exposure and outcome variables, whether or not this removal reduces net bias.

Some necessary properties of a confounder are, it must be associated :

- with the disease in the reference subpopulation of the source population (the unexposed if our exposed group is the target population), but not caused by disease;
- with exposure status in the total source population; but not caused by exposure

The major basis for identifying confounders in a given study is prior information of relevant effects or associations in the source population–not just statistical associations observed in one's data.

In the absence of such prior information, therefore, causal inference is extremely limited; the less we know about the exposure and disease in a non-randomized study, the less sure we can be that our effect estimate is unbiased.

Conclusions and Summary
Confounding *and* Confounder (control)

Attempts to assess confounders with data, ignoring or in the absence of prior information, can yield very misleading results.

For example, the change-in-estimate criterion for identifying confounders –i.e., comparing estimates adjusted and unadjusted for one or more covariates – can be misleading when:

- the association measure does not reflect a causal parameter (e.g. correlations) or the association measure can be non-collapsible in the presence of confounding (e.g. odds ratios and rate ratios)
- there is a discrepancy between observed associations in the data and corresponding associations (or estimated effects) in the source population due to random error or biases; or
- the covariate is affected by the exposure or disease.

Furthermore, testing or estimating associations between each covariate and disease or exposure status to identify confounders is often misleading as well as time consuming.

Conclusions and Summary
Confounding *and* Confounder (control)

In nonrandomized studies, the major burden of controlling for confounders is in the analysis.

Although it is not necessary to adjust for *all* confounders, in the absence of information about *sufficient sets* of confounders and effects in the source population, there is no mathematical algorithm or strategy, such as a stepwise or backward procedure in model fitting, that can identify from one's data an optimal or even adequate set of covariates to eliminate confounding.

Conclusions and Summary
Confounding *and* Confounder (control)

The reasons for this practical limitation are

- we cannot directly observe violations of the exchangeability assumption,
- the identification of confounders depends on prior information, which is usually incomplete

Furthermore, empirically assessing the confounding properties of each covariate depends on what other potential confounders are being controlled.

Consequently, control of confounding requires integration of prior information into the analysis; this demands contextual (subject matter) understanding as well as statistical expertise.

Stratified Analysis

One way to identify and control for confounders is to do a stratified analysis, which involves analyzing the data within categories (strata) of these covariates (potential confounders).

Specifically, we observe the association between exposure status and disease occurrence within each of several strata, where each stratum represents a category of one or more covariates.

Recall that we condition on a variable to block an open backdoor path between E and D (and we hope that in doing so we reduce the bias in the estimated E-D effect); performing a stratified analysis is one way of conditioning on a variable.

Stratified Analysis (cont.)

The tables below represent our notation for the j-th stratum of pure count (D, $\overline{D}$) data and case-person-time (D, PT) data, where j = 1...G. In the previous examples, the rows of each table represented different strata.

Case-Noncase Data

	D	$\overline{D}$	
E	a_j	b_j	n_{1j}
$\overline{E}$	c_j	d_j	n_{0j}
	m_{1j}	m_{0j}	n_j

Person-Time Data

	D	PT
E	a_j	L_{1j}
$\overline{E}$	c_j	L_{0j}
	m_{1j}	L_j

Where $\widehat{RR}_j = \dfrac{a_j/n_{1j}}{c_j/n_{0j}}$ $\qquad \widehat{IR} = \dfrac{a_j/L_{1j}}{c_j/L_{0j}}$

and where a= sum a_j; n_1= sum n_{1j}; etc.

Stratified Analysis (cont.)

Stratified analysis, however, involves doing more than just conducting a separate analysis within each stratum.

We would also like to *combine results across strata* to estimate the adjusted effect of the exposure–i.e., the overall effect, controlling for the effects of the covariates used to stratify the data.

One way to estimate such a summary measure is to compute a weighted average of the stratum-specific estimates.

Example: Weighted Averages

Suppose that we want to compute a final grade for each student in a course on the basis of two exam scores–each exam being analogous to one stratum.

Assume that both exam scores (S_j) are graded on a scale of 0-100 and are weighted as follows: midterm (35%) and final (65%). Consider the following data for 3 students:

Student	Exam Score (S_j)		Arithmetic Mean ($w_1 = w_2$)	Final Grade (weighted)
	Midterm ($w_1 = .35$)	Final ($w_2 = .65$)		
A	60	100	80	86
B	100	60	80	74
C	80	80	80	80

Sample calculation of final grade: Student A

$$\frac{\sum w_j S_j}{\sum w_j} = \frac{0.35(60)+0.65(100)}{0.35+0.65} = \frac{21+65}{1} = 86$$

Example: Weighted Averages

Student	Exam Score (S_i)		Arithmetic Mean ($w_1 = w_2$)	Final Grade
	Midterm ($w_1 = .35$)	Final ($w_2 = .65$)		
A	60	100	80	86
B	100	60	80	74
C	80	80	80	80

1) Use of the final grades to rank the overall performance of the three students is a fair comparison (analogous to valid estimates in epidemiology) because all three final grades were based on the same set of weights.

2) The weighted average depends on the ***relative*** sizes of the weights–i.e., their distribution –**not on their absolute values**, since we divide by the sum of the weights. Thus, for example, we could have used weights of 35 and 65 or 7 and 13, instead of 0.35 and 0.65, in the above example.

Example: Weighted Averages (cont.)

Student	Exam Score (S_j)		Arithmetic Mean ($w_1 = w_2$)	Final Grade
	Midterm ($w_1 = .35$)	Final ($w_2 = .65$)		
A	60	100	80	86
B	100	60	80	74
C	80	80	80	80

3) The value of a weighted average must lie between the highest and lowest stratum-specific estimates. Thus, for example, the final grade for student C must be 80, regardless of the weights, because both exam scores are 80.

4) If all weights are equal, the weighted average or adjusted estimate is equal to the simple arithmetic mean of the stratum-specific estimates–i.e., the mean is a special type of weighted average.

Adjusted measures as weighted averages

In general two approaches can be taken to summarize rates (or risks) across strata of confounders (e.g. strata of different age groups)

1. standardizing
2. pooling

Note: a standardized rate (or risk) is a weighted average of stratum specific rates (or risks):

$$R_s = \frac{\sum_i W_i I_i}{\sum_i W_i}$$

i = index for strata

W_i = stratum specific weight

I_i = stratum specific incidence or mortality rates (such as A_i/N_i)

Standardization

Used for averaging means or frequencies, the weights represent the distribution of the stratifying variables in a target or 'standard' population (possibly hypothetical or counterfactual).

The averages under the different patterns are then contrasted (e.g. by taking the ratios or differences) to create standardized effect measures.

Thus the method can be summarized as "first average the frequencies, then compare (calculate (rate) differences or ratios)."

Standardization

Two myths about standardization are pervasive:

- That there must be no effect-measure modification across strata
- And there must be no variation in the weights used across exposure patterns.

Both are wrong in principle

- We can always average over heterogeneity. E.g. when we talk of average income, and we can always compare these averages
- To produce valid effect measures, the weights should vary across exposure patterns *if (and only if)* the exposure patterns affect the distribution across strata (e.g. smokers die earlier, thus, age distribution is different for smokers and non-smokers); they should only vary to reflect those exposure effects, no more. (Note: Standardization of person-time rates that force the weights to be the same across strata will be biased when exposure affects the weights (see Ch 4 ME2)

population	exposed	unexposed	Total
Cases	A	B	M
Persons (or persontime)	N_1	N_0	T

ideally

we want the most precise estimate of effect

note

when comparing rates (or risks) from two different populations (e.g. when calculating the ratio of rates (or risks) from an exposed and an unexposed population) we need to use the same weights when averaging the rates (or risks) over strata

$$RR_s = \frac{\sum_i W_i(A_i/N_{1i})}{\sum_i W_i(B_i/N_{0i})}$$

sRR (SMR)

population	exposed	unexposed	Total
Cases	A	B	M
Persons (or persontime)	N1	N0	T

Rates (or risks) are standardized to the **confounder distribution** of the study population (which in general represents an **exposed population**), i.e. $\mathbf{W_i = N_{1i}}$

$$sRR = \frac{\sum_i N_{1i}(A_i/N_{1i})}{\sum_i N_{1i}(B_i/N_{0i})} = \frac{\sum_i A_i}{\sum_i N_{1i}(B_i/N_{0i})}$$

This estimator is sometimes called the **internally** standardized risk ratio (sRR or SMR). Assuming no residual confounding or other bias, it estimates the causal RR in the exposed group ($\mathcal{RR}_1$) –I.e. the probability of disease in the exposed (standard population) divided by the probability of disease in the absence of exposure.

The latter probability is counterfactual and is estimated by assuming that the exposed group (N_{1i}) would experience in the absence of exposure the same stratum-specific risks (B_i/N_{0i}) experienced by the unexposed group; this is the exchangeability assumption applied to each stratum of the source population

I. sRR (or SMR)

$$sRR = \frac{\sum_i N_{1i}(A_i/N_{1i})}{\sum_i N_{1i}(B_i/N_{0i})} = \frac{\sum_i A_i}{\sum_i N_{1i}(B_i/N_{0i})} \qquad \frac{\text{observed \# cases}}{\text{expected \#cases}}$$

Using this weight minimizes the variance of the weighted average, therefore - given that the true rate ratios are constant - the sRR (or SMR) is the minimum variance estimate of the common rate ratio. It is much less affected by instabilities of the age-specific rates than the SRR (see below)

a major **disadvantage** is the non-comparability of sRRs (SMRs) if the confounder distributions in two cohorts for which sRRs are compared for are not the same (i.e. while the unexposed referent group from which the rates are taken is the same, the weights (N_{1i}) come from the exposed populations and may not be the same)

I. SRR

population	exposed	unexposed	Total
Cases	A	B	M
Persons (or persontime)	N1	N0	T

Rates are standardized to the confounder distribution of the **reference population** (which in general represents the unexposed population), i.e. $W_i = N_{0i}$

$$SRR = \frac{\sum_i N_{0i}(A_i/N_{1i})}{\sum_i N_{0i}(B_i/N_{0i})} = \frac{\sum_i N_{0i}(A_i/N_{1i})}{\sum_i B_i}$$

If we want to estimate $\mathcal{RR}_0$, the RR for the risk (rate) increase that would have occurred in the unexposed group if they has been exposed, we would choose the unexposed group as the standard.

This measure is an example of what is sometimes called an " **externally** standardized RR" (jargon that only means that the exposed source is not the target, rather the unexposed is the target of our inference).

Note: it makes more sense if you think about "referent" group rather than "standard" group

II. SRR

$$SRR = \frac{\sum_i N_{0i}\,(A_i/N_{1i})}{\sum_i N_{0i}\,(B_i/N_{0i})} = \frac{\sum_i N_{0i}\,(A_i/N_{1i})}{\sum_i B_i}$$

Note:

best suited for '**internal reference**' group comparisons (e.g. choose the lowest exposure as the reference, then one can compare moderately and highly exposed to the lowest exposed group, i.e. the same reference group, thus, the weights are the same)

major disadvantage is the instability when the component rates (risks) are based on small numbers of diseased or deaths

Note: For the calculation of confidence intervals for standardized measures see ME 2 pages 262-265

Example calculations SRR&sRR

Table 2.9 Fictitious data used to illustrate the instability of the SRR

Age stratum (years)	Cohort		Standard population	
	Deaths (d)	Person-years (n)	Deaths (d)	Person-years (n)
45–64	10	10 000	140	150 000
65–84	9	3 000	290	70 000
85+	1	1	30	210
Totals	20	13 001	460	220 210

[a] Adapted from Mosteller and Tukey (1977)

II. SRR

$$SRR = \frac{\sum_i N_{0i}(A_i/N_{1i})}{\sum_i N_{0i}(B_i/N_{0i})} = \frac{\sum_i N_{0i}(A_i/N_{1i})}{\sum_i B_i}$$

$$SRR = \frac{150\,000(10/10\,000)+70\,000(9/3000)+210(1/1)}{460} = 1.24$$

Now drop the oldest case

$$SRR = \frac{150\,000(10/10\,000)+70\,000(9/3000)+210(0/1)}{460} = 0.78$$

I. sRR (or SMR)

$$sRR = \frac{\sum_i N_{1i}(A_i/N_{1i})}{\sum_i N_{1i}(B_i/N_{0i})} = \frac{\sum_i A_i}{\sum_i N_{1i}(B_i/N_{0i})}$$

$$sRR = \frac{20}{10\,000(140/150\,000) + 3000(290/70\,000) + 1(30/210)} = \frac{20}{21.9} = \mathbf{0.91}$$

Now drop the oldest case

$$sRR = \frac{19}{21.9} = \mathbf{0.78}$$

Adjustment of Epidemiologic Measures: Pooling

Estimation of common measures. Another adjustment method is to estimate the common value of the desired parameter in the index group–i.e., the value of the parameter that is *assumed* to be constant (homogeneous) across all strata.

The weights in this approach are not selected from a single population, but are chosen to enhance the precision of the adjusted or pooled estimate.

Thus, estimates of a common measure are generally more precise than standardized measures, especially when the cell sizes within strata are small, but they are appropriate only under the assumed condition of homogeneity of the desired parameter across strata.

Standardization, on the other hand, may be appropriate even when the desired parameter is heterogeneous across strata. (Note that homogeneity of a parameter does not necessarily mean that *estimates* of that parameter are constant across strata.)

III. Pooled RR (or RR_{MH})

population	**exposed**	**unexposed**	**Total**
Cases	A	B	M
Persons (or persontime)	N_1	N_0	T

Weighted average of stratum-specific rate ratios *(rather than the ratio of weighted averages of stratum-specific rates)*

$$RR_s = \frac{\sum_i W_i(A_i/N_{1i})/(B_i/N_{0i})}{\sum_i W_i}$$

i.e. if $W_i = B_i N_{1i} / T_i$ *also known as the Mantel-Haenszel method*

$$RR_{M\text{-}H} = \frac{\sum_i A_i N_{0i}/T_i}{\sum_i B_i N_{1i}/T_i}$$

NOTE: Given that the rate ratio is constant across all strata of the confounders all three estimators give the same result

e.g. $A_i/N_{1i} = M\ (B_i/N_{0i})$

substitute in each formula and you get RRs = M each time

For CI calculations see ME2 pages 269-272

Charles Poole. **Low P-Values or Narrow Confidence Intervals: Which Are More Durable? Epidemiology Vol 12; No3, 2001**

TABLE 1. Results from a Hypothetical Study of a Single Binary Exposure and Four Diseases or of a Single Disease and Four Binary Exposures

Exposure or Disease	RR (95% CI)	P	95% CLR
A	2.5 (0.80–8.0)	0.1	10
B	1.7 (1.2–2.4)	0.003	2
C	4.1 (1.2–14)	0.02	12
D	1.4 (0.80–2.4)	0.2	3

Abbreviations: RR = relative risk; CI = confidence interval; P = two-sided null P-value; CLR = upper-to-lower confidence limit ratio.

Charles Poole. **Low P-Values or Narrow Confidence Intervals: Which Are More Durable? Epidemiology Vol 12; No3, 2001**

Estimates B and D – not B and C – are this study's most precise estimates.

Estimates B and D stand the best chance of holding up, conditional on their validity, in the context of existing and future research.

Estimates B and D would weigh more heavily into meta-analyses and would exert stronger influences on probability distributions in properly conducted Bayesian analyses.

Estimates B and D are the results that should be put forth for emphasis as the most statistically stable results this study has to offer

Meta-analysis:
NOTE the largest RR is the least precise….and most different from the summary RR = 1.03

Source: Dennis LK, et al.
Problems with the assessment of dietary fat in prostate cancer studies. AJE. 2004 Sep 1;160(5):436-44.

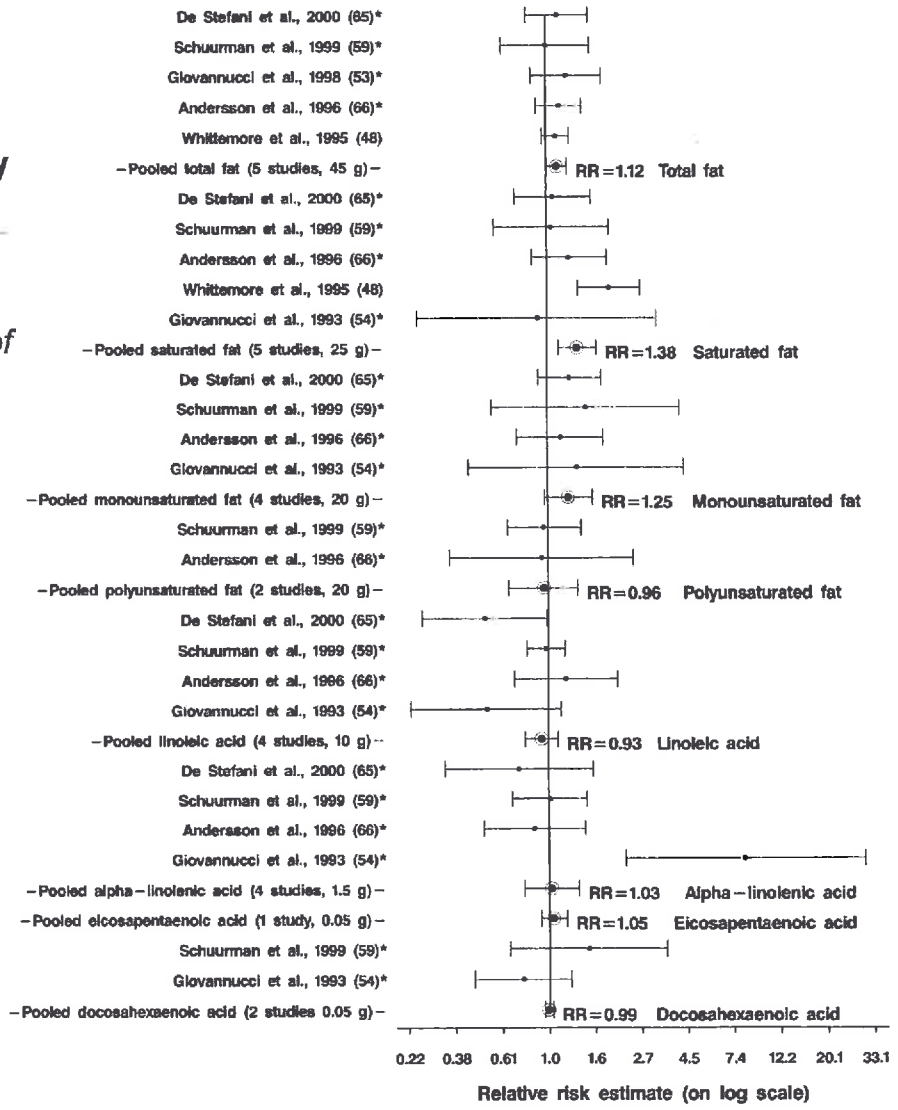


FIGURE 1. Relative risk (RR) estimate and 95% confidence interval for advanced prostate cancer and specific fatty acids sorted by first year of data collection, along with the pooled estimates based on a random-effects dose-response model from a meta-analysis of five of 29 studies.
* Studies that adjusted for energy intake.

RESEARCH REPORT

Unemployment and suicide. Evidence for a causal association?

T A Blakely, S C D Collings, J Atkinson

J Epidemiol Community Health 2003;57:594–600

Objectives: To determine the independent associations of labour force status and socioeconomic position with death by suicide.
Design: Cohort study assembled by anonymous and probabilistic record linkage of census and mortality records.
Participants: 2.04 million respondents to the New Zealand 1991 census aged 18–64 years.
Main outcome measure: Suicide in the three years after census night.

Conclusions: Being unemployed was associated with a twofold to threefold increased relative risk of death by suicide, compared with being employed. About half of this association might be attributable to confounding by mental illness.

Table 3 Age only and multivariable adjusted odds ratios (95% confidence intervals) of suicide among 1.27 million 25–64 year olds with complete data

	Women		Men	
	Age only	Multivariable	Age only	Multivariable
Marital status				
Married	1	1	1	1
Not married	1.81 (1.22, 2.69)	1.60 (1.02, 2.50)	2.08 (1.66, 2.61)	1.84 (1.45, 2.34)
Highest qualification				
Tertiary	1.23 (0.74, 2.07)	1.65 (0.95, 2.86)	0.54 (0.38, 0.77)	0.70 (0.49, 1.01)
Trade	0.86 (0.43, 1.72)	1.04 (0.52, 2.10)	0.88 (0.67, 1.15)	1.05 (0.80, 1.39)
School	1.33 (0.81, 2.18)	1.57 (0.95, 2.61)	0.92 (0.68, 1.25)	1.06 (0.78, 1.44)
Nil	1	1	1	1
Labour force status				
Employed	1	1	1	1
Unemployed	2.46 (1.10, 5.49)	2.34 (1.01, 5.42)	2.63 (1.87, 3.70)	2.26 (1.56, 3.28)
Non-active	2.57 (1.68, 3.94)	2.63 (1.63, 4.25)	3.16 (2.40, 4.17)	2.59 (1.89, 3.55)
Household car access				
Two or more	1	1	1	1
One	1.13 (0.73, 1.74)	1.01 (0.63, 1.62)	1.43 (1.14, 1.79)	1.18 (0.93, 1.50)
Nil	3.31 (1.91, 5.76)	2.37 (1.17, 4.79)	1.94 (1.27, 2.96)	1.01 (0.63, 1.62)
Equivalised household income				
≥ $50000	0.61 (0.35, 1.05)	1.20 (0.61, 2.33)	0.49 (0.36, 0.67)	0.87 (0.60, 1.27)
$30–$49999	0.67 (0.40, 1.11)	1.26 (0.70, 2.26)	0.60 (0.45, 0.80)	0.98 (0.71, 1.36)
$20–$29999	0.62 (0.34, 1.10)	0.97 (0.52, 1.79)	0.69 (0.51, 0.95)	0.96 (0.69, 1.33)
<$20000	1	1	1	1

Raw numbers are random rounded to the nearest multiple of three as per Statistics New Zealand protocol with a minimum released value of 6. However all regression analyses use exact counts. Multivariable logistic regression models control for variables as shown in the table, five year age group, ethnicity (Maori, non-Maori) and household tenure (owner occupied, private tenancy, and public tenancy).

This study of the entire New Zealand adult population finds that not being employed is strongly associated with suicide, that this association is not due to confounding by socioeconomic status, and is probably not due to either health selection or confounding by mental illness. Conversely, there is little suggestion of an independent association of socioeconomic status with suicide death after controlling for labour force status.

Table 4 Suicides in 1991–94 linked to a 1991 census record, and the relative risk (95% confidence intervals) of being linked for suicides from the most socioeconomically deprived 50% of small areas compared with the least deprived 50%

	Fraction of suicide deaths linked to census record (%)	RR of linkage for most compared to least deprived*
15–24 year olds		
Women	27/51 (53)	1.32 (0.67, 2.59)
Men	120/273 (44)	1.13 (0.82, 1.54)
25–44 year olds		
Women	69/111 (62)	0.83 (0.64, 1.06)
Men	261/450 (58)	0.97 (0.82, 1.13)
45–64 year olds		
Women	69/93 (74)	1.15 (0.90, 1.48)
Men	159/222 (72)	0.85 (0.72, 1.00)
25–64 years combined (both sexes)	555/873 (64)	0.93 (0.84, 1.02)

Raw numbers are random rounded to the nearest multiple of three as per Statistics New Zealand protocol with a minimum released value of 6. However, all regression analyses use exact counts. *The relative risk is calculated by a log-link regression of the probability of a suicide being linked, controlling for age. The analyses include 1037 of the total 1197 suicides [86.6%] with a valid value for small area deprivation.

Sensitivity Analysis

Table 5 Sensitivity analysis estimates of the relative risk of suicide among the unemployed compared with the employed controlling for mental illness, using the crude relative risk estimate of 2.59 for 25–64 year old men as the starting point

Prevalence of mental illness in the total population	10%			20%			30%		
RR of suicide for mentally ill compared with non-ill	5	20	50	5	20	50	5	20	50
RR of mental illness for unemployed compared with employed = 1.25	2.43	2.24	2.15	2.35	2.17	2.12	2.29	2.14	1.96
RR of mental illness for unemployed compared with employed = 1.5	2.13	1.98	1.85	2.16	1.88	1.79	2.07	1.83	1.77
RR of mental illness for unemployed compared with employed = 2.0	1.85	1.64	1.45	1.89	1.49	1.38	1.76	1.43	1.35

RR, relative risk. Modelling was based on the cohort of 25–64 year old men with complete data (that is, those represented in table 3). Of this cohort, 519195 were employed (168 suicide deaths during follow up), 39312 were unemployed (33), and 90243 were not in the labour force (84).

Screening/Misclassification of Disease or Exposure

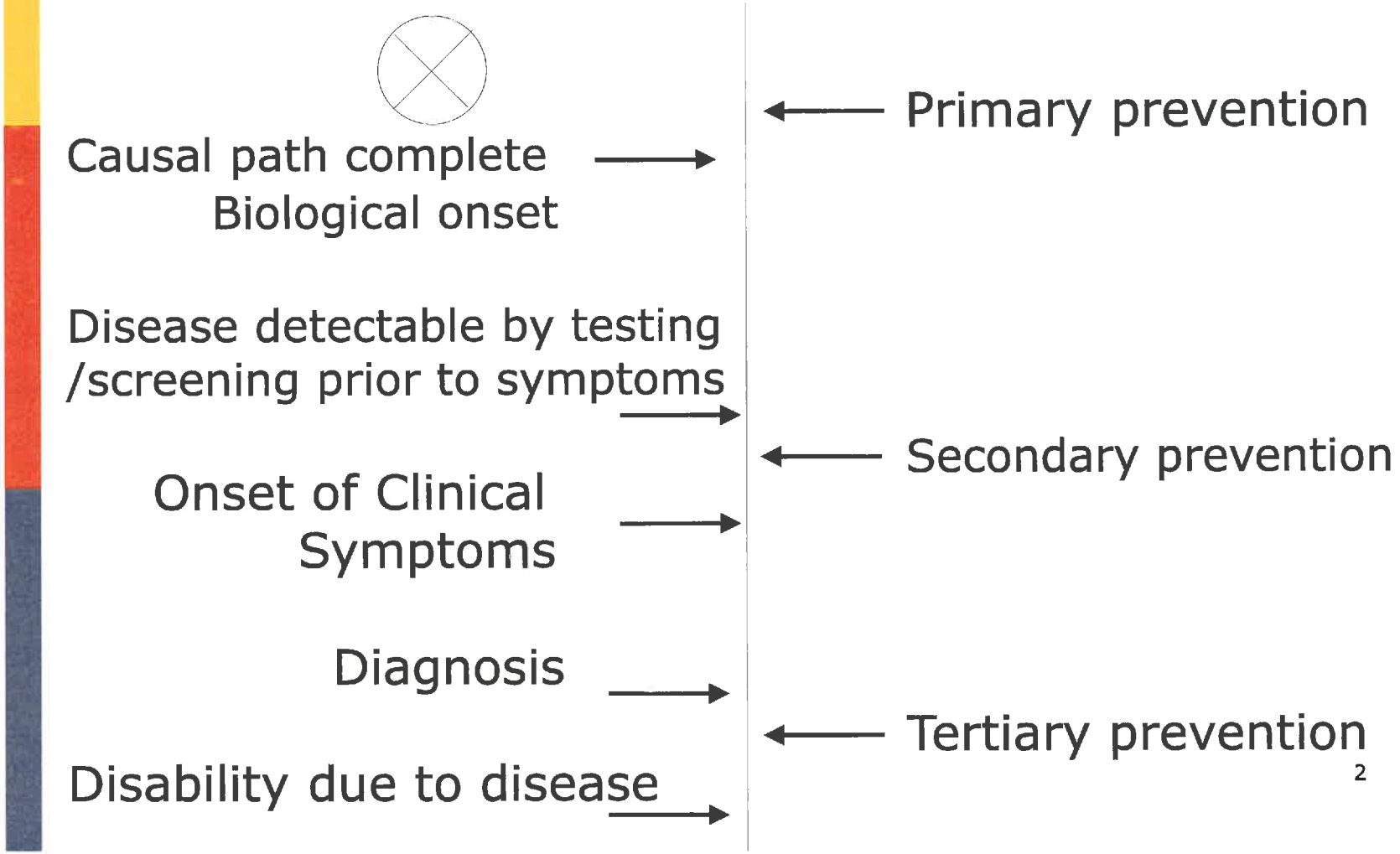
Information Bias

B. Ritz

EPI 200B, 2017

Note: some slides/examples are based on Drs. Morgenstern's and Olsen's materials

Types of Prevention- Time of Intervention



Types of Prevention

- Primary: prevent disease from starting/causal pie from completing
  - including healthy diet, regular exercise, avoidance of smoking, safe home and work environments, clean water and air, etc.
- Secondary: delaying onset of symptomatic or clinical disease.
  - identify asymptomatic individuals during the window between pathological onset/disease detectable by screening methods and the occurrence of clinical symptoms.
  - E.g. screening for HIV infection combined with the early use of highly active antiretrovirals to delay the onset of clinical symptoms, immune dysfunction, and mortality associated with AIDS.

Types of Prevention

- Tertiary: efforts after clinical diagnosis to slow or block the progression of disease, thereby reducing impairments and disabilities, and improving the quality of life and survival among diseased individuals.
  - E.g use of medications to prevent opportunistic infections among HIV-infected individuals.

Diseases appropriate for screening

- serious, progressive diseases
- treatment is more effective at an earlier stage.
- disease has a detectable preclinical phase.
- the detectable preclinical phase is fairly long and prevalent in the target population.
  - E.g. breast cancer, HIV infection, hypertension.

Note: some diseases may <u>not</u> be appropriate for screening e.g. some cancers, if early detection and treatment doesn't change mortality or morbidity.

Disease Screening Goals

- Screening requires a screening test
- Screening is not about diagnosing patients
- The aim is to identify people at high risk of having the disease
- The screening test is not a diagnostic test

Justification for screening:

Early treatment improves prognosis at reasonable cost

Screening Tests

- We talk about a test's sensitivity, specificity and predictive value
- What characterizes a good screening test?

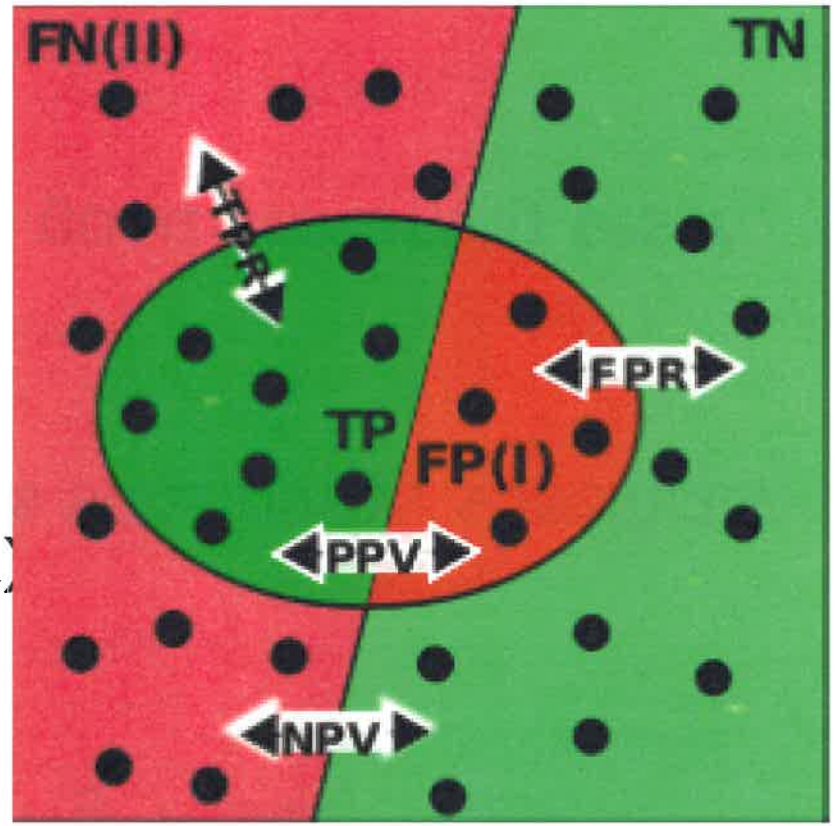
Binary classification:

Sensitivity and Specificity

- *True negatives (TN)*
- *True positive (TP)*
- *False positive (FP)*
- *False negative(FN)*

- Sensitivity or true positive rate (TPR)
- False positive rate (FPR)
- Specificity or true negative rate

- *Pred. value pos (PPV)*
- *Pred value neg (NPV)*



Binary classification:

Sensitivity and Specificity

	True disease status (gold standard)		
Test result	**D**	**$\bar{D}$**	**Total**
+	**a**	**b**	**M_3**
-	**c**	**d**	**M_4**
	M_1	**M_2**	**N**

Sensitivity = a/M_1 specificity= d/M_2

pred. value pos = a/M_3 pred. value neg= d/M_4

Parameters; sens = P (test+ | D); spec = P (test- | $\bar{D}$)

Predictive value pos test = P (D | test+)

Predictive value neg test = P ($\bar{D}$ | test-)

These are **conditional probabilities**

Example: Common vs. Rare disease

Test	True DISEASE		Total
	+	-	
+	**180**	22	*202*
-	20	***228***	*248*
total	*200 (45%)*	*250 (55%)*	450

Sensitivity= 180/200= 90%

Specificity= 228/250= 91%

Pred value pos= 180/202= 89%

Pred value neg= 228/248= 92%

Test	True Disease		Total
	+	-	
+	**21**	26	*47*
-	2	***401***	*403*
total	*23 (5%)*	*427 (95%)*	450

Sensitivity= 21/23= 91%

Specificity= 401/427= 94%

Pred value pos= 21/47= 45%

Pred value neg= 401/403= 99.5%

Note: predictive values depend strongly on the prevalence of disease, sensitivity and specificity do <u>not</u>

Bayes' formula

- Bayes' formula – predictive value depends upon sens, spec and PP (the prevalence proportion). From prior probability (PP) to a posterior probability $P(D \mid test_+)$
  - Prior probability = probability of a condition prior to data collection/testing
  - Posterior probability= probability of a condition combining data and the prior probability

1763 Richard Price presented a paper by Thomas Bayes "An essay toward solving a problem in the doctrine of chances".

Test	D	$\bar{D}$
+	PP x sens	(1-PP) (1-spec)
-	PP x (1-sens)	(1-PP) spec
	PP	(1-PP)

PP= prior probability (*or prevalence proportion*)

Predictive value of pos test

$$P(D \mid \text{test+}) = \frac{PP \times sens}{PP \times sens + (1-PP)(1-spec)}$$

Predictive value of a negative test

$$P(\bar{D} \mid \text{test-}) = \frac{(1-PP)\ spec}{PP \times (1-sens) + (1-PP)\ spec}$$

Test	D	$\overline{D}$
+	PP x sens	(1-PP) (1-spec)
-	PP x (1-sens)	(1-PP) spec
	PP	(1-PP)

Predictive value of pos test

$$P(D \mid test+) = \frac{PP \times sens}{PP \times sens + (1-PP)(1-spec)}$$

Test	True Disease		Total
	+	-	
+	**21**	26	*47*
-	2	***401***	*403*
total	*23* *(5%)*	*427* *(95%)*	450

pp	1-pp	sens	spec
0.05	0.95	0.91	0.94

ppv	npv	pp*sens	1-spec
0.45	1.00	0.05	0.06

P(D/test+)= 0.45

$$\frac{0.05 \times 0.91}{0.05 \times 0.91 + 0.95 \times 0.06}$$

Likelihood ratios (LR)

see also ME3 pp227-230

$$LR_+ = \frac{P(\text{test} + \mid D)}{P(\text{test} + \mid \overline{D})} = \frac{\text{Sens}}{\text{1-spec}}$$

$$LR_- = \frac{P(\text{test} - \mid D)}{P(\text{test} - \mid \overline{D})} = \frac{\text{1-sens}}{\text{spec}}$$

An easy way to use Bayes' theorem

$$\text{Prior odds} = \frac{\text{Prior probability}}{\text{1-prior probability}}$$

$$\text{Posterior odds} = \text{prior odds} \times \text{LR}$$

$$\text{Posterior probability} = \frac{\text{Posterior odds}}{\text{1+ posterior odds}}$$

Example: Screening for alcoholism

test sens = 0.90, spec = 0.60

Assume prior probability of alcoholism is 0.30, then

$$\text{Prior odds} = \frac{0.30}{0.70} = 0.43$$

$$LR_+ = \frac{0.90}{0.40} = 2.25$$

Posterior odds = 0.43 x 2.25 = 0.97

$$\text{Posterior probability of alcoholism} = \frac{0.97}{1+ 0.97} = 0.49$$

Note: You have increased your probability from 0.30 to 0.49 given the test was positive.

Assessing carcinogens

Is epoxy carcinogenic?

- Among 283 compounds tested, Epoxy tested positive in the Ames's test for carcinogenicity

Ames's test for carcinogens	Truly Carcinogenic compounds	Truly Non-carcinogenic compounds
Positive	157	14
Negative	18	94
	175	108

Assessing carcinogens

- Sens. 157/18+157 = 0.90
- Spec. 94/108 = 0.87

- Are we now 90% sure Epoxy is carcinogenic?

- Depends upon the prior probability

- Assume our prior probability is 1%, i.e. 1% of <u>all</u> chemicals ever screened are carcinogenic

Assessing carcinogens

Test	C	$\bar{C}$	
+	900	12870	13770
-	100	86130	86230
	1000	99000	100,000

Predictive value of pos test 900/13770 = 6.5%

- increases probability from 1% to 6.5%

Predictive value of negative test 86130/86230= 99.9%

- increases probability from 99% to 99.9%

Test values for HEME Select Test for Colorectal Cancer in a symptomless general population

test	D	$\bar{D}$	
+	22	418	440
-	10	7043	7053
	32	7461	7493

Sens = 22/32 = 0.688

Spec = 7043/7461 = 0.944

Predictive value of post test = 22/440 = 0.050

Test values for HEME Select in a clinical setting (patients come with complaints)

test	D	$\bar{D}$	
+	688	56	744
-	312	944	1256
	1000	1000	2000

Sens = 688/1000 = 0.688

Spec = 944/1000 = 0.944

Predictive value of post test = 688/744 = 0.925

Test performance PPV depends on PP in population

- Sensitivity will often depend on the stage of the disease and may well be lower for early stages of the disease.
- The predictive value of the test is closely dependent on the prevalence proportion of the disease.
- For this HEME test, predictive value of pos test is 0.11 if colon cancer has a prevalence proportion of 0.01 and 0.01 if PP is 0.001 in a population

Benefits and side effects of screening

test	D	D
+	a	b
-	c	d

a: True positives detected at screening – would benefit if detected before critical point

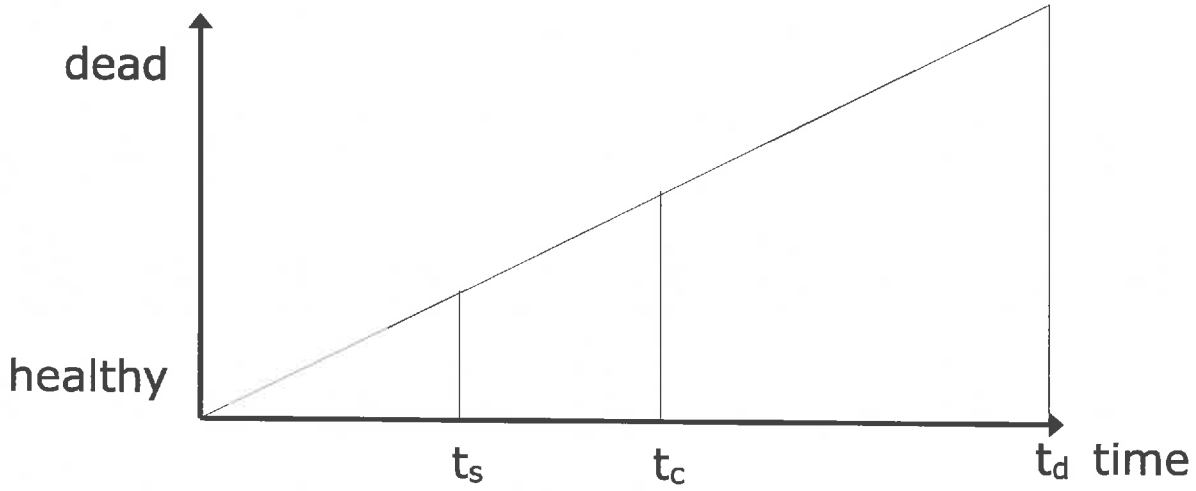
c: False negatives diseased but not detected at screening. Screening may delay their diagnosing

b: False positives are called in for diagnostic work up – are worried and diagnostic tests may carry risks

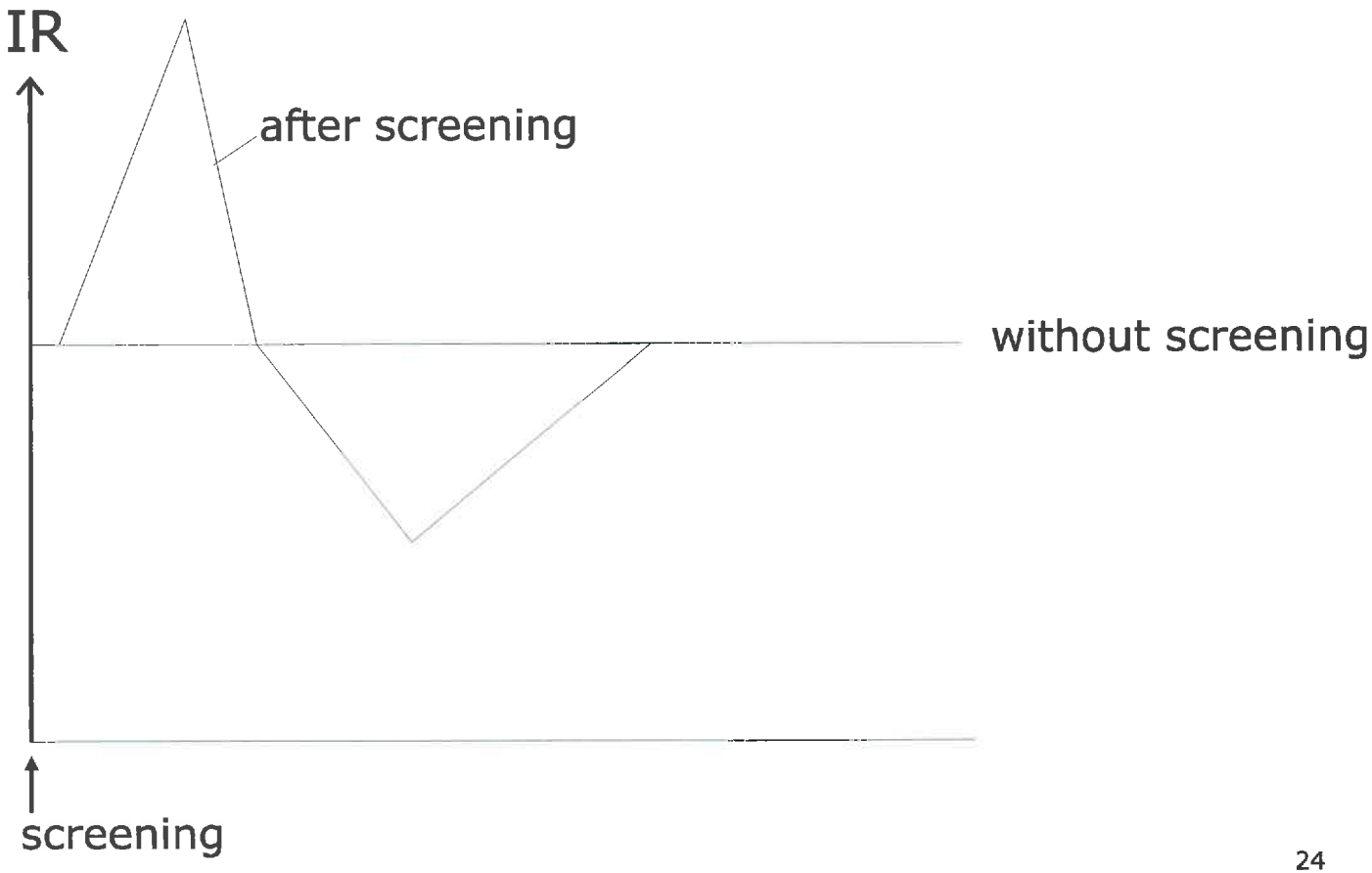
d: True negatives are happy and like the program

Main design issue: screening may have positive as well as negative effects. The sensitivity and specificity of the tests are key parameters together with the nature of the test, the disease and its treatment.

Screening may have negative as well as positive effects; thus, a screening program should be evaluated. It is not enough to show that those who were detected in a screening program had a longer survival than those not screened.



For this patient, the clinical survival time is t_d-t_c and the screening survival time is t_d-t_s; t_c-t_s longer. This time interval produces "lead time bias".


IR
after screening
without screening
screening

Lead Time Bias

- Lead time is the amount of time that the disease diagnosis is advanced by screening
  - length of time from disease detection by screening to the time that the diagnosis would have been made on the basis of symptoms.
- Because we can never know when disease would have been diagnosed due to symptoms, it is impossible to determine the actual lead time in a screened individual.
- However, we can estimate the distribution of lead times in a screening program by comparing the rate of clinical disease over time in the screened and a comparable unscreened group.

Lead Time Bias

- Usually we evaluate the success of a screening program by comparing the survival experience of a screened population to that of a similar unscreened population
- Survival is assessed as % patients alive in an interval after diagnosis (e.g., % surviving 5 years after diagnosis or average # of years a patient survives after diagnosis).
  - Note: survival is measured from the time of diagnosis to the time of death, thus diagnosis time is - by definition - different for screened individuals (shortly after screening) and unscreened individuals (onset of symptoms).
  - Thus, survival may appear longer among screened individuals because their diagnoses were made earlier, not because they lived longer. This phenomenon, known as lead time bias, will overestimate the benefit of screening and needs to be taken into account when evaluating a screening program.

Evaluating Screening Programs

- Screening programs can have both positive and negative effects
- All classical designs have been used for evaluation

Main concerns:

RCT: need to be large, may be out of date when finished, unbiased cause specific mortality may be difficult to obtain, difficult to randomize at individual level. Does not address normal practice. No "confounding by indication" argument for doing a RCT.

Follow-up: who complies to the program, high risk/low risk?

Case-control: not possible to evaluate all effects of interest

Ecological: ecological fallacy, but may be the best evidence after all

Additional design issues

- Screening may address an early pre-disease lesion (adenoma) or cancer at an early stage.
  - In the first situation, screening may reduce incidence but may have little impact on case fatality.
  - In the second situation, screening should reduce incidence (and case fatality?).
  - In both situations, cause specific mortality should be reduced (and total mortality?).

Additional design issues

- A case-control study addressing the first issue includes incident cases. For the second issue, cases are cause specific deaths.
- The source population are those who are invited to be screened and belong to the population at risk.

Additional design issues

- Incidence density sampling of controls is usually the only option.

- Exposure is 'being screened' in a given time interval up to case selection.

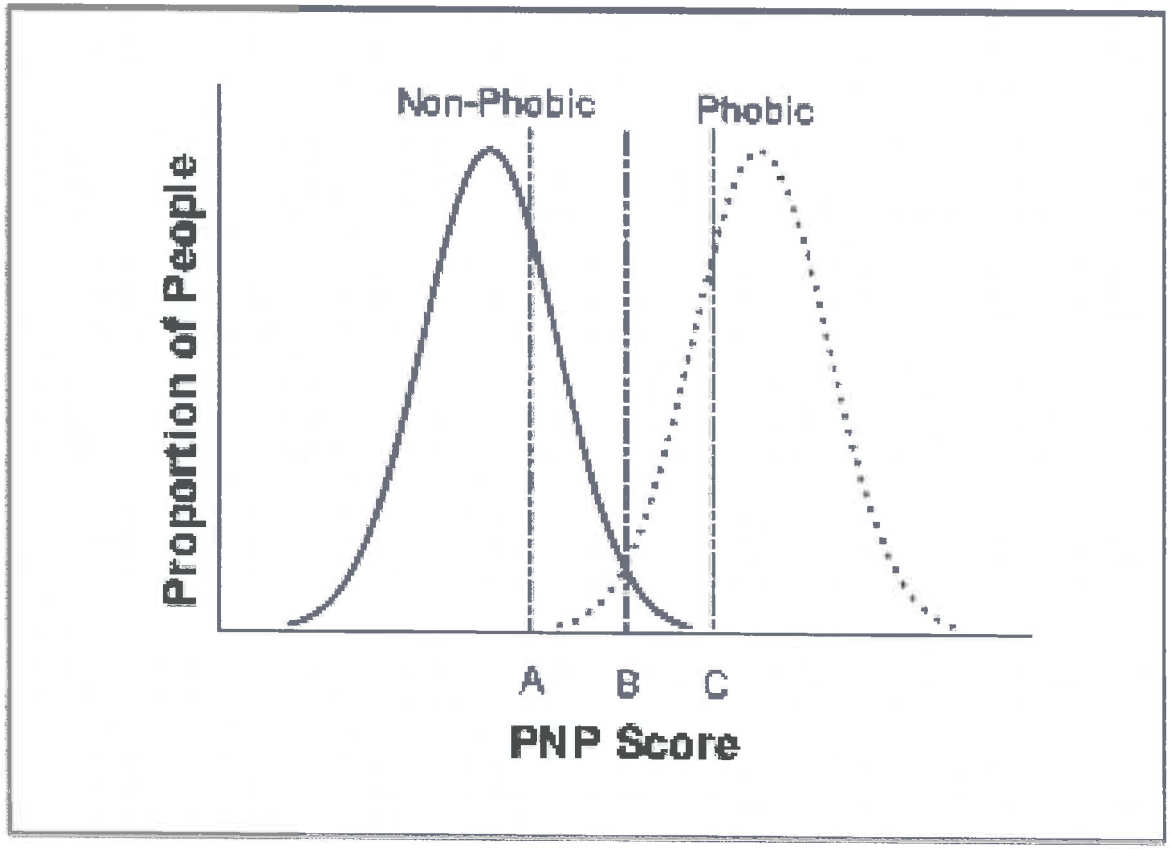
Receiver Operator Curve (ROC)

- ROC analysis is done to select the optimal cut point when dichotomizing a continuous scale.
- When separating respondents into 'normal' and 'abnormal' any cut point chosen will result in 2 types of errors:
  - false negatives
  - false positives
- Changing the cut point alters the numbers of erroneous judgments but will not eliminate the general problem

ROC: choice of cut-point

- Usually the 'optimal' cut points should minimizes the overall number of false positive and false negative errors
- The 'optimal' cut point shifts if the cost of FPs is higher than that of FNs, or vice versa
- Changing the purpose of the test (for example, from diagnosis to screening) requires a shift in cut points.
- A cut point that is ideal for one group may be less than ideal for another
- The accuracy of ROC analysis depends on the quality of the gold standard, which may not be golden i.e. may be far from perfect

Distributions of SPNP scores for individuals with and without phobia, with different cut scores



Streiner DL, Cairney J, What's Under the ROC? An Introduction to Receiver Operating haracteristics Curves. Can J Psychiatry 2007;52:121–128

Generating the ROC curve

Table 1 The number of individuals in each group receiving a given score

	Group		
SPNP Score	With phobia	Without phobia	Total
1	1	20	21
2	2	9	11
3	1	3	4
4	1	1	2
5	1	3	4
6	1	1	2
7	3	7	10
8	7	3	10
9	13	2	15
10	20	1	21
Total	50	50	100

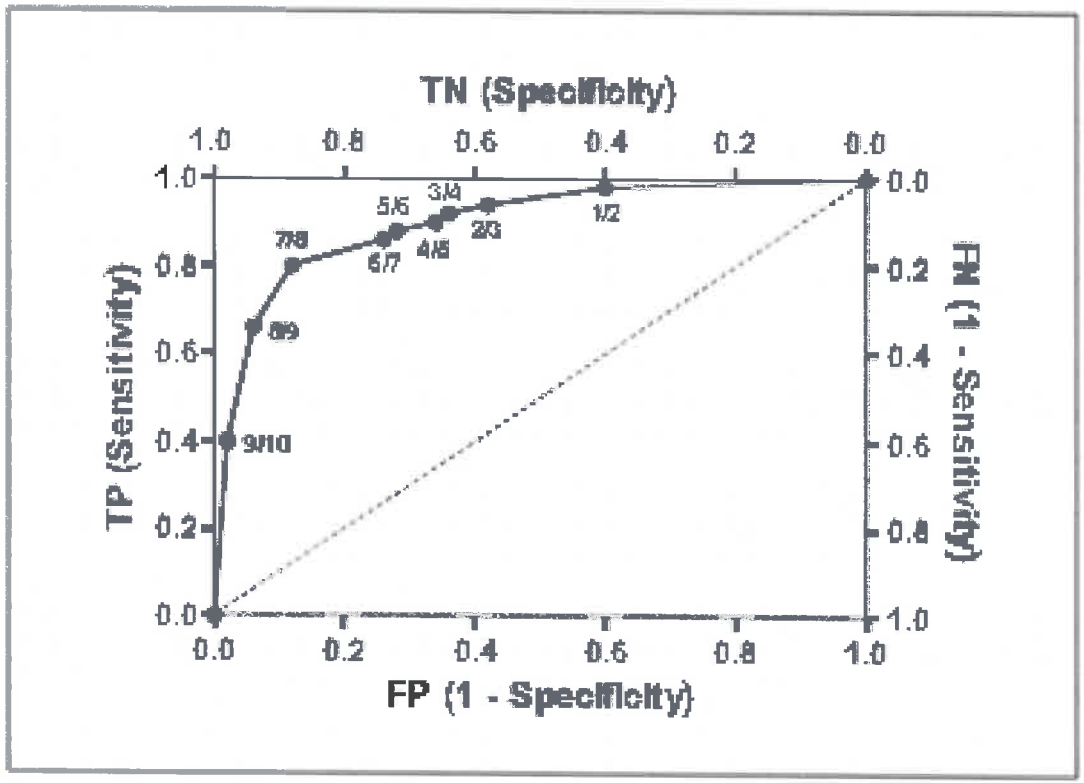
Table 3 Sensitivity and (1 – Specificity) for each cut point of the SPNP

Cut point	Sensitivity	1 – Specificity
< 1	1.00	1.00
1 / 2	0.98	0.60
2 / 3	0.94	0.42
3 / 4	0.92	0.36
4 / 5	0.90	0.34
5 / 6	0.88	0.28
6 / 7	0.86	0.26
7 / 8	0.80	0.12
8 / 9	0.66	0.06
9 / 10	0.40	0.02
> 10	0.00	0.00

Streiner DL, Cairney J, What's Under the ROC? An Introduction to Receiver Operating haracteristics Curves. Can J Psychiatry 2007;52:121–128

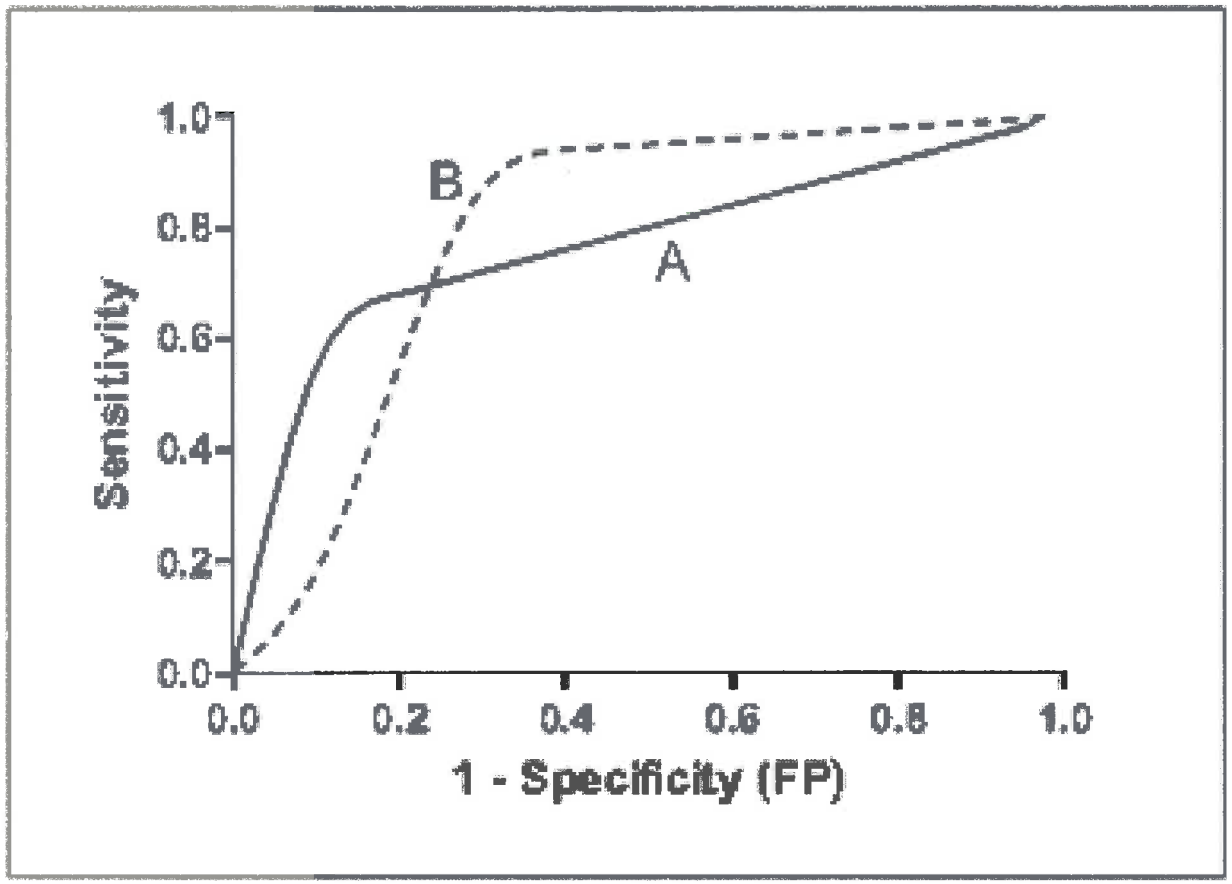
The ROC curve and the AUC

based on the data in Streiner and Cairney 2007



Streiner DL, Cairney J, What's Under the ROC? An Introduction to Receiver Operating haracteristics Curves. Can J Psychiatry 2007;52:121–128

Example of 2 different ROC curves with similar AUCs



Streiner DL, Cairney J, What's Under the ROC? An Introduction to Receiver Operating haracteristics Curves. Can J Psychiatry 2007;52:121–128

Conclusion on ROC curves

- the trade-off between being right or wrong and the costs of making mistakes in either direction.
- Statistics cannot substitute for thinking (what we sometimes refer to as clinical judgment), but they do provide a systematic approach to dealing with this problem.
- ROC curves allows determining the ability of a test to discriminate between groups, to choose the optimal cut point, and to compare the performance of 2 or more tests.

Information Bias

- Information:
  - exposures, end points, confounders, effect measure modifiers
- For discrete variables: classification error/ misclassification
  - Differential

  vs.
  - Non-differential misclassification: does not depend upon the value of other variables:
    - same error in diagnosis (sensitivity and specificity) among exposed and non-exposed;
    - or, error in exposure measurement is the same in cases and controls

Misclassification of the endpoint: sometimes a problem in follow-up studies

- Is this follow-up study vulnerable to differential misclassification of diagnosis?

Exposure	D	Obs time
+	a	t +
-	c	t -

- Follow-up studies are usually less vulnerable to recall bias but knowing the hypothesis may introduce bias, or if the exposure is a suspected cause of the disease under study

Non-differential misclassification

It is often stated that non-differential misclassification – not the same as random misclassification (random is only non-differential in the long term) – leads to bias towards no association (RR = IRR = OR = 1, RD = IRD = 0)

First argument for that was provided by Bross in the 1950's.

Differential misclassification

	Recorded smoker	True smoker	
		+	-
Lung cancer(L)	+	TP_L	FP_L
	-	FN_L	TN_L
ref. (r)	+	TPr	FPr
	-	FNr	TNr

P = proportion of smokers; P_L and Pr

(or prevalence of smoking among lung cases and referent population)

Test	D	$\overline{D}$
+	P x sens	(1-P) (1-spec)
-	P x (1-sens)	(1-P) spec
	P	(1-P)

$$TP = P \times sens$$

$$FN = P \times (1\text{-}sens)$$

$$FP = (1\text{-}P)\ (1\text{-}spec)$$

$$TN = (1\text{-}P)\ spec$$

If we take interest in the difference between P_L and Pr, $D = P_L - Pr$

We are only able to estimate P_L and Pr, and then

$$\hat{D} = \hat{P}_L - \hat{P}r$$

$$\hat{P}_L = P_L \times TP_L + (1 - P_L)FP_L$$

$$\hat{P}r = Pr \times TPr + (1 - Pr)FPr$$

Include $D = P_L - Pr$

and in case of non-differential misclassification

$FP_L = FPr = FP$ $\quad$ $FN_L = FNr = FN$

Then

$\hat{D}$ = D (1– (FN + FP))

Meaning

$\hat{D}$ ≠ D if FN and FP ≠ 0 (sens + spec < 2)

FN + FP < 1.0 $\hat{D}$ < D (but same sign)

FP + FN = 1.0 $\hat{D}$ = 0

FN + FP = 2 $\hat{D}$ = -D (coding!)

Also true for ORs

Disease Misclassification

- When estimating relative effect measures a high specificity is wanted

True cohort data

Exp	N	D	$\bar{D}$	RR
+	20,000	400	19,600	
-	10,000	100	9900	2.0

If sensitivity is 0.8 but specificity is 1

Exp	N	D	RR
+	20,000	400 x 0.8 = 320	
-	10,000	100 x 0.8= 80	2.0

If sensitivity is 1 but specificity is 0.80

Exp	N	D	RR
+	20,000	400 + 3920 = 4320	
-	10,000	100 + 1980 = 2080	1.04

If sensitivity is 0.8 and specificity is 0.9

Exp	N	D	RR
+	20,000	400 x 0.8 + 19600 x 0.10 = 2280	
-	10,000	100 x 0.8 + 9900 x 0.10 = 1070	1.07

The corresponding case-cohort studies would produce the following (similar) results

True data

Exp	Cases	Controls	OR
+	400	333.33	
-	100	166.66	
All	500	500	2.0

If sensitivity is 0.8 but specificity is 1

Exp	Cases	Controls	OR
+	320	266.66	
-	80	133.33	
All	400	400	2.0

If sensitivity is 1 but specificity is 0.80

Exp	Cases	Controls	OR
+	4320	4266.66	
-	2080	2133.33	
All	6400	6400	1.04

If sensitivity is 0.8 and specificity is 0.9

Exp	Cases	Controls	OR
+	2280	2233	
-	1070	1117	
All	3350	3350	1.07

If we get a reference pathologist to eliminate all FP cases, we would get (for the last table)

Exp	Cases		Controls	OR
+	2280 – 1960 =	320	266.66 or 266	
-	1070 – 990 =	80	133.33 or 134	
		400	400	2.0 or 2.02

Adjusting for misclassification is possible if sens and spec are known

Diagnosis	D+	D-	All
+	P x sens	(1-P)(1-spec)	$\hat{P}$
-	P(1-sens)	(1-P)spec	$1-\hat{P}$
All	P	1-P	

$$\hat{P} = P \times sens + (1 - P)(1 - spec)$$

$$\hat{P} = P \times sens + 1 - spec - P + P \times spec$$

$$\hat{P} + spec - 1 = P\,(sens + spec - 1)$$

$$P = (\hat{P} + spec - 1) \,/\, (sens + spec - 1)$$

Example

Sex	Questionnaire – bronchitis		
	+	-	All
M	350	1427	1777
F	277	1787	2064

RP = (350/1777) / (277/2064) = 1.47

sens = 0.44 spec = 0.94;

based upon comparison with "Golden Standard" – clinical diagnosing

Sex	Questionnaire – bronchitis		
	+	-	All
M	350	1427	1777
F	277	1787	2064

Assume:
sens = 0.44
spec = 0.94;

Exp P (M) =

(350/1777 + 0.94 – 1) / (0.44 + 0.94 – 1)
= 0.360 (640 with the disease)

Exp P (F) =

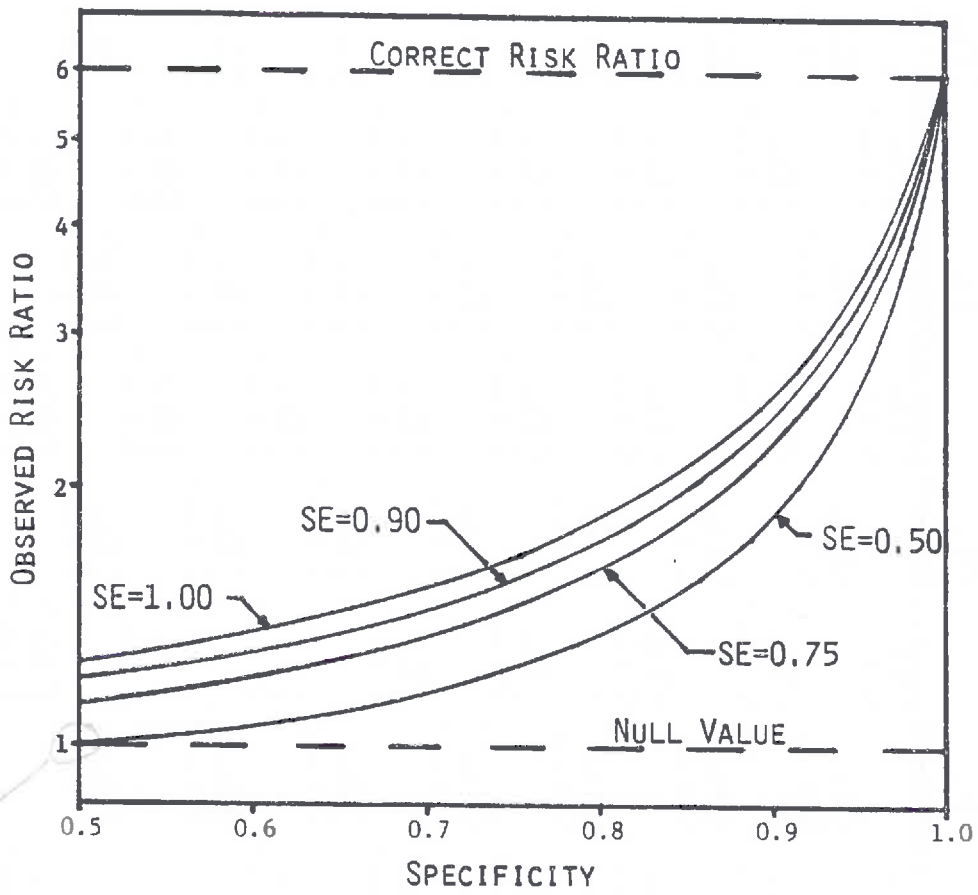
(277/2064 + 0.94 – 1) / (0.44 + 0.94 – 1)
= 0.195 (403 with the disease)

$$RP = \frac{640/1777}{403/2064} = 1.85$$

In case of <u>differential</u> misclassification, use sex specific sens and spec

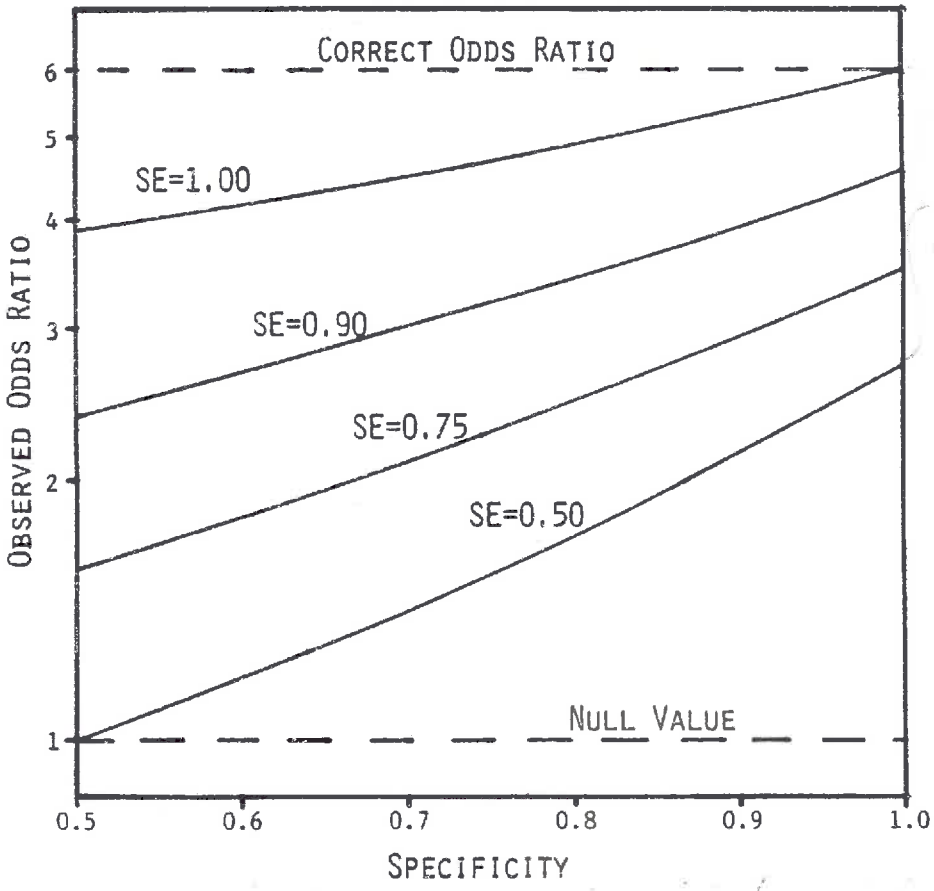
Nondifferential Disease Misclassification in a (fixed) cohort study

- 50% are exposed and 50% unexposed, risk of 30% in the exposed and 5% in the unexposed; thus correct risk ratio is 6
- Figure shows observed Risk ratio (RR) expected for various combinations of sens and spec for disease detection (assumed equal for exposed and unexposed
- Note: bias is affected more by same reduction in Spec than Sens because there are more noncases than cases
- If spec = 1 the risk ratio is correct even if sens is low (regardless of sens) but this does not apply to the RD or the rate ratio or odds ratio



Nondifferential Disease Misclassification in a case control study

- Compare a large number of cases with an equal number of noncases.
- Assume exposure prev. is 40% among true cases and 10% among true nor cases; thus correct risk ratio is 6
- Figure shows observed O expected for various combinations of sens and spec for disease misclassification (assume equal for exposed and unexposed



Nondifferential Disease Misclassification in a (fixed) case control study

- Note: classification probabilities of disease status in a case-control study are in general not equivalent to the classification probabilities in the source population since cases and controls are selected in an arbitrary ratio from the misclassified base population, thus sens has more influence in this design

Nondifferential Disease Misclassification in a case control study

Non-differential disease misclassification: 90% sens , 90% spec

Source population

	correctly classified			misclassified		
	cases	controls		cases	controls	
exposed	50	2000	2050	245	1805	2050
unexposed	50	8000	8050	845	7205	8050
	100	10000	10100	1090	9010	10100
	OR=4.0			OR=1.16		

Case control study

	Misclassified when selected from misclassified source pop			Diagnoses in cases only corrected after selection from miscl. source		
	cases	controls		cases	controls	
exposed	245	218.4	463.4	45	218.4	263.4
unexposed	845	871.6	1716.6	45	871.6	916.6
	1090	1090.0	2180	90	1090.0	1180
	OR=1.16			OR=3.99		

Misclassification of a Confounder

'May bias a result in any direction'

(Greenland & Robins. Am J Epidemiol 1985:122;495-506)

Let this be the true data:

E	C	Cases	Controls	OR
+	+	100	200	
	-	25	100	2.0
-	+	20	40	
	-	100	400	2.0

The confounder has an effect (OR=2)

The exposure has no effect (OR=1);
note the crude OR is confounded !!

E	C	Cases	Controls	OR
+	+	100	200	
	-	25	100	2.0
-	+	20	40	
	-	100	400	2.0

When stratifying on the confounder
True data

C	E	Cases	Controls	OR
+	+	100	200	
	-	20	40	1.0
-	+	25	100	
	-	100	400	1.0

E	C	Cases	Controls	OR
+	+	100	200	
	-	25	100	2.0
-	+	20	40	
	-	100	400	2.0

Now assume exposure and disease status is recorded without error.

Only the confounder is non-differential misclassified (sens=0.8 and spec=0.9), we thus get misclassified data:

E	C	Cases	Controls	OR
+	+	82.5	170	
	-	42.5	130	1.48
-	+	26	72	
	-	94	368	1.41

E	C	Cases	Controls	OR
+	+	100	200	
	-	25	100	2.0
-	+	20	40	
	-	100	400	2.0

Misclassified data

C	E	Cases	Controls	OR
+	+	82.5	170	
	-	26	72	1.2
-	+	42.5	130	
	-	94	368	1.5

Misclassification is likely if

- we ask for sensitive data (alcohol intake),
- the relevant time window is short (teratology),
- we give little attention to the data collection or too much attention to the data collection.

Recall Bias

- a form of differential misclassification bias of particular concern in interview-based case-control studies,
  1. Cases who are diseased may ruminate about prior exposure and report it more completely than controls,(cases might exaggerate exposure while subjects without the disease under investigation)
  2. Controls might not recall exposures, since they do not have an incentive to do so

Factors impacting recall
(Coughlin, 1990)

1. the **time interval since exposure** and the degree of detail required, with less time having passed and less detail required leading to more reliable results,

2. **personal factors** of the study subjects such as age, educational attainment, and socioeconomic status

3. the **significance, duration, frequency, and meaningfulness** of the event asked to be recalled,

4. **social desirability** of the reported behavior and

5. interviewing **techniques**, design of questionnaires, and the **motivation** of the respondent.

Recall bias:
Correction by restricting controls?

Reduce Recall bias?

- Select controls not just randomly from the base population:
  - restrict them in a way that the selected control informants have the same motivation to report events and exposures as case informants,
    - e.g. selecting as controls for veterans suffering from lung cancers other veterans suffering from types of cancer not under investigation.

Recall Bias:
Correction by restricting controls?

Pearce and Checkoway (1988) warned:

- Restricting controls may produce selection bias if the exposure under study also determines whether or not a subject is included in the restricted control group:
  - e.g. if we choose bladder cancer patients as the control group for the index cases with lung cancer and the carcinogen under investigation also causes bladder cancer we would expect more exposed subjects among the bladder cancer controls than among non-diseased controls.
- Also, selecting controls with other conditions does not guarantee the elimination of case-control differences in recall (Brown et al. 1978).

Recall bias:
correction efforts may not be useful!

- Drews and Greenland (1993):
- even when recall bias exists, the observed association can be closer to the true association in a population-based control series compared with using a restricted control group:
  - even relatively large differences in recall accuracy failed to bias the association away from the null
  - restricting control-series does not eliminate non-differential misclassification.
  - the effects of recall bias and nondifferential misclassification may cancel each other out under many circumstances, resulting in relatively little bias in population-control based results

see also Drews and Greenland 1990

Recall Bias: Recommendations

Drews and Greenland (1993): the use of restricted controls may create more bias than it prevents

Recommendation

- evaluate the influence of misclassification and selection bias in a study through sensitivity analysis
  - since the impact of differential recall depends on a fair number of ancillary parameters such as sensitivity, specificity and prevalence of exposure
- Might want to do a validation sub-study.
  - Yet, Greenland (1988) argued that one rather should opt to **conduct a *smaller* study** which **applies the criterion measure to all subjects** - possibly even at lower costs i.e. this may give higher cost efficiency instead of conducting a validation sub-study

Self-report = Recall Bias?

- *Recall bias* is considered a serious problem in case control studies that are based upon subject's recall of exposures
- However, **recall** is sometimes the best method for assessing exposures….

Recall or Recording Bias?

- Hungarian case-control surveillance of congenital abnormalities (Rockenbauer M, Olsen J, Czeizel AE, Pedersen L, Sørensen HT; EuroMAP Group. **Recall bias in a case-control surveillance system on the use of medicine during pregnancy.** Epidemiology. **2001 Jul;12(4):461-6)**

Drug use = self-reported data (interview, memory aids)[=gold standard/why?]

= log-book: medicine prescribed by doctors

	Self-reported drug use	
Log-book drugs	Yes	No
Yes	a	b
No	c	d

Sensitivity a/(a+c) [TP]

Specificity d/(b+d) [TN]

Short-term drugs

Case status	Sensitivity	Specificity
All cases	0.16	0.98
Severe	0.21	0.98
Visible	0.18	0.98
Controls	0.28	0.98

Note: If recall bias is present sensitivity in cases should be lower than in controls (more entries in c-cell i.e. women report more than the logbook shows), with largest differences in visible and severe malformations (not seen)

Long-term drugs

Case status	Sensitivity	Specificity
All	0.25	0.97
Severe	0.16	0.95
Visible	0.29	0.97
Controls	0.46	0.97

What to do to reduce this recall information bias?

- Use of hospital controls may, in some cases, help to reduce information bias.
- The disease used as comparison condition must NOT be associated with the exposure under study (must not be a cause or a preventive factor). Catchment population!
- Use blinding if possible to reduce differential misclassification

Conclusions

- Misclassification has an impact on estimates of effect sizes and study power
- A smaller study with better quality data may be preferable than a large study with poor quality data
- Collect data as accurate as possible – also true for confounders.
- Avoid differential misclassification (blinding)
- If possible estimate sens and spec of key variables, estimate/reduce misclassification in nested study
- Avoid low specificity when measuring ratios (RR, IRR, OR)

Misclassification vs. dependence in error (ME3 page 138)

- Differential misclassification (measurement error in discrete variables) depends on the **actual** value of other variables
- Non-differential misclassification does not depend on the **actual** value of other variables

- Dependent (or classification) error depends on the **error** in measuring /classifying other variables
- Independent/non-dependent error does not depend on the **error** in measuring /classifying other variables
- *Correlated error* is a dependent error with a non-zero correlation coefficient
- Note: dependent error is likely to happen when disease and exposure are measured/determined in the same (error prone) way e.g. via interview/self-report

Measurement Bias in DAGs

from: Hernan and Robbins

Note: the term "misclassification" is synonymous for "measurement error" for discrete variables.

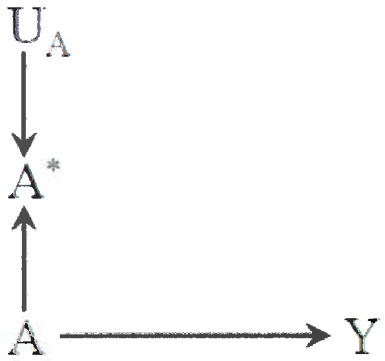


Figure 9.1

Measurement Bias

from: Hernan and Robbins
two properties: *independence* and *nondifferentiality*.

Is the path open or blocked?

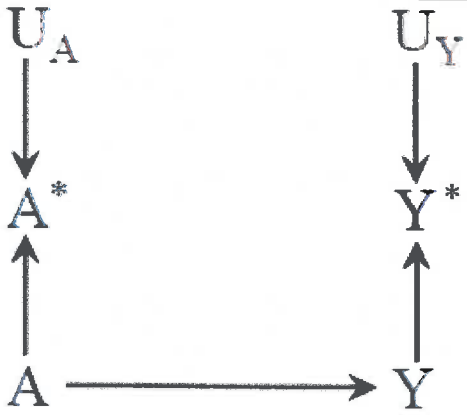


Figure 9.2

Independent and non-differential

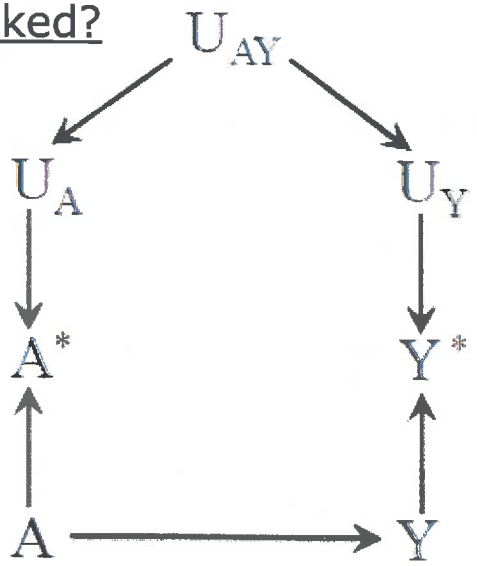


Figure 9.3

Dependent and non-differential

Non-differential measurement error:

- Errors for treatment/exposure *UA* is independent of the true **value** of the outcome
- Error for the outcome *UY* is independent of the true **value** of treatment/exposure

The structure of measurement error

two properties: *independence* and *nondifferentiality*.

from: Hernan and Robbins

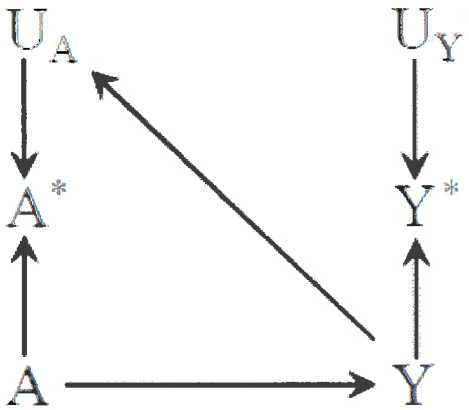


Figure 9.4

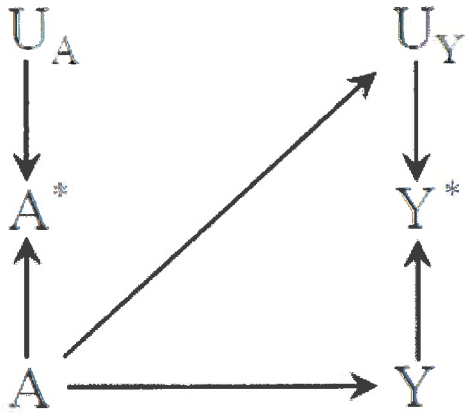


Figure 9.5

Independent but differential:
True **value** of outcome affects measurement **error** of treatment or vice versa

Examples:
Recall bias
Reverse causation when using a biomarker
Heightened vigilance increasing disease detection in exposed

The structure of measurement error

two properties: *independence* and *nondifferentiality*.

from: Hernan and Robbins

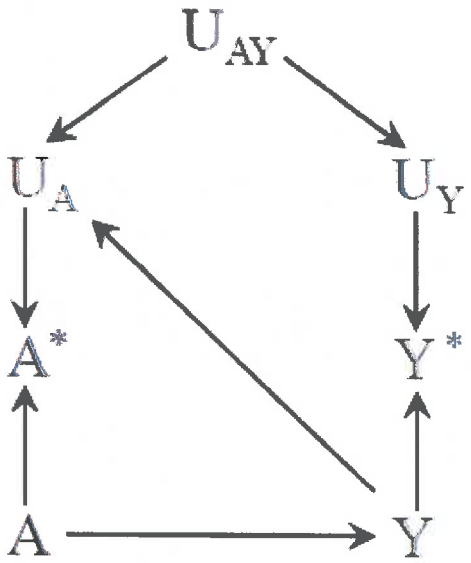


Figure 9.6

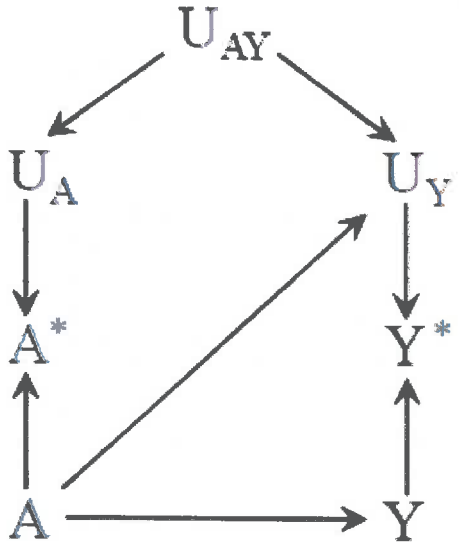


Figure 9.7

Dependent and differential:
True **value** of outcome affects measurement of treatment or vice versa; and measurement **errors** are not independent

Mis-measured confounders

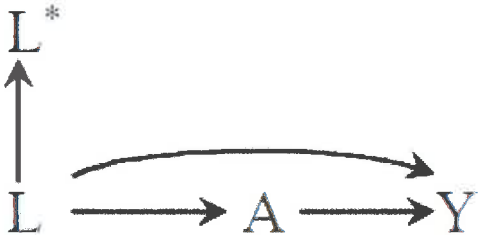


Figure 9.8

Can the backdoor path from Y to A through U be blocked by conditioning on L*?

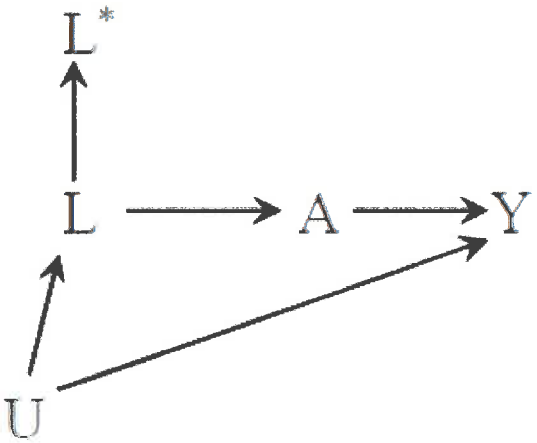


Figure 9.9

Mismeasured Collider
– selection bias

Figure 9.10

Effects of Agricultural Work and Other Proxy-derived Case-Control Data on Parkinson's Disease Risk Estimates. *Am J Epidemiology* 1995, Vol. 141(8).

Karen M. Semchuk[1-3] and Edgar J. Love[1]

This study examined the effects on Parkinson's disease risk estimates of exposure misclassification in proxy-derived data on agricultural work, pesticide use, rural living, well water drinking, head trauma, smoking, and family history of Parkinson's disease or essential tremor. The data were collected in 1989 as part of a population-based case-control study of Parkinson's disease in Calgary, Canada. Nondemented cases (n = 130) were selected from a case register of Calgary residents with neurologist-confirmed Parkinson's disease. For each case, two matched (sex and age ± 2.5 years) community controls were selected by random digit dialing. Forty cases and 77 controls were randomly selected as index respondents. The cases, controls, and one proxy respondent (spouse or offspring) for each index respondent were interviewed using a structured questionnaire. The data were analyzed using conditional logistic regression. Incorporation of proxy-derived data for 30% of the cases or controls, or both, resulted in considerable misclassification of exposure for some variables and, in most cases, attenuation of the odds ratio. The results indicate that pooling dichotomously classified data derived in part from self- and proxy respondents may result in biased estimates of Parkinson's disease risk associated with agricultural, family history, and head trauma factors. *Am J Epidemiol* 1995; 141:747–54.

case-control studies; epidemiologic methods; head injuries; Parkinson disease; pesticides; smoking

Example: Measurement error in proxy-derived exposure data

TABLE 2. Index-proxy pairs and sensitivity and specificity of the proxy-derived data, by exposure variable and study group: Calgary, Canada, 1989

Variable	Case pairs*				Sensitivity of the proxy responses	Specificity of the proxy responses	Control pairs*				Sensitivity of the proxy responses	Specificity of the proxy responses
	++	−−	+−	−+			++	−−	+−	−+		
Environmental variables												
Rural living	14	20	4	2	0.78	0.91	24	43	7	3	0.77	0.94
Farm living	13	21	4	2	0.77	0.91	23	44	6	4	0.79	0.92
Well water	12	11	4	1	0.75	0.92	27	21	9	2	0.75	0.91
Agricultural variables												
Agricultural work	9	23	5	3	0.64	0.89	12	54	6	5	0.67	0.92
Crop farming	9	24	5	2	0.64	0.92	11	56	6	4	0.65	0.93
Grain farming	5	27	6	2	0.46	0.93	7	59	7	4	0.50	0.94
Herbicide use	4	27	4	3	0.50	0.90	1	65	3	4	0.25	0.94
Insecticide use	1	31	3	3	0.25	0.91	2	62	7	4	0.22	0.94
Fungicide use	1	25	5	1	0.17	0.96	3	64	2	2	0.60	0.97
Other variables												
Family history of Parkinson's disease	4	30	5	1	0.44	0.97	4	69	1	0	0.80	1.00
Head trauma	4	24	4	4	0.50	0.86	4	60	2	4	0.67	0.94
Family history of essential tremor	5	28	6	1	0.46	0.97	2	64	3	7	0.40	0.90
Smoking	20	17	2	1	0.91	0.94	56	17	1	3	0.98	0.85

* The first symbol represents the index subject, and the next symbol represents the proxy respondent, with a "+" denoting a positive exposure and a "−" denoting a negative exposure.

Source: Semchuk KM and Love EJ. Effects of Agricultural Work and Other Proxy-derived Case-Control Data on Parkinson's Disease Risk Estimates. *Am J Epidemiology* 1995, Vol. 141(8).

Example: Measurement error in proxy-derived exposure data

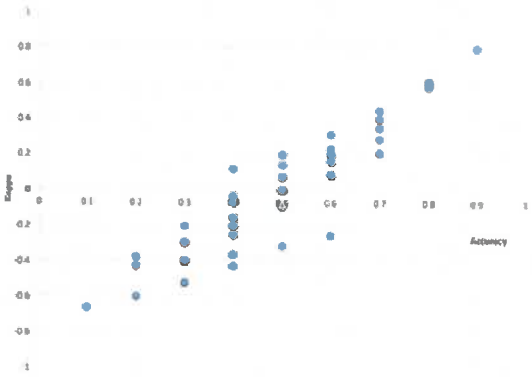
TABLE 3. Crude odds ratios for Parkinson's disease,* 95% confidence intervals, and ratios of odds ratios, by exposure variable and analysis design: Calgary, Canada, 1989

Variable	Design	Case/ control sets	Crude odds ratio	95% confidence interval	Ratio of odds ratios†
Herbicide use	A	127	3.06	1.34–7.00	
	B	127	2.69	1.20–6.03	0.9
	C	127	2.52	1.19–5.34	0.8
	D	127	2.36	1.10–5.04	0.8
Family history of Parkinson's disease	A	128	5.76	2.60–12.77	
	B	128	4.12	1.95–8.68	0.7
	C	128	7.64	3.14–18 .63	1.3
	D	128	5.12	2.28–11.50	0.9
Head trauma	A	130	3.10	1.67–5.75	
	B	126	3.10	1.67–5.77	1.0
	C	130	2.68	1.50–4.80	0.9
	D	126	2.80	1.54–5.08	0.9
Family history of essential tremor	A	125	2.37	1.20–4.69	
	B	125	1.68	0.82–3.45	0.7
	C	125	1.95	1.00–3.81	0.8
	D	125	1.37	0.67–2.80	0.6
Smoking	A	130	0.48	0.29–0.80	
	B	130	0.46	0.28–0.77	1.0
	C	130	0.47	0.29–0.78	1.0
	D	130	0.45	0.27–0.75	0.9

Source: Semchuk KM and Love EJ. Effects of Agricultural Work and Other Proxy-derived Case-Control Data on Parkinson's Disease Risk Estimates. *Am J Epidemiology* 1995, Vol. 141(8).

Assess Performance of a job-exposure matrix (JEM) vs. expert assessment

- Show overall agreement between JEM and experts graphically, or statistically using e.g.
  - a Kappa value (categorical exposure)
    - measures inter-rater agreement for qualitative items
  - sensitivity or specificity (dichotomous exposure)



Job-exposure matrix (JEM) based exposure assessment

- JEMs are created when it is **not** possible to obtain individual level exposure data
- As a proxy for exposure measurements per individual worker:
  - e.g. measurements taken for current workers or samples collected at current workplaces and extrapolated to past conditions in company
  - expert ratings of job titles by agents or base it on a literature review
- JEM information has to be linked to study subjects by some known group characteristics like job titles, location, calendar time, task etc.
- We loose statistical power and introduce potential misclassification bias since subjects are grouped by jobs/tasks etc ('average exposure' in the group of workers with same job or 'ecologic measure of exposure')

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Retrospective Assessment of Occupational Exposure to Chemicals in Community-Based Studies: Validity and Repeatability of Industrial Hygiene Panel Ratings

GEZA BENKE, MALCOLM SIM, ANDREW FORBES AND MICHAEL SALZBERG

Background. Occupational hygiene panels are increasingly being used to rate retrospective occupational exposures to chemicals in community-based studies. This study aimed to assess the validity, reliability and feasibility of using such an expert panel in a brain tumour case-control study.

Methods. A panel of five experts was recruited to rate exposure to 21 chemicals for 298 job descriptions to investigate the level of agreement. Validity was assessed by comparing the ratings of the experts for 49 of the jobs with objective quantitative exposure data which existed for these jobs. Repeatability was assessed by comparing the results for 50 resubmissions.

Results. Specificity was high for reporting that exposure occurred (all above 90%), but sensitivity was variable with values between 48% and 79%. Weaker validity was found for rating exposure level and exposure frequency. The raters showed the greatest inter-rater agreement for exposure to three of the 21 chemicals considered (κ = 0.64 for cutting fluids, κ = 0.57 for welding fumes and κ = 0.42 for lubricating oils). Intra-rater reliability, based on the 50 resubmitted jobs, was fair to good (κ = 0.46, 0.73).

Conclusions. The potential effect of exposure misclassification from using expert panels was quantified and found to be a significant source of bias. The optimum situation occurred where three of the five raters concurred, where an odds ratio of 2.2 was observed for a true odds ratio of 4.0. Future studies which plan to use expert panels should screen the experts for their suitability by validating their performance against jobs with known exposure data.

Keywords: epidemiology, exposure assessment, reliability, validation

JEM Expert Assessment Validity and Reliability

TABLE 1 *Pairwise agreement statistics between raters assessing 199 jobs for exposures to 21 chemicals*

Exposure	% prevalence[a]	(Range)	Pairwise agreement (%)	κ[b]	(Range)
Other organic solvents	29.0	(8.0,54.3)	71.0	0.31	(0.14,0.54)
Lubricating oils and greases	17.5	(8.0,33.2)	83.1	0.42	(0.27,0.62)
Soldering fumes	9.0	(2.5,15.6)	90.1	0.38	(0.17,0.56)
Welding fumes	8.3	(4.0,13.6)	93.4	0.57	(0.42,0.74)
Cutting fluids	8.1	(5.5,13.1)	94.5	0.64	(0.44,0.81)
PAHs[c]	7.4	(0.5,17.1)	89.4	0.22	(0.05,0.38)
Lead	6.9	(0.5,15.1)	90.1	0.23	(0.06,0.36)
Toluene	6.2	(1.5,17.1)	90.2	0.19	(0.08,0.56)
Benzene	4.7	(0.0,13.1)	93.0	0.19	(0.0,0.49)
Chromates	3.9	(0.5,8.5)	94.0	0.12	(−0.01,0.27)
Formaldehyde	3.3	(1.0,7.0)	94.7	0.16	(−0.03,0.32)
Organochlorine pesticides	3.2	(1.5,6.0)	95.9	0.34	(0.18,0.50)
Arsenic	1.5	(0.0,4.5)	97.1	0.02	(−0.02,0.13)
Mercury	1.3	(0.0,3.0)	97.6	0.03	(−0.01,0.39)
Ethylene oxide	0.9	(0.0,1.5)	98.5	0.13	(−0.02,0.80)
N-nitroso compounds	0.9	(0.0,2.0)	98.4	0.05	(−0.01,0.56)
Jet-fuel	0.7	(0.5,1.5)	99.0	0.30	(−0.01,1.0)
Phenol	0.4	(0.0,1.0)	99.2	−0.003	(−0.01,0.0)
Vinyl chloride	0.4	(0.0,1.0)	99.2	−0.003	(−0.01,0.0)
Acrylonitrile	0.2	(0.0,0.5)	99.6	−0.001	(−0.01,0.0)
TDI[d]	0.2	(0.0,0.5)	99.6	−0.001	(−0.01,0.0)

[a] % prevalence, is the mean prevalence across the five raters per chemical exposure.
[b] Summary kappa statistic (see text).
[c] Polycyclic aromatic hydrocarbons.
[d] Toluene di-isocyanate.

Source: Benke G et al. Retrospective Assessment of Occupational Exposure to Chemicals in Community-Based Studies: Validity and Repeatability of Industrial Hygiene Panel Ratings. *Intl J of Epidemiology*, 1997, 26(3):636-642.

JEM expert Assessment

TABLE 2 *Intra-rater reliability of exposure identification by raters for all 21 chemicals (listed in Table 1) for 50 resubmission jobs*

Rater	Prevalence[a]	κ[b]	95% CI[c]
1 (Physician)	2.7%	0.46	(0.31,0.61)
2 (Physician)	7.8%	0.64	(0.53,0.75)
3 (Hygienist)	3.4%	0.60	(0.48,0.72)
4 (Hygienist)	5.9%	0.73	(0.65,0.81)
5 (Hygienist)	6.7%	0.54	(0.42,0.66)

[a] Prevalence, total exposures identified across all chemicals for the 50 resubmission jobs by the particular rater.
[b] kappa statistic.
[c] Confidence interval.

Source: Retrospective Assessment of Occupational Exposure to Chemicals in Community-Based Studies: Validity and Repeatability of Industrial Hygiene Panel Ratings. *International J Epidemiology* 1997 Vol. 26 (3)

JEM expert Assessment

TABLE 3 *Validity of exposure identification by raters for all 21 chemicals (listed in Table 1) for the 49 dummy jobs*

Rater	Prevalence[a]	Sensitivity	Specificity
1 (Physician)	4.2%	48.1%	97.9%
2 (Physician)	9.3%	69.2%	93.9%
3 (Hygienist)	7.6%	57.7%	94.9%
4 (Hygienist)	13.0%	78.9%	90.9%
5 (Hygienist)	9.5%	65.4%	93.3%

[a] Prevalence, total exposures identified across all chemicals for the 49 dummy jobs by the particular rater.

Source: Benke G et al. Retrospective Assessment of Occupational Exposure to Chemicals in Community-Based Studies: Validity and Repeatability of Industrial Hygiene Panel Ratings. *Intl J of Epidemiology*, 1997, 26(3):636-642.

JEM expert Assessment

TABLE 4 *Exposure misclassification matrix for level ratings by the five raters for the 49 dummy jobs*

Rater exposure levels	True exposure levels		
	No exposure (n = 4885)	Low level (n = 160)	Medium and high level (n = 100)
% no exposure (range)	94.1 (90.7,97.7)	37.5 (21.9,46.9)	34.0 (20.0,60.0)
% low level (range)	4.4 (1.7,7.6)	22.5 (12.5,34.4)	25.0 (15.0,35.0)
% medium and high level (range)	1.5 (0.6,3.0)	40.0 (28.1,56.2)	41.0 (25.0,50.0)
TOTAL	100%	100%	100%

Source: Benke G et al. Retrospective Assessment of Occupational Exposure to Chemicals in Community-Based Studies: Validity and Repeatability of Industrial Hygiene Panel Ratings. *Intl J of Epidemiology*, 1997, 26(3):636-642.

JEM expert Assessment

TABLE 5 *Exposure misclassification matrix for frequency ratings by the five raters for the 49 dummy jobs*

Rater frequency levels	True frequency levels		
	No exposure (n = 4885)	Low and medium frequency (n = 90)	High frequency (n = 170)
% no exposure (range)	94.1 (90.7,97.7)	43.3 (16.7,61.1)	32.4 (23.5,47.0)
% low and medium frequency (range)	5.5 (1.7,9.3)	47.8 (22.2,83.3)	50.0 (26.5,76.5)
% high frequency (range)	0.4 (0.0,1.0)	8.9 (0.0,22.2)	17.6 (0.0,29.4)
TOTAL	100%	100%	100%

Source: Benke G et al. Retrospective Assessment of Occupational Exposure to Chemicals in Community-Based Studies: Validity and Repeatability of Industrial Hygiene Panel Ratings. *Intl J of Epidemiology*, 1997, 26(3):636-642.

TABLE 6 *Validity of panel using different combinations of raters assessing job exposure for the 49 dummy jobs*

No. of raters[a]	Sensitivity	Specificity	PPV[b]	NPV[c]
All 5	28.8%	99.3%	68.2%	96.3%
⩾4	42.3%	98.6%	73.3%	97.0%
⩾3	67.3%	98.5%	70%	98.3%
⩾2	82.7%	96.7%	57.3%	99.1%

[a] Number of raters correctly assessing an exposure.
[b] Positive predictive value.
[c] Negative predictive value.

Source: Benke G et al. Retrospective Assessment of Occupational Exposure to Chemicals in Community-Based Studies: Validity and Repeatability of Industrial Hygiene Panel Ratings. *Intl J of Epidemiology*, 1997, 26(3):636-642.

JEM Expert Assessment

TABLE 7 *Effects on odds ratio of rating misclassification for different combinations of raters for the 49 dummy jobs*

Rater	Sensitivity	Specificity	Prevalence of exposure in cases	[a]$OR_T = 2$ [b]OR_O	$OR_T = 3$ OR_O	$OR_T = 4$ OR_O
1	48.1	97.9	0.01	1.10	1.14	1.16
			0.05	1.39	1.60	1.72
4	78.9	90.9	0.01	1.04	1.06	1.06
			0.05	1.19	1.27	1.32
All 5 correct	28.8	99.3	0.01	1.17	1.24	1.28
			0.05	1.55	1.89	2.12
≥4 correct	42.3	98.6	0.01	1.13	1.18	1.21
			0.05	1.47	1.73	1.90
≥3 correct	67.3	98.5	0.01	1.19	1.26	1.31
			0.05	1.59	1.96	2.22
≥2 correct	82.7	96.7	0.01	1.11	1.16	1.18
			0.05	1.43	1.66	1.80

[a] True odds ratio.
[b] Observed odds ratio.

Source: Benke G et al. Retrospective Assessment of Occupational Exposure to Chemicals in Community-Based Studies: Validity and Repeatability of Industrial Hygiene Panel Ratings. *Intl J of Epidemiology*, 1997, 26(3):636-642.

UNITED STATES DISTRICT COURT
NORTHERN DISTRICT OF CALIFORNIA

IN RE: ROUNDUP PRODUCTS LIABILITY LITIGATION	MDL No. 2741
	Case No. 16-md-02741-VC
THIS DOCUMENT RELATES TO ALL CASES	

CONFIDENTIAL - SUBJECT TO PROTECTIVE ORDER

VIDEOTAPED DEPOSITION OF AARON EARL BLAIR, Ph.D.
WASHINGTON, D.C.
MONDAY, MARCH 20, 2017
8:59 A.M.

Reported by: Leslie A. Todd

Deposition of AARON EARL BLAIR, Ph.D., held at the offices of:

HOLLINGSWORTH, LLP
1350 I Street, N.W.
Suite 1000
Washington, DC 20005
(202) 898-5800

Pursuant to notice, before Leslie Anne Todd, Court Reporter and Notary Public in and for the District of Columbia, who officiated in administering the oath to the witness.

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EXHIBIT 19-6
RITZ
Date: 9/18/2017
Reporter: Lisa Moskowitz
CSR 10816. RPR. CRR. CLR

C O N T E N T S

E X H I B I T S

(Attached to transcript)

E X H I B I T S C O N T I N U E D

(Attached to transcript)

E X H I B I T S C O N T I N U E D

(Attached to transcript)

E X H I B I T S C O N T I N U E D

(Attached to transcript)

E X H I B I T S C O N T I N U E D

(Attached to transcript)

P R O C E E D I N G S

THE VIDEOGRAPHER: We are now on the record. My name is Daniel Holmstock. I'm the videographer for Golkow Technologies. Today's date is March 20th, 2017, and the time is 8:59 a.m.

This deposition is being held at the law offices of Hollingsworth, LLP, at 1350 I Street, Northwest, in Washington, D.C., in the matter of In Re Roundup Products Liability Litigation, MDL No. 2741. The case is pending before the United States District Court of the Northern District of California.

Our deponent today is Dr. Aaron Blair.

Counsel, would you please identify yourselves and whom you represent.

MR. MILLER: Yes, good morning. I'm Michael Miller, and I represent the plaintiffs, together with my law partner Nancy Miller, law partner Jeff Travers, and an attorney from Denver Kathryn Forgie.

MS. FORGIE: With Andrus Wagstaff.

MR. LASKER: David?

MR. GREENE: I'm sorry. David Greene. I represent Dr. Blair.

MR. HOLLINGSWORTH: Joe Hollingsworth. I represent Monsanto,

MS. SHIMADA: Elyse Shimada. I represent Monsanto.

MR. LASKER: Eric Lasker for Monsanto.

THE VIDEOGRAPHER: Anybody via telephone, please identify.

MS. WAGSTAFF: Good morning, everyone. This is Aimee Wagstaff from Andrus Wagstaff, and I represent the plaintiffs in this matter.

THE VIDEOGRAPHER: Anybody else via telephone?

Okay. Our reporter is Leslie A. Todd, who will now administer the oath.

WHEREUPON,

AARON EARL BLAIR, Ph.D.,

called as a witness, and having been first duly sworn, was examined and testified as follows:

DIRECT EXAMINATION

BY MR. MILLER:

Q Good morning, Dr. Blair.

A And good morning.

MR. LASKER: Mike, as you said, just before we get started, a statement on the record. This is Eric Lasker for Monsanto.

Based upon discussions we had with Dr. Blair's counsel when this deposition was subpoenaed and -- subpoenaed by plaintiffs, it is our understanding that Dr. Blair has been produced solely as a fact witness to provide testimony about his factual knowledge and his experiences in connection with issues for which he will be questioned, and not to offer any expert opinions in this litigation. And we have prepared for the deposition accordingly.

MR. MILLER: Well, and we agree to the extent that we -- we have not retained Dr. Blair as an expert. I don't believe Monsanto has retained Dr. Blair as an expert, but as we get into the deposition, and we both know Dr. Blair was part of a committee that formulated opinions, and we'll only ask about opinions that were formulated within that process and not for expert opinion as he sits here today. We certainly are not asking that.

So let's get going and see if we can complete our day.

MR. LASKER: As questions are asked, we will object or not according to our understanding.

MR. MILLER: As the rules allow.

BY MR. MILLER:

Q All right. Good morning, Dr. Blair.

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A Good morning.
Q How are you, sir?
A Okay.
Q Good. What -- would you please state your name on the record.
A Aaron Earl Blair.
Q All right, sir. And Aaron Earl Blair, and you're a doctor?
A Ph.D.
Q Ph.D. You've got -- I'm going to start and go through a little bit of your credentials, if I may, sir.
A Sure.
Q Okay. You graduated in 1965 with a degree in biology from Kansas Wesleyan University?
A Yes.
Q Master of Science degree in '67 from North Carolina State University?
A Yes.
Q And a Ph.D. in genetics at North Carolina State University?
A Yes.
Q And then in 1976, you got a MPH. What is an MPH?
A Masters in Public Health.

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Q And that's -- your CV says epidemiology?
A Correct.
Q Okay. And what is epidemiology?
A The study of causes and distribution of diseases.
Q Have you -- have you been professionally since 1976 studying the causes of diseases?
A Yes.
Q And explain it to me, if you would. Where and how have you been studying the causes of diseases since 1976?
A The study of disease in human populations, evaluating various factors that might be related to the initiation or etiology of those diseases.
Q As the -- you say you've spent your professional life with this doctorate degree studying the causes of diseases. Have you studied the causes of cancer?
A Yes.
Q And within the broad field of studying the causes of cancer, have you studied the causes of non-Hodgkin's lymphoma?
A Yes.
Q I'm a lay person. Tell me what is

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non-Hodgkin's lymphoma.
A Lymphatic and hematopoietic tumors have a variety of different specific diseases. One is Hodgkin's disease, you've probably heard of. It's a lymphoma. Non-Hodgkin's lymphoma is all the lymphomas that aren't Hodgkin's disease.
Q So non-Hodgkin's lymphoma is a form of cancer. You have to answer --
A Yes.
Q And non-Hodgkin's lymphoma is a form of cancer in the blood?
A Yes.
Q So any kind of blood cancer that is not Hodgkin's lymphoma would be called non-Hodgkin's lymphoma?
A No. It is --
Q All right. Explain to me why I'm --
A -- any type of lymphoma --
Q I see.
A -- that isn't Hodgkin's disease is non-Hodgkin's lymphoma.
Q So there can be other blood cancers such as leukemia?
A Yes.
Q I understand. Thank you for that

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correction.
Now, it sounds like you spend an awful lot of time at the National Cancer Institute. Is that right?
A Yes.
Q What is the National Cancer Institute?
A It is one of the institutes, the National Institutes of Health devoted to studying cancer.
Q And you started there in 1976?
A Yes.
Q I think we're about the same age. How many years ago was that?
A Quite a few.
Q Yeah. Thanks for clearing that up.
And how long did you stay there, from 1976 until when? Are you still there or are you retired or --
A I am retired now, but I have an emeritus position, which means I go in a couple of days a week and do what I've always done. I just don't get paid.
Q Sounds like an interesting promotion, Dr. Blair.
All right. So you started there in 1976. You were a staff fellow for the Environmental Epidemiology Branch at the National Cancer Institute?

A Correct.
Q Went on 1978 to '82, became the acting chief of the occupational study section of the Environmental Epidemiology Branch, National Cancer Institute?
A Yes.
Q Describe for us what it is you are doing there and --
A Studying various sorts of exposures that occur in occupations and to see if they are related to cancer.
Q Would farming be one of those occupations that you've studied for the causes of cancer?
A Yes.
Q Wouldn't that be true for your entire profession -- professional career?
A That was one of the early things I started doing was studies of farmers.
Q Did there come a time when you saw an increase in cancers in farmers?
A Yes.
Q All right. Let's go on then. You became the chief of the occupational study section in 1982, right?
A Yes.

Q Okay. Remained the chief for, and I will do this math, 14 years until 1996?
A Sounds right.
Q Okay, sir. And I have -- you have a copy of your CV there. I have a copy here. If you want to look at it, feel free.
And what I will do, I will mark as Exhibit 1 a copy of your CV or curriculum vitae, okay?
(Blair Exhibit No. 1 was marked for identification.)
BY MR. MILLER:
Q And hand it to you. And you can let me know if this is -- all right. Thank you, sir.
MR. MILLER: A copy for counsel.
MR. LASKER: Thank you. Yeah, do that.
BY MR. MILLER:
Q Is this your CV, sir?
A Yes.
Q Okay. So we were down here, we were looking at some of your professions. You were at the National Cancer Institute after receiving your Ph.D. --
MR. LASKER: Mike, for the record, are these highlights your highlights on the document?

MR. MILLER: Yes. Yes. Yes, they are. Thanks for asking.
MR. LASKER: That's the document that you will be using for the deposition?
MR. MILLER: I -- I think we're allowed to do that, if I recall, under the rules.
MR. LASKER: Okay, that's fine.
MR. MILLER: Yeah. I'm just highlighting to aid the jury along the way.
BY MR. MILLER:
Q These highlights aren't yours, are they, Dr. Blair?
A No.
Q Okay. It's all important, isn't it? Your whole body of work, do you feel like it's important?
A Oh. Yes, sure.
Q All right. So after being the chief for 14 years at the Occupation and Environmental Epidemiology Branch, you went on to become in 2004 a senior investigator. Please tell us what that means.
A It means I stepped down as head of the unit and just retained a position at the National Cancer Institute, and that is a senior position.
Q Okay. And then you retired from

full-time work there in 2007.
A Yes.
Q And have been working for free as a professor emeritus there ever since.
A Yes.
Q Very good. All right.
And the reason I'm asking about your background, sir, there came a time when this organization asked you to do some scientific work for them. Is that fair?
MR. LASKER: Objection to form.
THE WITNESS: Yes.
BY MR. MILLER:
Q Who is WHO?
A World Health Organization.
Q Okay. So the World Health Organization, what did they ask you to do? What did they ask you to do, sir?
A Are you asking about a particular time or --
Q You know, that's a fair question. When was the first time the World Health Organization contacted Aaron Blair and asked him to perform some professional services?
A I -- I don't --

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MR. LASKER: Objection to form.
You can answer.
THE WITNESS: I don't actually remember the earliest year that it was, but I have served on various World Health Organization groups over the years.
BY MR. MILLER:
Q Could you just let the jury know some of those groups that you served at the request and for the World Health Organization.
A Well, the main one is the International Agency for Research on Cancer, which is part of the World Health Organization.
Q Okay. And is that also referred to as IARC?
A Correct.
Q Okay. So -- and that stands for International Association --
A Agency.
Q I'm sorry. International Agency for the Research on Cancer?
A Correct.
Q And that is an organization which is part of the World Health Organization.
A Yes.

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Q And how many times have you served as an IARC volunteer?
A You know, I don't actually remember the -- the number. Seven maybe.
Q Okay. And I'm going now to your CV to page 3, and it shows that you served on IARC as early as 1985.
Does that sound about right, Dr. Blair?
A Sounds about right.
Q Okay. And you were at -- you were involved in an IARC monograph. I guess we will stop there. What's a monograph?
A Just a publication, a book.
Q Okay. So it's an International Agency for the Research of Cancer book on the evaluation of carcinogenic -- I guess that's cancer?
A Yes.
Q -- of cancer risks to humans.
A Yes.
Q And you -- Volume 35, these books come out from the World Health Organization in volumes, I guess?
A Yes.
Q Okay. So Volume 35 was probably one of the first ones that you worked on.

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A Yes.
Q So off and on, as requested by World Health Organization, it would be fair to say you've been involved in working with them since 1985, right?
A Yes.
MR. LASKER: Objection to form.
BY MR. MILLER:
Q Or about -- is that 32 years? I'm real bad with math. Sound about right?
A Sounds right.
Q Okay. All right. So that was Volume 35.
Did there come a time when you were asked to be involved with the World Health Organization, the International Association of Cancer, to what has now become Volume 112 of the monographs?
A Yes.
MR. LASKER: Objection to form.
BY MR. MILLER:
Q And I'm going to put a copy under the highlighter -- and that is my highlighting, so we all know -- I'll tell you what I will do, I will use a non-highlighted copy and a highlighter to work with.
(Blair Exhibit No. 2 was marked for identification.)
BY MR. MILLER:

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Q And a copy for you, Doctor.
MR. MILLER: And a copy for counsel.
Q All right. Here, Doctor.
A Thank you.
Q All right. So what we have here, can you identify this document, which is Exhibit 2, please?
A Well, it is one of the monographs.
Q Okay. And I just want to ask you a few questions about the front page of this document. So it says -- again, we've been talking about it, but it's a World Health Organization, right?
A Yes.
Q And it's the International Agency for Research on Cancer.
A Yes.
Q Also known as IARC, right?
A Yes.
Q All right. Now, this is a preamble. What is a preamble?
A Sort of the beginning discussion of what follows in the monograph.
Q Okay. And they meet in a place called Lyon, France?
A Correct.
Q All right. And this preamble was written

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in 2006. Have you reviewed this before?
A Yes. Not -- not recently.
Q Well, I know, and I'm not -- it's not a test, but I just want to go over a couple of things with you.
And will go, if you would, sir, to the first page of the preamble, and it says here that the IARC was established in two -- in 1965.
Is that your understanding?
A Yes.
Q All right. It says: Through the IARC" -- I'm sorry, I will quote exactly.
"Through the monographs program, IARC seeks to identify the causes of human cancer."
That's true, isn't it, sir?
A Yes.
Q Okay. And some terms, so the jury and I can understand them. In this preamble they tell us, the World Health Organization, that a cancer hazard is an agent that is capable of causing cancer under some circumstances. While a cancer risk is an estimate of carcinogen -- carcinogenic effects expected from exposure to a cancer hazard.
I mean, is that what we should understand?

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A Yes.
Q Okay. All right. And there's in the preamble a discussion of the selection of agents for review by IARC, and I want to ask you about it.
It says: "Agents are selected for review" -- is that for review to see if they cause cancer?
A Yes.
Q -- "on the basis of two main criteria: There is evidence of human exposure, and there is some evidence or suspicion of carcinogenicity."
Is that your understanding, Dr. Blair?
A Yes.
Q Okay. And IARC has in this preamble a discussion of what they will review as they consider these issues, right, sir?
A Yes.
Q Okay. And it talks about with regard to epidemiological studies -- now, first, let's stop there.
What is an epidemiological study?
A It's a study of -- in humans to evaluate risk of disease or risk factors.
Q To find out if some agent may cause some condition?

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A Right.
Q Okay.
MR. LASKER: Object to form.
BY MR. MILLER:
Q What is a cancer bioassay?
A It's an experimental study. Usually it means studies in animals.
Q Okay. What do we mean by "mechanistic and other relevant data"?
A What are the biologic processes that might lead from an exposure to development of cancer.
Q Yes, sir.
"Only reports that have been published or accepted for publication in openly available scientific literature are reviewed."
Is that true, sir?
A Yes.
Q And why is that true? Why -- why does IARC only review those publications that have been published in available scientific literature or have been accepted for publication?
MR. LASKER: Objection to form.
BY MR. MILLER:
Q You can answer.
A Because these materials are then

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available to anyone.
Q And IARC also reviews those exposure data?
A Yes.
Q And exposure data means how are humans exposed to that agent, right?
A Yes.
Q Okay. And IARC extends invitations to scientists around the world to participate in the creation of a monograph for a book, right?
A Yes.
Q And it -- in this preamble it tells us: "Before an invitation is extended, each potential applicant participant, including the IARC Secretariat, completes a WHO declaration of interest to report financial interests, employment, and consulting, and individual and institutional research support related to the subject of the meeting."
Is that your understanding?
A Yes.
Q So before these folks are invited to be on this IARC panel, they have to declare their interests?
A Yes.
MR. LASKER: Objection to form.

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BY MR. MILLER:
Q And it says in this monograph preamble that a working group -- and I want to ask you, what is a working group?
A It's the group of people invited to perform this activity.
Q And the working group meets at IARC for seven to eight days to discuss and finalize the text and to formulate the evaluation.
Is that your experience?
A Roughly that number of days, yes.
Q Excuse me. All right. Page 8. I want to ask you about this if I can.
It says: "Regarding occurrence and exposure, data that indicate the extent of past and present human exposure, the sources of exposure, the people most likely to be exposed, and the factors that contribute to exposure are reported."
Is that your experience, sir?
A Yes.
Q And one more sentence here. It says, quote: Information is presented on the range of human exposure, including occupational and environmental exposure.
Occupational exposure I guess would mean

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being exposed to the agent at work?
MR. LASKER: Objection to form.
THE WITNESS: Yes.
BY MR. MILLER:
Q And environmental exposure means what, sir?
A Usually not exposed at work. In other ways.
Q All right. And I'm -- I just want to ask you a few more questions. Page 9, there's a whole section, and I'm not going to read it, but that IARC considers the quality of studies considered, right?
A Yes.
Q Okay. And then on page 10, IARC considers meta-analysis?
A Yes.
Q Now, could you tell the jury what is a meta-analysis?
A It is a quantitative or statistical way of summing up results from several studies.
Q Okay. And does IARC not only consider meta-analysis that are available in the public literature, but does IARC in fact do their own meta-analysis?
A Sometimes.

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Q Okay. And we're going to get to the IARC monograph on Roundup in a minute, but now I will jump out of turn and ask, did they -- did IARC working group do a meta-analysis on Roundup --
MR. LASKER: Objection to form.
BY MR. MILLER:
Q -- and the epidemiology concerning the issue of Roundup in non-Hodgkin's lymphoma?
A I'm not sure I remember.
Q All right. We will take a look in a minute then. Thank you.
And does IARC also review pooled analysis?
A Yes.
Q Okay. All right. And IARC looks at temporal effects, right, sir?
A Yes.
Q So they analyze both the detailed analysis of both relative and absolute risk in relation to temporal variables. Now, that's a mouthful.
Detailed analysis of both relative and absolute risk. What is a relative risk?
A It would be the calculation of a rate in one group compared to a rate in another.

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Q I see. Perhaps a group who's been exposed to an agent compared to a group that has not been exposed to an agent?
A Yes.
Q Okay. And an absolute risk would -- would be what, sir?
A The rate of occurrence of disease in a group.
Q Yes, sir. They consider age at first exposure, time since first exposure, duration of exposure, cumulative exposure, peak exposure, when appropriate and time sense -- cessation of exposures are reviewed and summarized when available. Is that right, sir?
A Yes.
Q All right. Going, if we would, to page 11 in the preamble for IARC, it tells us that they use a criteria to establish causality, right, sir?
MR. LASKER: Objection to form.
BY MR. MILLER:
Q You can answer.
A Yes.
Q And in their criteria for cruality -- causality, excuse me, in making its judgment, the

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working group considers several criteria for causality. Hill, 1965.
Do you see that, sir?
A Yes.
Q And that is Sir Bradford Hill?
A Yes.
Q Okay. It says in the preamble for IARC: "If the risk increases with exposure, this is considered a strong indication of causality."
Is that true, sir?
A Yes.
Q IARC also considers studies of cancer in experimental animals?
A Yes.
Q Page 15. In the preamble they discuss that IARC considers mechanistic and other relevant data. Is that right, sir?
A Yes.
Q Okay. And that would include toxicokinetic data.
Now, what does toxicokinetic data mean, Dr. Blair?
A Sort of the processes of chemicals interacting with human systems.
Q Okay, sir. And they consider data on

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mechanisms of carcinogens?
A Yes.
Q And what is that?
A Various pathways appear to lead to carcinogenicity.
Q And after -- even before this seven- to nine-day working group meeting in France, does the working group review materials in the time before that?
MR. LASKER: Object -- objection to form.
THE WITNESS: The individuals on the working group --
MR. MILLER: Yes.
THE WITNESS: -- review materials before then.
BY MR. MILLER:
Q Okay. And for what period of time approximately do individuals in the working group review material?
A A couple of months. Three months. It's a while.
Q Okay. And then after they review, there is a determination made whether the agent being reviewed is carcinogenic or not. Is that fair?
MR. LASKER: Objection to form.

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THE WITNESS: Yes.
BY MR. MILLER:
Q And there are different categories. There's 1, 2A, 2B, 3, that sort of thing?
A Yes.
Q Okay. Category 2A is the agent is probably carcinogenic to humans, right?
A Yes.
Q And carcinogenic means causes cancer, right?
A Yes.
Q Okay. So -- and we're going to talk about it in more detail, but you were selected for the working group that looked at Roundup, right?
MR. LASKER: Objection to form.
BY MR. MILLER:
Q You can answer.
A Yes.
Q And your group -- I think there were 17 scientists on that group?
A Sounds about right.
Q Yeah, I understand. We'll look at it in a sec.
But that group decided that Roundup and glyphosate was probably carcinogenic to humans,

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right?
MR. LASKER: Objection to form.
THE WITNESS: Yes.
BY MR. MILLER:
Q You have to answer again. 2A, "yes" is the answer?
A Yes.
Q Okay. All right. And so we're going to look at how that process was played out and see if we can understand it.
A Okay.
Q I want to look at Exhibit 3, which is -- one moment.
Okay. Exhibit 3, Dr. Blair, is a list of participants for the IARC Monograph on Evaluation of Carcinogenic Risk to Humans, which included a review of glyphosate, okay? I have a copy for you and a copy for counsel. So it will be Exhibit 3.
Here.
MR. MILLER: All right. Counsel.
(Blair Exhibit No. 3 was marked for identification.)
BY MR. MILLER:
Q All right, Dr. Blair. This is a list of participants for the IARC Monograph on the Evaluation

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of Carcinogenic Risk to Humans, right, sir?
A Yes.
Q So it's Volume 112 of these monographs we've been talking about, right?
A Yes.
Q And one of the things that -- one of the agents that IARC Volume 112 looked at was glyphosate, right?
A Yes.
Q And the meeting occurred in Lyon, France, March 3rd through 10th, 2015, right?
A Yes.
Q And the list of participants -- I would like to go over it for -- if I could, included Aaron Blair, National Cancer Institute, retired --
That's you, right, sir?
A Yes.
Q -- from the United States of America, and you were the overall chair of the group, weren't you?
A Yes.
Q Okay. How much did they pay you for that?
A We're not paid.
Q It's a volunteer assignment, isn't it?
A Yes.

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Q So you reviewed all these materials for months. Right?
MR. LASKER: Objection to form.
THE WITNESS: Yes.
BY MR. MILLER:
Q You flew to France.
A Yes.
Q Spent seven to nine days -- I'm sorry, it looks like seven days reviewing these materials with these other scientists, and you volunteered and did it all for free.
A Other than travel expenses.
Q Okay. They paid your airfare. Okay. Thank you.
All right. Let's look at -- did all 17 of these people do this as volunteers?
A Yes.
Q Okay. I want to look at some of them.
Also from America, Gloria Jahnke. Am I pronouncing that right?
A I'm not sure.
Q She's from the National Institute of Environmental Health Sciences of the United States?
A Yeah.
Q Do you know her?

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A No.
Q Okay.
A Other than through this meeting, I mean.
Q Yes, I understand. You spent seven days with her.
Charles Jameson from CWJ Consulting, LLC, United States. He is a subgroup chair in cancer in experimental animals.
Do you see that, sir?
A Yeah.
Q So how many subgroups are there or were there in this particular group?
A Four.
Q Okay. And there were people from the Environmental Protection Agency who volunteered and served on this panel that concluded that glyphosate was a probable cause of human cancer.
MR. LASKER: Objection to form.
THE WITNESS: Yes.
BY MR. MILLER:
Q One of them is Matthew Martin, right?
A Yes.
Q And Matthew Martin is -- was employed in 2015 by the United States Environmental Protection Agency, right?

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MR. LASKER: Objection to form.
THE WITNESS: Yes.
(Counsel conferring.)
BY MR. MILLER:
Q Oh, I skipped somebody. Peter -- I'll never pronounce this right, Peter Egeghy?
A I don't know.
Q I don't know either. From the United States Environmental Protection Agency, unable to attend.
Now, would he participate either by phone or not have participated, or how does that work?
A Well, I -- I think everyone is there.
Q Okay. All right. So if you're not there, you don't vote, or how does that work, do you know?
A I don't know of an example where someone was not there and voted.
Q Okay. From Canada, John McLaughlin, University of Toronto.
A Yes.
Q Do you know him?
A Yes.
Q I mean before the meeting.
A Yes.

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Q Okay. How do you know him?
A We're both epidemiologists doing the same work.
Q Yes, sir. All right.
And from Mississippi State University, Matthew K. Ross. My wife wouldn't let me -- I would be in trouble if I didn't bring out Mississippi State University.
Do you know him?
A Yes.
Q All right. And what sort of professional is he?
A He's a toxicologist, a bioassay person.
Q And from Texas A&M, Ivan Rusyn, he was a sub -- subgroup chair in mechanism.
Did you know him professionally before?
A Yes.
Q Do you know any of these people socially?
A A few.
Q Okay. Who?
A Andrea 't Mannetje; John McLaughlin. If "socially" means sometimes I see them not strictly in a professional meeting.
Q Have dinner after a meeting or something?
A Occasionally.

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Q Yeah, sure.
All right. From California Environmental Protection Agency, Lauren Zeise. Do you know what her profession is?
A No.
Q Okay. So those were the members.
Now, these people were the ones that ultimately voted that Roundup or glyphosate was a probable human carcinogen for non-Hodgkin's lymphoma.
Was the vote unanimous?
MR. LASKER: Objection to form.
BY MR. MILLER:
Q You can answer.
A I actually don't remember for sure. I think so.
I just want to say one thing --
Q Please do.
A -- these are the people who voted. You've just underlined a whole bunch of them.
Q Yes, sir.
A They all voted.
Q Oh, I understand, sir. Yes, sir. I wasn't trying to suggest otherwise. Everyone on here voted, right?
A Yes.

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Q And you think it was unanimous, but you're not a hundred percent sure. Is that fair?
A Yeah.
Q Now, I want to ask you, an invited specialist, what is an invited specialist?
A It may be that someone brings special expertise so it would be of value to the working group.
Q And the World Health Organization decided that there was an invited specialist they wanted to invite for this issue of glyphosate. Is that fair?
MR. LASKER: Objection to form.
THE WITNESS: Or for the other pesticides being evaluated.
BY MR. MILLER:
Q Sure.
A I don't know why they did it.
Q Yes, sir, I understand. You didn't make the invitation?
A I did not make the invitation.
Q But an invitation was extended to Christopher Portier, who was from the Agency for Toxic Substances and Disease Registry in the United States.
A Yes.

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Q Do you know Dr. Portier?
A Yes.
Q Okay. Also present was a gentleman by the name of Jesudosh -- I'm sorry if I'm pronouncing it wrong -- Jesudosh Rowland from the United States Environmental Protection Agency.
Do you see that, sir?
A Yes.
Q Do you know him?
A No. You know, he was at the meeting. I probably met him --
Q Right, I understand.
A -- at the meeting, but -- yeah.
Q I understand. And there were observers at the meeting. Now, what's the function of an observer?
A That usually means they are sort of stakeholders in the issue being evaluated.
Q Okay.
A A few who were invited to come.
Q And the Monsanto Company was allowed to have an observer at the meeting, weren't they, sir?
A Yeah.
Q That was a Dr. Thomas Sorahan, right?
A Yes.

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Q Do you know Dr. Sorahan?
A I do.
Q And did he -- was he allowed to speak up at the meeting?
A Yes.
Q Okay. Did he object to or complain about the unanimous decision to declare glyphosate a probable human carcinogen for non-Hodgkin's lymphoma?
MR. LASKER: Objection to form.
THE WITNESS: I don't think I remember this for sure, but typically invited specialists are asked to comment on specific things, not on the formal evaluation.
BY MR. MILLER:
Q I understand. All right.
(Counsel conferring.)
BY MR. MILLER:
Q All right. So after this selection of these 17 people IARC put together, you were the chairman. After months of review, a seven-day meeting, there was a report issued. Is that fair to say?
A Yes.
(Blair Exhibit No. 4 was marked for identification.)

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BY MR. MILLER:
Q Okay. Let's take a look at what I believe to be the IARC report for glyphosate. And I marked it as Exhibit 4, and I have a copy for you and counsel. And I put 4 on it so you know when somebody goes back to it later, you're going to know what number it is.
MR. MILLER: Counsel, here you go.
BY MR. MILLER:
Q This is a report from IARC for glyphosate?
A Okay. Yes.
Q Yes? Okay.
And glyphosate is the active ingredient in Roundup?
A Yes, sir.
Q Okay. And I want to ask you a few questions about the report, spend a little time going over it.
I'm not going to ask you about the molecular structure. I didn't do very well in high school chemistry. You'll forgive me.
If you would go to page 4.
The report says that: "Glyphosate is widely used for household weed control throughout the

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world. In the USA, glyphosate was consistently ranked as the second most commonly used pesticide (after 2,4-D) in the home and garden market sector between 2001 and 2007, with an annual use of 2,000 to 4,000 tonnes." And you cite the authority for that comment.
That was your understanding after researching the matter?
A That's my understanding.
MR. LASKER: Objection to form. Lacks foundation.
BY MR. MILLER:
Q All right. I want to go to page 45 of this report.
IARC studied obviously the drug in humans and studied it in exposed humans. That's a fair statement?
A Yes.
MR. LASKER: Objection to form.
BY MR. MILLER:
Q Okay. You looked at the study, one of -- was it about a thousand studies you guys looked at in this process?
MR. LASKER: Objection to form.
THE WITNESS: I don't actually know what

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the total number across all types of studies is. It was a lot, but I -- I don't know if that's the right number or not.
BY MR. MILLER:
Q Can you give me an estimate?
A Not really because I'm on the epidemiology panel.
Q Okay.
A And I sort of look at it. I mean the monograph lists all of them --
Q Right.
A -- that we looked at.
Q Right, right. Okay. So you not only chaired the entire panel but you subchaired the epidemiology section.
A I was on the epidemiology --
Q I'm sorry. Well, was there a subchair?
A There was.
Q Who?
A I don't remember.
Q Okay, fair enough.
The report says: "The baseline frequency of binucleated cells with micronuclei" -- excuse me -- "was significantly higher in subjects from the three regions where there had been aerial spraying

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with glyphosate formulations."
Do you remember reading the Bolognesi study?
MR. LASKER: Objection to form. And objection to using this witness just as a basis for reading in portions of the document and not having a set of questions with respect to that.
BY MR. MILLER:
Q You can answer.
A This is a toxicologic study. I'm an epidemiologist. Different subgroups evaluate different components. I'm really familiar with epidemiology, not so much the other.
Q That's fair. All right. All right. Thank you.
Let's look at the epidemiology then. I think that probably would make more sense. There's a table in the report with the epidemiology on it, isn't there?
A Yes.
(Counsel conferring.)
BY MR. MILLER:
Q Okay. Going to page 78 of your report, "Cancer in Humans." We're on page 78. Do you see this, Doctor?

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It says: "There is limited evidence in humans for the carcinogenicity of glyphosate. A positive association has been observed for non-Hodgkin's lymphoma."
What does a "positive association" mean, sir?
MR. LASKER: Objection to form.
BY MR. MILLER:
Q Yeah, you can answer. I'm sorry.
A It means there were studies that showed an excess risk for people exposed.
Q And that would include the epidemiological studies that were done.
A Yes.
MR. LASKER: Objection to form.
BY MR. MILLER:
Q And we'll take a look at a lot of them, but all right.
Your report goes on to say: "There is strong evidence that exposure to glyphosate or glyphosate-based formulations is genotoxic based on studies in humans in vitro and studies in experimental animals."
That's what your 17-expert committee found?

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MR. LASKER: Objection to form.
THE WITNESS: Yes.
BY MR. MILLER:
Q You also concluded: "There is strong evidence that glyphosate and glyphosate-based formulations, and aminomethylphosphonic acid can act to induce oxidative stress based on studies in experimental animals and in studies in humans in vitro."
Now, that's a mouthful, so I've got to ask you, why did you mention aminomethylphosphonic acid?
MR. LASKER: Objection to form.
THE WITNESS: Again, this comes from the subgroups with a discipline that I'm not as knowledgeable about.
BY MR. MILLER:
Q Okay.
A And I think this is a breakdown product, but I'm not sure.
Q I understand. Well, we'll pass that off to people that study the breakdown products. Okay.
MR. LASKER: Objection to form to that last comment.
BY MR. MILLER:

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Q To be clear, though, before we leave the "Conclusion" section, this report is in March of 2015, right?
A Yes, sir.
Q And "the positive association has been observed for non-Hodgkin's lymphoma," IARC has not retracted that statement in any way, shape or form as we sit here in March of 2017?
A Not to my knowledge.
Q And there's been requests by Monsanto Corporation to retract that, hasn't there?
MR. LASKER: Objection to form.
THE WITNESS: I understand that to be true.
BY MR. MILLER:
Q Now, let's look at some of the epidemiology in the -- all right. There we go.
Table 2.2 is a table about the epidemiology -- well, let's look at it. And it's quite a long one here.
Okay. Table 2.2 is -- I got it from here -- is case-control studies of leukemia and lymphoma and exposure to glyphosate, right, sir?
A Yes.
Q Okay. Now, I'm not going to ask about

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leukemia. But the first study in 1992, Cantor did not show any statistical significance, right, sir?
A Correct.
Q Explain to a lay person what "statistical significance" means.
A In statistical analyses, there is a phenomenon known as noise, which means if you do different studies, you don't get exactly the same response. And statistical approaches are used to decide if it is sort of outside the bounds of what you would anticipate to occur being just from noise.
Q Okay. So whenever -- explain to us -- in parentheses here, this 0.7-1.9, what does that tell us?
A The estimate of 1.1 says that is an estimate of elevated risk from this exposure. It's like a 10 percent increase, but it's not very big. And these other two numbers, 0.7 to 1.9, said we have -- I think in this case it's a 95 percent confidence interval that the real true estimate is somewhere between those two numbers.
Q Yes, sir. So then moving on in time, the next study we see on your chart for non-Hodgkin's lymphoma is a study by De Roos in 2003, right?
A Yeah.

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Q And what Dr. De Roos and others did -- and this is an epidemiological report from a peer-reviewed journal?
A Yes.
Q What do we mean by "a peer-reviewed journal"?
A You send a manuscript to a scientific journal, and they send it out if they think it might be worthy of fitting in that journal to other scientists to review it and make comments about its quality.
Q Okay. And Dr. De Roos and others in this peer-reviewed journal studied people who were exposed to glyphosate in Nebraska, Iowa, Minnesota, Kansas, from the period 1979 to 1986, right?
A Yes.
Q And what they found was that there was over a doubling of the risk of non-Hodgkin's lymphoma for people who had been exposed to glyphosate, right?
MR. LASKER: Objection to form.
THE WITNESS: Yes.
BY MR. MILLER:
Q And because our numbers here, 1.1 to 4.0 are higher than 1.0, they've taken chance out of it at 95 percent, right?

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MR. LASKER: Objection to form.
THE WITNESS: Yes.
BY MR. MILLER:
Q Is it -- is this finding of a doubling of the risk of non-Hodgkin's lymphoma, is it statistically significant?
A Yes.
MR. LASKER: Objection to form.
BY MR. MILLER:
Q Is this one of the pieces of evidence upon which your committee based their opinion there was a positive association between exposure to glyphosate and non-Hodgkin's lymphoma?
A Yes.
(Counsel conferring.)
BY MR. MILLER:
Q All right. So I'm going to go -- the Lee study was also about non-Hodgkin's lymphoma. Is that right, sir?
A Yes.
Q And it showed an increased risk of 40 percent but could not rule out chance. Is that fair or am I misinterpreting it?
A Correct.
Q Okay.

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MR. LASKER: Objection to form to the last question.
BY MR. MILLER:
Q And then in 2001, there was a large study -- well, strike that.
There was a study from Canada called the McDuffie study, right, sir?
A Yes.
Q Would you describe it as -- for a case-control study -- a large study or not?
A Yes.
Q And they examined people who had been exposed to glyphosate from 1991 to 1994, right, sir?
A They examined cases who occurred in that time period, I think, who might have been exposed.
Q Yes, sir. And they did exposure, unexposed. They did people that had been exposed for zero to two days and for people who had been exposed to greater than two days in that time period, right?
A Yes.
Q And for people that had been exposed to zero to two days, they found no increased risk of non-Hodgkin's lymphoma, right?
MR. LASKER: Objection.
THE WITNESS: That actually is the

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reference population.
BY MR. MILLER:
Q That's the reference population?
A So it's set at 1.0.
Q Oh, I see. Of course. All right.
But for people that were exposed for greater than two days, they found a doubling of the risk of non-Hodgkin's lymphoma from exposure to Roundup or glyphosate?
A Yes.
MR. LASKER: Objection to form.
BY MR. MILLER:
Q And they found that was statistically significant, that is to say it did not occur by chance?
MR. LASKER: Objection to form.
THE WITNESS: Outside the realm of chance.
BY MR. MILLER:
Q Yes, sir.
A Yes.
Q Okay. How would you pronounce this, Karunanayake? I'm sorry. I don't know how to pronounce that.
A Okay. I'm sorry, I can't quite read it.

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Q K-A-R-U-N-A-N-A-Y-A-K-E.
A I don't know.
Q Okay. He did a study out of Canada in -- for exposure period from '91 to '94, published in 2012, did not find a statistically significant increased risk in his study. Is that fair?
A Yes.
Q The next year, 2013, Kachuri, et al, in six provinces in Canada, studying multiple myeloma.
Is multiple myeloma a form of non-Hodgkin's lymphoma?
A No. Non-Hodgkin's lymphomas had different definitions over time. When this study was done, it was not a form of non-Hodgkin's lymphoma.
Q All right, sir.
All right. Excuse me. Continuing on your table of epidemiological studies, we have Hardell and Eriksson in 1999 do a study on non-Hodgkin's lymphoma from northern and middle Sweden during a three-year period, '87 to '90.
Do you see that, sir?
A Yes.
Q Now, they found under ever used glyphosate univariate analysis -- what is a univariate analysis?

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A Just looking at the relationship in a statistical analysis that includes glyphosate and not much of anything else.
Q All right. And what is an ever glyphosate multivariate analysis?
A They have included other factors that they think might be related to this cancer.
Q I see.
And what they concluded was, just using glyphosate, they had a doubling of the risk, but it was not statistically significant. Is that a fair assessment?
MR. LASKER: Objection to form.
THE WITNESS: Yes.
BY MR. MILLER:
Q And if ever used glyphosate as a multivariate analysis, they had an over 500 percent increased risk, but again, not statistically significant, right?
MR. LASKER: Objection to form.
THE WITNESS: Correct.
BY MR. MILLER:
Q So then we go to the Hardell study in Sweden, 2002 -- and all these are peer reviewed or they wouldn't be in your table, right?

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A Yes.
Q And what they do, they take Sweden, four northern counties, and they take studying non-Hodgkin's lymphoma and Hodgkin's lymphoma, and what they conclude -- I'm sorry. They don't. I've just been corrected.
Non-Hodgkin's lymphoma and hairy cell, right, which is a form of non-Hodgkin's --
A Hairy cell leukemia.
Q Yes, which is a form of non-Hodgkin's lymphoma?
A Depends on the time frame, but I think it was at that time. I'm not sure.
Q Okay. And they find a 300 percent increased risk statistically significant?
MR. LASKER: Objection to form.
THE WITNESS: Yes.
BY MR. MILLER:
Q Okay. Meaning that they've eliminated chance to the 95 percent.
A Yes.
Q Okay.
MR. LASKER: Objection to form.
BY MR. MILLER:
Q All right. So now we go to the next page

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of your table where you report on the study of Eriksson, an epidemiological study on non-Hodgkin's lymphoma published in 2008, and exposure to any glyphosate, they've got a doubling of the risk of non-Hodgkin's lymphoma statistically significant, right?

MR. LASKER: Objection to form.

THE WITNESS: Yes.

MR. LASKER: You're just going to read from one of those? There's two.

BY MR. MILLER:

Q They go on to look at days of use. Do you see that, sir? Less than ten days use?

A Yes.

Q Greater than ten days use?

A Yes.

Q So for less than ten days use, they have a nonstatistically significant increased risk of 69 percent, right?

MR. LASKER: Objection to form.

THE WITNESS: Yes.

(Interruption in the proceedings.)

MR. MILLER: Do you need to take a break?

THE WITNESS: No.

MR. LASKER: And for the record, for this

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whole line of questioning, we make an objection to testimony of studies based upon a table as opposed to the studies themselves. So objection based on lack of foundation as well.

BY MR. MILLER:

Q Okay. So for the Eriksson study, less than ten days use, 69 percent increased risk, not statistically significant, correct?

A Correct.

MR. LASKER: Objection to form.

BY MR. MILLER:

Q Well, tell us what the findings were for less than ten days use from the Eriksson study.

A So you just read what the findings were.

Q He's objected to me reading. He wants you to explain it.

A Oh. There was a 1.69 relative risk calculated for less than 10 years use that was not statistically significant.

Q For ten days use.

A For less than ten days use, it was not statistically significant.

Q All right, sir.

And for greater than ten days per year use, what did the Eriksson study reveal about

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non-Hodgkin's lymphoma after exposure to ten days of glyphosate?

MR. LASKER: Objection to form.

THE WITNESS: For this category of use, it was -- the relative risk was 2.36, which was statistically significant.

BY MR. MILLER:

Q And 2.36 would be how much of an increase in risk?

MR. LASKER: Objection to form.

THE WITNESS: It's better if you just say the relative risk. It's the relative risk is 2.36.

BY MR. MILLER:

Q Okay. Would it be --

A It's more than doubling.

Q It's more than doubling. All right.

And what is dose response?

A As level of exposure goes up, the risk or relative risk goes up.

Q Did we see dose response here in the Eriksson study for non-Hodgkin's lymphoma in exposure to Roundup?

MR. LASKER: Objection to form, calls for expert opinion.

THE WITNESS: Yes.

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BY MR. MILLER:

Q And the preamble to IARC said dose response was strong evidence of causality; is that true?

A Yes.

Q All right. Let's go to lymphatic -- I'm sorry, lymphocytic lymphoma B-cell. Do you see that?

A Yes.

Q Exposure to glyphosate?

A Yes.

MR. LASKER: Objection to form.

BY MR. MILLER:

Q Tell us what the findings were by Eriksson.

A For this subgroup of lymphoma, the relative risk was 3.35, which was statistically significant, because the confidence interval, the lower level was greater than 1.0.

Q And I know you don't like to put a percentage on it, but would that be a 300 percent increased risk?

MR. LASKER: Objection to form.

THE WITNESS: Roughly.

BY MR. MILLER:

Q Yes, sir. Okay.

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And unspecified non-Hodgkin's lymphoma and exposure to glyphosate, what were the findings, and were they statistically significant?

A The relative risk was 5.63, and the confidence interval did not include 1.0, so it was statistically significant.

Q Would that be synonymous with a five times risk?

A Roughly.

MR. LASKER: Objection to form. Objection to the selective questioning regarding the table.

BY MR. MILLER:

Q There was a study called Orsi, but is it fair to say none of his findings were statistically significant; is that accurate?

A I'm looking. None were statistically significant on this page.

Q Study from the Czech Republic, the Cocco study on the issue of B-cell lymphoma. And, first, B-cell lymphoma is a form of non-Hodgkin's lymphoma?

A Yes.

Q And this study, what were the findings of this study, Dr. Blair?

A The relative risk was 3.1, and the

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confidence interval was less -- the lower amount was less than 1.0, so it was not statistically significant.

Q And even though it was not statistically significant, does this inform us or aid us in reaching the conclusions the panel was charged with or -- or not? How does that play out?

A All studies inform us.

Q Okay. There was -- we've looked at the big thick hundred-and-some-page report of IARC on glyphosate. There was also a shorter summary of the findings published in Lancet. Do you remember that?

A Yes.

Q And Lancet is a peer-reviewed journal?

A Yes.

Q And would it be fair to say -- or you tell me, is Lancet a prestigious medical journal?

A Lancet Oncology is a prestigious journal.

Q Yeah.

(Blair Exhibit No. 5 was marked for identification.)

BY MR. MILLER:

Q And so I want to look at the IARC findings published in Lancet Oncology, and I've marked them as Exhibit 5. And I got a copy for you

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and a copy for counsel.

Do you want to take a break?

A No.

Q Okay. All right. So what we're looking at, Doctor, is from the Lancet Oncology, right?

A Yes.

Q And it was published hard copy May 2015; published online, it tells us, March 20th, 2015.

Do you see that?

A Yes.

Q Okay. And it's carcinogenicity of several things, which we're not involved in, but one of them we are, and that's glyphosate, right?

A Yes.

Q Okay. And it tells us there were 17 experts from 11 countries who met at the International Agency for the Research on Cancer to assess the carcinogenicity of these products, including glyphosate, right?

A Correct.

Q Okay. There was only one cancer that the committee found to be associated with glyphosate, right?

MR. LASKER: Objection to form.

THE WITNESS: Yes.

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BY MR. MILLER:

Q And that's non Hodgkin's lymphoma?

A Correct.

Q And the mechanistic evidence was what, sir?

MR. LASKER: Objection to form. Lacks foundation.

BY MR. MILLER:

Q I'm sorry. You can answer. He objects, but you can answer.

A That it was genotoxic and had another possible effect with oxidative stress.

Q Did you help author this article in Lancet?

A Yes.

Q Okay. You say here: "Glyphosate" -- and I'm on page 2 -- "is a broad spectrum" -- there it is right there -- "broad spectrum herbicide currently with the highest production volume of all herbicides. It is used in more than 750 different products for agriculture, forestry and home application. Its use has increased sharply with the development of genetically modified glyphosate-resistant crop varieties."

And that was part of the research that

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you folks developed in preparing this report?
MR. LASKER: Objection to form.
BY MR. MILLER:
Q You can answer.
A It was part of the evidence we reviewed.
Q Okay. And we've just been talking about them, but I want -- "case-control studies" -- those are the studies that we just talked about, right?
A Yes.
Q Okay. "-- of occupation exposure in the United States, Canada, and Sweden, reported increased risk for non-Hodgkin's lymphoma that persisted after adjustment for other pesticides."
What does that mean?
MR. LASKER: Objection to form.
THE WITNESS: It means that's the multivariate analysis. You include other things that might include a disease in the analysis until you know which is doing what.
BY MR. MILLER:
Q Okay. Now, for the first time we're talking about a study here, the AHS study. I want to ask you about it: "The AHS cohort did not show a significantly increased risk of non-Hodgkin's lymphoma."

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So there was a study that did not show the association between -- between glyphosate and non-Hodgkin's lymphoma, right?
A Yes.
MR. LASKER: Objection to form.
BY MR. MILLER:
Q And in fact, you were the author of that study, or one of them, right, sir?
A One of the authors.
Q And in spite of being the author of the study that didn't show the association, you voted that in fact there was an association based on the totality of the evidence, right, sir?
MR. LASKER: Objection to form.
THE WITNESS: Yes.
BY MR. MILLER:
Q Okay. All right. "And glyphosate has been detected in the blood and urine of agricultural workers indicating absorption."
What does that mean, sir?
MR. LASKER: Objection to form, lacks foundation.
BY MR. MILLER:
Q You can answer.
A If it's in the blood, it had to get there somehow.
Q Sure.
A So it had to be absorbed through some tissue.
Q After you and your working group volunteered, looked at all of this material, concluded there was a positive association between glyphosate and non-Hodgkin's lymphoma, did Monsanto attack you and other members of the IARC panel?
MR. LASKER: Objection to form.
THE WITNESS: I don't think I quite know how to answer that.
BY MR. MILLER:
Q I understand. Let's take a look at this document, and it will I think help -- helps us look at it.
This is going to be marked as Exhibit 10 -- is it 10 already?
MR. LASKER: 10?
MR. MILLER: Six. Oh, it's six. Wrote the wrong one. Hardest part of my job.
All right. Six. It shall be marked as Exhibit 6. And I have a copy for you, Doctor, and a copy for counsel. Here you go.
(Blair Exhibit No. 6 was marked for

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identification.)
BY MR. MILLER:
Q This has been produced by IARC on these issues, and I want to ask you a little bit about it, okay?
Have you seen this before, Doctor?
A Well, I -- I think so.
Q Well, let's look at it. If at any time you want to stop and read it, it's okay with me. All right. I don't want to -- I don't want to go too fast and don't expect you to have read everything.
But this is promulgated by IARC. It says: "Originally prepared as a confidential briefing for government councilmembers on IARC evaluation of glyphosate and requests for meetings from CropLife."
Do you know who CropLife is?
A It's an organization that includes many pesticide manufacturers on it.
Q And IARC says here in point number 2 that: "Monsanto rejected and attacked the IARC findings, calling it junk -- junk science, and immediately requested that the World Health Organization retract the International Agency for the Research of Cancer evaluation, and privately lobbied

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the USEPA to reject IARC's findings."
You see that?
A Yes.
MR. LASKER: Objection to form, foundation, hearsay. 601, 801.
BY MR. MILLER:
Q Have you been aware --
THE REPORTER: I'm sorry?
MR. LASKER: I'm sorry. 601, 602, 801.
BY MR. MILLER:
Q Have you felt some of this pressure from IARC -- excuse me -- from Monsanto?
A Well, I know -- I've seen this.
Q Okay. I didn't know that. Okay.
A I mean, I've seen that sort of information, yes.
Q Yes.
MR. LASKER: Same objection.
BY MR. MILLER:
Q Did you help prepare this or do you know who did?
A No.
Q Probably Kathy Geiten, you think, or --
MR. LASKER: Objection to form.
THE WITNESS: I don't know.

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BY MR. MILLER:
Q Okay. On 4d, Monsanto claimed, quote: The data evaluated do not represent, quote, real world exposures.
But IARC writes: "This ignores the fact that cancer epidemiology based on real world exposures associated with cancer risk in humans is the cornerstone of IARC Monograph evaluation."
That's true, isn't it?
MR. LASKER: Objection to form.
Counsel, the witness has already said he doesn't -- is not sure he has seen this document and he did not write the document.
BY MR. MILLER:
Q You can answer.
A Epidemiology is based on real world exposures. That's what humans get.
Q And is epidemiology the cornerstone of what IARC Monographs are about?
A It is at least one of them.
Q And are -- and is epidemiology, is it based on real world exposures?
A Yes.
Q Okay. They go on to say that: "Other members of the working group and IARC Secretariat are

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now being subject to intimidating letters from Monsanto lawyers."
Did you get a letter from Monsanto lawyers about this?
MR. LASKER: Same objection.
BY MR. MILLER:
Q It's okay to answer.
A No.
Q Did Monsanto lawyers call you?
A I don't think so.
Q Okay. You have spoken to one of the lawyers that represents plaintiffs at one time, right, just to be fair about all this?
A Yes.
Q But you're not an expert for either side in this case, are you?
A No.
Q Okay. Are you aware that Monsanto has been lobbying the House of Representatives to cut off funding for IARC because of this?
MR. LASKER: Objection to form.
BY MR. MILLER:
Q You can answer.
A Yes.
Q How do you feel about that?

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MR. LASKER: Objection to form.
THE WITNESS: I don't see why that's pertinent.
BY MR. MILLER:
Q I -- pertinent in the sense that if scientists are being intimidated for their conclusions, that's probably relevant in this lawsuit.
MR. LASKER: Objection to form.
THE WITNESS: Do I have to answer?
BY MR. MILLER:
Q No. If you don't want to, I will withdraw the question. Okay?
MR. MILLER: All right. Why don't we take a five-minute break and --
THE VIDEOGRAPHER: The time is 10:14 a.m. We're going off the record.
(Recess.)
THE VIDEOGRAPHER: The time is 10:33 a.m., March 20th, 2017, and we are on the record with video 2.
BY MR. MILLER:
Q So what we were just talking about off record, and we shared with your counsel, it's a protective order that the court wants us to have

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witnesses sign before they look at documents. We haven't had any problems. There are lots of experts on both sides who have signed it. They've looked at documents.

I will be frank with you, Dr. Blair, my experts have already seen the document I'm going to show you, so you wouldn't be the only one that looked at it. I have lots of fellows and gals who have looked at it. But we all know you're a man of honor, you sign this, you're not going to show it to anybody. So that's all we're asking.

A So that's not my question.

Q What's your question?

A My question is I don't -- I do sign it, I never tell anyone, it gets leaked, and I get accused because people know I had it. What's my protection?

Q Well, I mean, I see your point. I mean, I'm in the same boat. I've signed --

A There is none.

Q Well, I guess honesty is your protection. You really won't leak it, so you won't -- I've seen -- and you guys can speak to this, but I've seen one litigation one lawyer who leaked something, and Zyprexa comes to mind, and there is some sort of coding in the documents or something, I don't know,

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but they will know it's not you. We're not going to give you a copy. You're going to leave without a copy anyway, so you couldn't leak it.

MR. GREENE: Dr. Blair, I've had a number of cases where we've had confidentiality agreements because of documents being produced in my cases by the defendant, and my clients have signed it. It's just part of the discovery process. And I've never had any repercussions from anybody or anything dealing with these agreements.

I would suggest, as your counsel, that you can sign this.

THE WITNESS: Okay. Okay.

MR. MILLER: Okay, great. Do you need a pen?

THE WITNESS: I need a pen.

MR. MILLER: Yes, sir. Here you go, sir.

MR. GREENE: Mr. Miller, can I keep a copy of it?

MR. MILLER: Absolutely. Absolutely.

THE WITNESS: This is me here, right?

MR. MILLER: Yes, sir.

THE WITNESS: (Witness signs document.)

MR. MILLER: All right. Thank you, Doctor.

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All right. You've got it. Okay.

Here you go, Jeffrey. You're in charge of those, and if you want, we will send a copy of the signed one.

MR. GREENE: Just out of curiosity, do you want me to sign something?

MR. MILLER: I don't think you have to. I don't think it's required.

MR. LASKER: Actually, it probably is.

MR. MILLER: Okay. Well, then hand it on down.

MR. LASKER: Since you're not counsel of record.

MR. GREENE: (Counsel signs document.)

(A discussion was held off the record.)

BY MR. MILLER:

Q All set?

All right. Doctor, thank you for your patience.

I want to ask you a little bit about the North American Pooled Project, the NAPP. It's "Pooled analyses of case-control studies of pesticides and agriculture exposures, lymphohematopoietic cancers" --

A Yes.

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Q -- "and sarcomas."

Are you one of the authors of this new study?

A One of the authors of these papers, yes.

Q Yes. And I will mark it as Exhibit 7, a poster presentation concerning the NAPP study. All right?

(Blair Exhibit No. 7 was marked for identification.)

BY MR. MILLER:

Q And here is a copy, sir. Thanks.

And that's one of the reasons we had you sign a protective order is because I got this from the files of Monsanto. Okay.

A Then I have a question.

Q Sure.

MR. LASKER: For the record, I don't think this document was marked "Confidential." It's a public document.

MR. MILLER: This is a public document, but my copy is marked "Confidential." I'm just being --

THE WITNESS: Yes, it's published in the proceedings.

MR. MILLER: Yes, I understand.

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MR. LASKER: I don't think these are confidential documents.
MR. MILLER: Yeah, right, this is not a confidential document.
MR. LASKER: It doesn't say "Confidential" on this.
MR. MILLER: All right, it's not a confidential document.
BY MR. MILLER:
Q So let me ask you about Exhibit 7, and just generally, let me ask you about the North American Pooled Project. Please tell me something about this study that you're one of the authors of.
MR. LASKER: Objection.
THE WITNESS: Pooling is assembling data from different individual studies and putting it together for analysis, which makes the analyses more robust because there are larger numbers.
BY MR. MILLER:
Q And are you still -- is this study still ongoing?
A Yes.
Q And has it generated some results?
A I think only this, although maybe there is one other paper on another cancer. I sort of

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forget for sure now. But other things are ongoing.
Q Okay. Got it.
Do you know John Acquavella?
A I do.
Q How do you know John Acquavella?
A John is an epidemiologist that has studied farmers and pesticide exposures.
Q In the agriculture workers study, did -- which you were an author of we just spoke briefly about, right?
A Yes.
Q Previously. Did John Acquavella provide some of the input on how to collect the data in that study?
A No.
Q No? Okay. All right.
(Blair Exhibit No. 8 was marked for identification.)
BY MR. MILLER:
Q All right. Well, let me show you what I marked as Exhibit 8, and this is a series of e-mails from Dr. Acquavella that we've gotten from -- from Monsanto. And you probably haven't seen that before. If you want a second to look at it, that's certainly fine.

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A (Perusing document.)
Q And what I wanted to ask you about was on the second page.
A (Perusing document.)
Q And this gentleman, I believe his name is Bill Haydens -- we've actually had the privilege of taking his deposition, an employee of Monsanto -- he talks about the results for -- am I -- wait. Let me see. Okay.
-- results unadjusted for other pesticides, subjects who ever used glyphosate had a significantly elevated non-Hodgkin lymphoma risk, odds ratio 1.43; confidence interval, 1.11 to 1.83. Glyphosate used for 3.5 years increased SLL risk 1.98; confidence interval, 0.69 to 4.39.
Handling glyphosate for two days was associated with significantly higher odds of non-Hodgkin lymphoma. Odds ratio, 2.42; confidence interval, 1.4, 3.96.
This is a pooled analysis from the NAPP study, right, sir?
MR. LASKER: Objection to form. I think you started off saying that Bill -- this is just is a reprint of a presentation. This isn't any of this Bill Haydens' words.

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MR. MILLER: I'm not suggesting these are Bill Haydens' words.
BY MR. MILLER:
Q These are the numbers, the findings from the NAPP study, right?
MR. LASKER: Objection to form.
THE WITNESS: I guess. I wouldn't want to -- I think so. But --
BY MR. MILLER:
Q Is this data published now?
MR. LASKER: Lack of foundation.
BY MR. MILLER:
Q Or any data, it's not published --
A Only the abstract.
Q I see. And when do you anticipate publication of the final NAPP study?
A I'm not sure when that will be out.
Q Within a year, do you think?
A Probably within a year.
Q Okay. Do you know what journal it's been presented to for publication?
A I don't think it's been submitted yet.
Q I see. Okay. All right.
But these numbers are generally consistent with what you remember the findings being?

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A Yes.
(Counsel conferring.)
BY MR. MILLER:
Q Okay. I'm going to show you a publication that you and others published in Environmental Health Perspectives in February of 2015, and just ask you a few questions about it, and I'm getting about to where I'm about at the end of the line with my questions. You've been very patient with me.
Here is a copy for you, sir.
MR. MILLER: And I have a copy for counsel.
(Blair Exhibit No. 9 was marked for identification.)
BY MR. MILLER:
Q All right. This is a publication "IARC Monographs: 40 Years of Evaluating Carcinogenic Hazards to Humans."
Do you remember that?
A Yes.
Q And you're one of the authors?
A Yes.
Q All right. I just put the sticker on the wrong copy. Hang on.

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All right. A few questions on it, and then we'll move on.
Basically, what you were looking at here was to look historically at IARC's findings to see if they had gotten it right or wrong over the years. Is that a fair assessment?
A And to discuss the process that they go through.
Q And what you concluded, and correct me if I'm wrong, was -- was that IARC got it right most of the time, or wrong?
A That they get it right most of the time.
Q It says, for background: "Some critics have claimed that IARC working groups, failures to recognize study weaknesses and biases of working group members, have led to inappropriate classification of a number of agents as carcinogenic to humans."
That was the background for which caused you to want to research this subject, right?
A Yes.
Q And what did you do to investigate this to see if in fact IARC had been getting it right more often than not?
MR. LASKER: Objection to form, soliciting expert opinion.
BY MR. MILLER:
Q You can answer.
A Well, we looked at the process that IARC followed, the historical examples of what they had done, and whether or not later changes were made to the evaluations to indicate general agreement with what IARC had done or not.
Q And you concluded, "you" being this group of scientists, concluded that these recent criticisms are unconvincing, right?
MR. LASKER: Objection to form, beyond the scope.
THE WITNESS: Yes.
BY MR. MILLER:
Q I'm not real good with numbers, but I'm going to give it a try. One, two -- there's over 110 scientists that authored this paper.
A Right.
Q So you're 40 years in -- in your field now?
A Yeah, right.
Q And over that 40 years of studying this issue, you have observed that farmers have an increased incidence of this hematopoietic cancer,

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right?
A Among others.
Q And non-Hodgkin lymphoma is a cancer of the hematopoietic system, right?
A Yes.
Q And you agree farmers have a good recall of what pesticides they've used, right?
A Yes.
Q Even homeowners are aware of what they spray on their products -- I mean on their gardens and their lawns?
A Less so than farmers.
Q Are they good, though, or no good at it, do you think?
A It depends.
Q And exposure misclassification can occur in a cohort study, can't it?
A It can occur in all studies.
Q Yes, sir. Confounding is a problem but it rarely occurs; is that fair?
MR. LASKER: Objection to form.
THE WITNESS: That's fair.
BY MR. MILLER:
Q Exposure miss -- exposure misclassification most likely causes false negatives;

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is that fair?
A Correct.
MR. LASKER: Objection to form, beyond the scope, calls for expert opinion.
MR. MILLER: I've taken enough of your time. I may come back and ask some rebuttal questions. I'm now going to yield the floor to the attorneys for the Monsanto Corporation.
THE WITNESS: Okay.
MR. MILLER: Thank you so much for your time, Dr. Blair.
MR. LASKER: Go off the record.
THE VIDEOGRAPHER: The time is 10:52 a.m., And we're going off the record.
(Recess.)
THE VIDEOGRAPHER: The time is 10:57 a.m., and we're back on record.
CROSS-EXAMINATION
BY MR. LASKER:
Q Good morning, Dr. Blair. My name is Eric Lasker on behalf of Monsanto. I have some questions for you this morning.
A Okay.
Q Let's start off where you left off with plaintiffs' counsel. You have been doing research

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regarding cancer in farmers for, what, 40 years now?
A Close.
Q And, in fact, you have publications on cancer and hematopoietic cancers in farmers dating back, from my research, at least to 1979?
A Yes.
Q And there have been epidemiological studies that have associated farming with hematopoietic cancers and non-Hodgkin lymphoma dating back to the 1960s, right?
A Yes.
Q And that was well before glyphosate was on the market, correct?
A Yes.
Q So it's fair to say that there is some -- something going on with farmers that appears to be associated with an increased risk of non-Hodgkin lymphoma that predated glyphosate being on the scene, right?
A Yes.
Q There is something going on with farmers and non-Hodgkin's that is associated with an increased risk -- strike that. Strike that.
There is something going on with farmers and their exposures that is leading to an increased

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risk of non-Hodgkin lymphoma that we know for a fact can't be glyphosate, correct?
A Yes.
Q And when plaintiffs' counsel was asking you about the issue of confounding, that is in epidemiology when there are other factors that may be in play that cause an association between a disease in a certain population aside from the one you're looking at, correct?
A That is part of the definition of "confounding." Only part.
Q But for farmers, when we're studying farmers today and we're looking at various pesticides, and in particular, when we're looking at glyphosate, we know that there are other factors out there that would be independent of glyphosate that would increase risks for farmers of non-Hodgkin lymphoma, correct?
A Probably. When you say we know for a fact --
Q Well --
A -- is I think not true.
Q Okay. But when you're studying glyphosate in epidemiology, when you're focusing on glyphosate in farmers, you want to make sure that you

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control -- that you can control for those other possible confounders to be sure that you are actually studying glyphosate, correct?
A Yes.
Q Now, your research into farmers has included both case -- what's called case-control studies and cohort studies, correct?
A Yes.
Q And you played a significant role -- I think this was referred to briefly in your testimony with questions from plaintiffs' counsel -- about the formation of the Agricultural Health Study, correct?
A Correct.
Q And the Agricultural Health Study is a collaborative effort involving the National Cancer Institute, the National Institute of Environmental Health Sciences, and the United States Environmental Protection Agency, correct?
A Those three, and also the National Institute of Occupational Safety and Health, and the University of Iowa.
Q And the Agricultural Health Study is what's called a cohort study, correct?
A Yes.
Q And that is when you get a group of

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individuals, and in this case, farmers, correct?
A Yes.
Q And you --
A And their spouses.
Q And their spouses.
And you find out various exposures they've had, various facts about them before they have any -- the disease in question that you're going to be studying, correct?
A Correct.
Q And then you follow them over time to determine whether or not that disease develops --
A Yes.
Q -- or certain diseases develop?
And in this case you brought together -- how many -- how many farmers and their wives did you gather information on in your study?
A About 80,000.
Q And for those 80,000 then, you obtained information about all sorts of different exposures that they may have had, correct?
A Yes.
Q And that included obtaining information regarding any exposures to glyphosate, correct?
A Yes.

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Q And at the time you gathered that information, you were not -- you were looking at exposures, historical exposures going back in time, correct?
A Yes.
Q And the Agricultural Health Study was initiated and formed to address some of the limitations in the earlier case-control studies that had been conducted regarding risks of pesticides or other exposures in farmers, correct?
A It -- it was initiated and formed to provide a different design to look at the same issue.
Q It was initiated, at least in part, to address some of the limitations of the case-control studies, correct?
A Yes.
Q And, for example, one of the limitations of the case-control studies was something called recall bias, correct?
A It's a potential limitation.
Q The Agricultural Health Study was initiated in order to have a study that was examining the possibility of exposures, for example, glyphosate and non-Hodgkin lymphoma that did not have this problem with recall bias, correct?

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A Correct.
Q The issue of recall bias is that when you are asking individuals who have a disease already about their past exposures, the concern is that they will recall more exposures than people who don't have the disease, correct?
A That's a concern.
Q If you have recall bias, then you're going to have an artificial increase in that odds ratio, those numbers we were looking at previously, that is due to the fact that the individual with cancer just recalls more exposures, not that he actually had more exposures, right?
A Of course, it depends on the direction of the bias. It can be either direction.
Q But for recall bias, if a person with cancer recalls more exposures than a person who doesn't have cancer and hasn't been thinking about that --
A If they record more exposures, that would be true. If they recalled less, it would be the other direction.
Q Understood. And so the Agricultural Health Study was designed to avoid that problem altogether, correct?

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A Correct.
Q The Agricultural Health Study was also designed to try and deal with issues of misclassification of exposures by going to farmers who you -- you testified earlier have better recall and also periodic follow-up, correct?
A Yes.
Q At the time of enrollment and -- and if you don't have this recollection, I understand. I will show you some studies and we can talk about it.
But at the time of enrollment, the members of the AHS cohort had an average of about 15 years of experience mixing or applying pesticides, correct?
A Sounds about right.
Q And you have been -- just to step back, you've been researching the issues of potential association between pesticides and cancer for nearly your entire professional career, correct?
A Correct.
Q The effort to determine pesticides that might be associated with cancer has been your life's work, correct?
A Well, one of them.
Q You certainly invested a lot of time into

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looking for potential expose -- associations between pesticides and hematopoietic cancers, correct?
A Yes.
Q When you heard that IARC was going to look at this issue that you've been studying for 40 years of pesticides and cancer, you reached out to them to ask them about what their -- what analyses they were going to undertake, correct?
Let me strike that and ask again.
When you learned that IARC was going to be looking at pesticides and cancers, your life's work, you contacted IARC about that, correct?
A Well, when IARC start -- that may be true, but just let me explain a little. When IARC decides they're going to do something, they send out information to people who might be able to provide them with relevant papers and that sort of thing. So if that happened, then I probably contacted them.
Q Now, Dr. Blair, you provided counsel to both sides with certain documents from your own files.
A Yes.
Q Well, I'm going to ask you some questions about some of those documents. I know we haven't talked about them yet with plaintiffs' questioning.

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Let me mark as the next exhibit in line, and we will make this --
MR. LASKER: How have we been doing this? Has it just been sequential?
MR. MILLER: I would continue with the numbering.
What is the next number?
MR. LASKER: It's 10.
MR. MILLER: 10? That will continue.
(Blair Exhibit No. 10 was marked for identification.)
BY MR. LASKER:
Q And this is an e-mail, Dr. Blair, that we obtained from your files, just in order to refresh your recollection. This is dated March 19th, 2014, and this is an e-mail from you to Kurt Straif, correct?
A Yeah.
Q And who is Kurt Straif?
A He's the head of the IARC Monograph program.
Q And seeing this e-mail, does this refresh your recollection as to whether or not you reached out to IARC after you found out that they were going to be conducting an analysis of pesticides and --

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A Yeah, after the announcement about the meeting had occurred.
Q Now, do you recall how IARC responded to your e-mail?
A No.
(Blair Exhibit No. 11 was marked for identification.)
MR. LASKER: And counsel.
BY MR. LASKER:
Q And I'm going to show you a highlighted document that I've highlighted to help you focus on parts of this.
(A discussion was held off the record.)
BY MR. LASKER:
Q So, Dr. Blair, in response to your inquiry, Kathryn Guyton sent you an e-mail back. Who is Kathryn Guyton?
A She was the -- like the IARC coordinator for that evaluation of pesticides that included glyphosate.
Q And Kathryn Guyton asked whether you would be interested in participating in the Volume 112 meeting of IARC, correct?
A Yeah.
Q And do you recall how you responded to

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that request?
A I think initially I was saying, well, maybe not.
Q Okay. Let's mark the next exhibit in line. Well, strike that.
Do you recall having a concern about serving on working group 112 because the working group would be looking at many of the studies that you had been conducting that you had published as part of your life's work?
A Yep, that's one of them.
Q Your concern was that, given that this was your life's work, it might be viewed as -- by others as improper for you to be sitting on a committee that was going to be evaluating whether or not what you had been researching for 40 years actually indicated an association of certain pesticides and cancer, correct?
A Correct.
Q IARC continued, though, to solicit your involvement in this working group despite that concern, correct?
A Yes.
Q And in fact, Kathryn Guyton of IARC asked that you chair the entire committee that was going to

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be looking at this issue, correct?
A Yes.
Q When plaintiffs' counsel showed you the part of that preamble that asks individuals on the working group to disclose potential interests that might give rise to questions of bias, does that disclosure form require individuals to disclose their prior research activities and whatever interest they may have in the outcome of a monograph because of those research activities?
A I'm not sure.
Q Did you fill out a conflict of interest form that listed as conflicts your life's work in trying to find associations between pesticides and cancers?
A I -- actually, I don't recall.
Q You don't recall doing that?
A I mean, I had to fill one out, but generally, the -- the conflicts aren't the research you have done. The conflicts is hire for money, that sort of thing.
Q So if there are individuals invited to be members of IARC working groups who have personal interests in the outcome of the IARC evaluation but do not have financial conflicts, that information

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does not have to be disclosed, correct?
A I don't think so.
Q Dr. Blair, the IARC working group that considered glyphosate also review -- reviewed four other pesticides, correct?
A Yes.
Q The other four pesticides were TCVP, parathion, malathion, and diazinon, correct?
A Yes.
Q For each of these five pesticides, am I correct that there were four different subgroups formed: One for exposure, one for epidemiology, one for animal toxicology and one for mechanism?
A Right.
Q And I think you stated that maybe three months before the meeting, individuals on the working group would be tasked to look at certain parts of the science with respect to the various pesticides that were being reviewed, correct?
A To look at the certain parts of?
Q Certain parts of the scientific literature.
A Yes, right.
Q The members of the working group would not be looking at all the scientific literature on a

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pesticide before they went to the meeting, correct? For example, you didn't look at anything outside of epidemiology, correct?
A Up until shortly before the meeting when drafts, other drafts were distributed on it.
Q Okay.
A But mainly you focused on your discipline and the working group you were in, yes.
Q Is it also fair to say that prior to that week -- that one-week meeting, you would be focusing on specific assignments that had been given to you to write certain parts of the Monograph?
A That would be the main focus, not the only focus. And the next focus is the subgroup you're in, to look at that literature because that's where your expertise lies.
Q Okay. And with respect to working group 112, the working group members split up the work that they had with respect to all five of these pesticides and all four different subgroup analyses, correct?
A Yes.
Q And I'd like to show you a document we received from another IARC working group member, Dr. Ross, and I think there was some testimony about him earlier today. And this is going to be --

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MR. LASKER: Exhibit number again? Marked this Defense Exhibit 11, is that the correct number?
MR. MILLER: 12.
MR. LASKER: 12?
(Blair Exhibit No. 12 was marked for identification.)
MR. MILLER: Yeah, 11 was an e-mail from Kathryn Guyton. And you have a copy of 12 --
MR. LASKER: Yep.
BY MR. LASKER:
Q Actually, Dr. Blair, if you can just trade -- oh, no, never mind. Got one.
Give this one -- you can actually have this one so the court reporter can have the official exhibits.
And, Dr. Blair, I don't expect you to remember the various assignments that individuals on the working group had, but if this is -- if you look at the second page of this document, on the bottom it says "last update," and you can look at the one in your hand, but "Last update, November 20, 2014." So this is about three-and-a-half months before that working group meeting, the plenary session, the one-week meeting we've talked about, correct?

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A Yes.
Q So that's about consistent with your testimony earlier that it was about three months beforehand that people started getting to work and looking at some of the science, correct?
A Yes.
Q And for working group 112, they had a lot of different eyes of science that they had to look at, correct? They had -- what is it, one, two, three, four, five, six, seven, eight, nine, ten, eleven, twelve, thirteen, fourteen, fifteen, sixteen -- seventeen different sections of science or groups of science that they had to look at for malathion, correct?
A Yes.
Q And there was equally -- it looks like about 15 or more bodies of scientific literature they were looking at for parathion. Correct?
A Yes.
Q And there were 15 categories of science for diazinon and also for glyphosate and for tetrachlorvinphose (phonetic). Is that correct?
A Phos.
Q Phos.
And for each of these different

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pesticides, individual members of the working group were assigned responsibility to look at the scientific literature in that area, correct, and then to prepare the initial draft analysis that the working group would look at during that one-week meeting, correct?
A Yes.
Q And I've looked through this listing of assignments, and correct me if I'm wrong, but you were not given any assignment to write up any individual portions of the working group's draft Monographs prior to the meeting; is that right?
A No. Bottom of the second page, "Studies of Cancer in Humans on Tetrachlorvinphos."
Q Okay. So your focus prior to the meeting and prior to the one-week meeting was to review the literature on tetrachlorvin -- tetrachlorvinphos?
A Tetrachlorvinphos, yes.
Q And prepare a report that would then form the basis of the discussion of the epidemiology subgroup on tetrachlorvinphos at that meeting, correct?
A Yes.
Q And that was the focus of the research you were doing or the study you were doing prior to

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that meeting, correct?
A Tetrachlorvinphos was in those studies, that's right.
Q And for each of the individual pesticides, and, for example, with respect to glyphosate, there was particular individuals who were the people who during those -- that three-month period prior to the meeting were looking at the literature with respect to glyphosate. So, for example, with epidemiology, that was Dr. Forrest -- Forastiere, correct?
A Forastiere.
Q Forastiere. And for animal toxicology, that was Dr. Jameson, correct?
A Yes.
Q Those would been the individuals -- those would have been the individuals who within that three-month period were -- prepared an analysis on either the epidemiology of glyphosate or on animal studies and glyphosate that would then be presented to that working group during that one-week meeting, correct?
A Preparing a document and the tables, yes.
Q You mentioned previously that those documents then were distributed to the working group

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members shortly before the meeting; is that correct?
A Sometime before the meeting, shortly. I must admit I don't quite remember the time frame, but of --
Q Do you remember -- do you remember how many days before the working group meeting --
A No.
Q -- you obtained copies of any of the --
A That I don't. It's because there were -- there's websites where they're on, and you can go to the website. The ones you -- people pay most attention to, of course, is the working group you're in, but the documents are fed into a website that is available to group members.
Q So there's no process to actually physically send to working group members any analyses of these pesticides or glyphosate before the working group meeting --
A I don't think that was the case. I think you used the website.
Q So for individual members of the working group, they either did or did not look at -- go to the website to find out something before the meeting began, correct?
A I assume so, yeah.

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Q Some of the working group members may have just shown up at the meeting and seen these analyses for the first time when they -- when the working group plenary session -- or when the working group meeting began, correct?
A I have no way of knowing.
Q Well, for you personally, would I be correct in my understanding that you did not look at any analyses for glyphosate, for example, for anything other than epidemiology before you got to that meeting?
A No, I don't think that's correct. I don't remember how many of all the things I scanned, but I did at least look at a lot of -- whether I looked at every single one, I don't know, but I looked at a lot of them because I knew you were going to have to evaluate things.
Q Do you recall how many days that was before the meeting began that you looked at those?
A No.
Q And you do not know what was reviewed by other working group members before that one-week meeting began, correct?
A No, other than each draft was assigned a secondary reviewer, and so every draft had a

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secondary reviewer who looked at it before the meeting.
Q Okay. So it would -- there would be at least two people of the working group, but you're not sure how many others who would have looked at drafts of analyses before that one-week meeting began?
A True.
Q The bulk of the work then of doing the analysis for the working group of all the data took place during that one-week session, correct?
A Well, that -- I mean it's a little hard to answer because a lot of work goes into reviewing all the papers by the people who did -- wrote the draft and so forth, but the bulk -- now I don't know, this is adding up minutes.
Q Right.
A I don't know.
Q So putting aside sections for which an individual was the principal author or maybe the secondary author, the bulk of the work then for the working group in analyzing the scientific literature would take place during that one-week session, correct?
A Well, a lot of it would. The bulk -- I'm just quibbling with the bulk because I don't have any

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information to tell you about that other than those documents are available.
Q So you don't know one way or the other whether --
A I don't know one way or other. So I can't answer your comment where the bulk of it was --
Q So it's possible that working group members would be looking at the science for the first time at the beginning of that one-week meeting or it's possible not, you just can't say one way or the other; is that fair?
A I can't say one way or the other.
Q So let's talk about that one-week period then. During that one week, the working group needed to research -- specifically with Volume 112, the working group needed to reach classifications under the IARC scheme of cancer rating for five different pesticides, correct?
A Correct.
Q So is this a -- is this -- are you working through weekends, or is it a five-day workweek, or how long was this?
A You work however much time you have available while you're there. It often means nights and weekends.

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Q So for the one-week session for each of the five pesticides, you had maybe a day or a little bit more of a day of time to be able to reach a determination, correct?
A Doing the division, that is correct. But you understand that it isn't done -- things are done first all things on one day and all things on the next.
Q Right.
A They repeat it and come back to it.
Q Understood. And if I understood correctly, during the first week of the week the working group splits up into those subgroups, correct?
A Yes.
Q So you have subgroup meetings for the first part of the week, and then you meet together as a plenary group, the entire group about midway?
A There's -- there are plenary sessions every day. Always plenary sessions. In the early part, they are more instructive rather than evaluative.
Q When does the working group as a whole first have an evaluative meeting to reach an assessment?

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A I would be guessing at what day that actually comes on.
Q Sometime in --
A I mean it's not the first day.
Q The evaluative process of determining whether or not the science in particular categories point one way or the other, first is conducted by the subgroup that has responsibility for that area, correct?
A Correct.
Q So, for example, when you broke into the epidemiology subgroup, you would be then looking at the analyses that were prepared by the individual assigned for each of five different pesticides, correct?
A In some serial order.
Q Yes, obviously.
You would then listen to the presentations of the individual working group member who had been assigned to prepare the analysis for that pesticide, correct?
A Prepare the document for that pesticide.
Q And over the next maybe two or three days, the subgroup would go through each of those analyses and reach their conclusion based upon the

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subgroup expertise as to how they are classified as science with respect to each of those pesticides, correct?
A Would go through the documents of the review of the papers to come to that conclusion. I just object to your use of "analyses."
Q Okay. I'm sorry.
A Some of the times it's just putting things in a table. That's hardly an analysis. It's an assembly of the data.
Q Fair clarification. So let me go back then.
The -- the work that was being done during that three-month period before the meeting, the responsibility was to assemble the data and put into tables. It was not to come up with an evaluation during that prior period, correct?
A Right.
Q So the evaluation process doesn't begin until the start of that one-week period, correct?
A Correct.
Q So -- and then during that one-week period for Monograph 112, which is the monograph for glyphosate, the working group was then doing the analysis for five different pesticides, correct?

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A What analysis was done and evaluation of five different pesticides.
Q So the analysis and evaluation that led to the classification of glyphosate was -- and I recognize it was split over the week -- but was a total combined time of roughly a day plus doing the math, correct?
A Understanding it's just doing the math, and I don't actually remember how many -- how much -- how many hours it took, and it varies by how easy it is to come to a decision.
Q So you would have maybe a day or two of analysis and evaluation that went into the IARC working group's classification of glyphosate, correct?
A Roughly correct.
Q So --
A But spread over the five days.
Q Right.
A So it -- you know, it's important that it's not just done this day and then it's done.
Q Right.
A It's done, you look at it, you think about it, you come back to it, you look at it and think about it, you come back to it.

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Q Right.
A That's a different process than just you got this day.
Q Understood. And that would be the same process for the other subgroups. So, for example, IARC's -- the IARC working group analysis of the science with respect to animal toxicology of glyphosate would have been conducted with different -- over different days for a total amount of time, but maybe a day plus for glyphosate, correct?
A In the same procedure of looking at it, evaluating, reconsidering, coming back a day later and so forth.
Q The analysis of glyphosate science with respect to mechanism of toxicity and the like, that would have been a combined total time of approximately a day or a little bit more than a day for the IARC working group, correct?
A Again, in the same procedure that people go through, just doing the math. I don't actually know how much time they spent.
Q Well, it's obviously something less than a week's worth of time, some portion, one-fifth or a little bit more of the time --

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A Yes.
Q -- they spent on glyphosate.
So that's a lot of work in a short period of time.
A Except the documents are already there.
Q So -- but for the analysis, it's a lot of work in a short period of time. The analysis of the --
A No. Again, you keep saying "analysis."
Q Okay.
A It's not an analysis. It's a document with tables that have been prepared that the people look at.
Q I understand. My -- my mistake. Let me clarify.
The evaluation analysis only takes place during that one-week period, correct?
A Yes.
Q And for the working group for that one-week period where you actually do the evaluation and the analysis of five different pesticides with four different categories of science, that's a lot of work in a week.
A It is a lot of work.
Q For glyphosate -- well, strike that.

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When you have the first plenary session, which is evaluative -- I think that's the term you used -- well, strike that.
At the end of that process where the subgroup is doing its evaluations of the literature in its -- in its discipline, does it then provide a presentation to the plenary of what the subgroup has determined is its conclusion with respect to that -- the strength of that science for that pesticide?
A Yes.
Q So the epidemiology subgroup would give its presentation to the full plenary session on the epidemiologic evidence for each of the different pesticides, correct?
A Yes. Not all at one time. Again, as they come along.
Q Right. Understood.
For glyphosate, the full working group ultimately determined that the epidemiology on glyphosate and cancer was limited, right?
A For the full working group?
Q Yes.
A Well, for the full working group, it's listed as probable.
Q I'm sorry. I'm limiting it just to the

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epidemiology, not for the -- not for the full analysis.
A Yes.
Q But the full working group does --
A Does look at each one of them, yes.
THE REPORTER: You're talking at the same time. It's?
THE WITNESS: It was limited.
BY MR. LASKER:
Q So for the full --
A That was a recommendation of the subgroup, and the working plenary group agreed.
Q So just so I'm clear, the IARC working group, both the subgroup and the full working group, determined that the evidence of glyphosate with respect to non-Hodgkin lymphoma was limited, correct?
A For epidemiology, yes.
Q The term "limited" as used by IARC, and as you understood it when you were making that finding, is that epidemiology -- epidemiology studies have found an association between glyphosate and cancer, but that chance, bias and confounding could not be excluded as explanations for the finding, correct?
A Correct.

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Q Now, you had previously in your previous answer talked about the separate evaluation that IARC came to as far as overall the 2A classification, correct? So epidemiology is a part of that, right?
A Yes.
Q But the 2A classification for glyphosate was based, at least in part, on a separate determination regarding the animal studies, correct?
A Yes.
Q The 2A classification for glyphosate is based upon the determination that the animal studies provided strong evidence of carcinogenicity in animals for glyphosate, correct?
A Yes, that's as I recall it. Because now you're going to the subgroup --
Q Right.
A -- that I didn't sit in on, you know, and I just have to remember what they said. Yes, I think that's right.
Q When the animal subgroup did its initial assessment of glyphosate and presented their conclusions to the plenary session, it had not classified the animal studies of glyphosate as providing strong evidence of cancer in animals, had it?

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A I don't remember.
Q Do you recall whether or not in fact the animal toxicology subgroup had determined that the animal studies provided limited to inadequate evidence that glyphosate could cause cancer in animals?
A I -- I don't recall.
Q Well, Dr. Blair, let me -- let me show you another document that's been provided to us, and I will represent in -- from Dr. Blair -- Matthew Blair, and Dr. Blair was another member of the working group 112, correct?
A I think so.
Q You testified about him earlier. He did the work for Mississippi State, correct?
A No.
Q I think you said he's an expert in animal --
A You said Matthew Blair?
Q I'm sorry.
A Ross.
Q Matthew Ross. I understand. My apologies.
A Yes.
Q This is a document you received from

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Dr. Ross, and Dr. Ross was a member of working group 112, correct?
A Yes.
Q You had mentioned that Dr. -- Dr. Ross was an expert in cancer -- animal cancer bioassays, right?
A Yes.
MR. LASKER: And this is 13?
(Blair Exhibit No. 13 was marked for identification.)
BY MR. LASKER:
Q And I would like to ask you --
MR. MILLER: May I have a copy, please, Counsel?
MR. LASKER: Yes. If I can.
BY MR. LASKER:
Q If I could ask you -- and this is -- these are --
MR. MILLER: I want to object first. Lack of foundation.
MR. LASKER: Understood.
BY MR. LASKER:
Q And if I could ask you just to take some time to look through, and we will take time and -- to read -- for you to read through this, these notes.

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And why don't we do that first so you can just familiarize yourself with the notes and -- and what they appear to set forth.
A (Perusing document.)
Q And just for the record, these notes at the top of the first page state: "March 6, 2015, Plenary General Remarks." And this date would be about halfway through that working group one-week meeting, correct?
A Yeah. Yes.
Q And the process that appears to be reflected in these notes of presentations to the plenary session by different groups for different substances would be consistent with the process that you told us about a little while ago, right?
A Yes.
Q So what would happen is the plenary group got together, and the subgroup -- people in the individual subgroups for the individual pesticides would then give presentations to the full working group, correct?
A Report where they are in the process, what they were thinking, yes.
Q And so these notes would reflect about midway through the working group one-week meeting,

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correct?
A If that time frame fits midway through, I --
Q And if I could direct you to the last page of this document and -- actually, let me take you first to the second page of the document, because there's -- there's these different groups identified, Group 1, Group 2, and then Group 3. So -- and Group 4.
Am I correct in my understanding that from that Group 1 would be the exposure assessment, Group 2 would be epidemiology, Group 3 would be animal studies -- I'm sorry -- and then Group 4 then would be mechanistic data, correct?
A Correct.
Q And then the final page of this document, there is the presentation of each of these subgroups as of March 6th, 2015, with respect to glyphosate, correct? Right here (indicating), glyphosate?
A The last page?
Q Is it the last page? I believe it's the last page of the document. The very bottom of the last page, do you see Glyphosate Group 1, Glyphosate Group 2, Glyphosate Group 3, and Group 4?
A Here is the last page of mine.

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Q Yeah, right here (indicating). Glyphosate, glyphosate, right there (indicating).
A Okay.
MR. MILLER: Again, I object to the entire line of questions for lack of foundation for the document.
BY MR. LASKER:
Q So with respect to glyphosate as reflected in these notes, there is a presentation by the -- there is a presentations by the exposure group, by the epidemiology group, by the animal cancer -- animal bioassay group, and the mechanistic group, Groups 1 through 4, correct?
A Yes.
Q And Group 2 is your group, the epidemiology group, correct?
A Yes.
Q And the notes here state: "Glyphosate, negative non-Hodgkin lymphoma. Case-control glyphosate," arrow, "non-Hodgkin lymphoma. AHS, negative data."
Is this consistent with your recollection of the epidemiology working group's presentation of the data on glyphosate and non-Hodgkin lymphoma?
A Yeah, roughly so. The case -- there were

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case-control studies were positive and AHS was negative, yeah.
Q For Group 3, for the subgroup that was responsible for looking at the animal data for glyphosate and cancer, the determination was that that evidence was limited to inadequate, correct?
A I -- that is what it says. I actually don't remember.
Q And so you -- sitting here today, can you exclude the possibility that the animal toxicology subgroup of IARC determined that the animal data associating glyphosate with cancer was limited to inadequate?
A No.
Q Do you recall what happened from the time of this initial plenary session in March -- on March 6, 2015, through to the end of the working group that led to the change of the evaluation of the animal data from limited or inadequate to strong?
MR. MILLER: Object to the form of the question.
THE WITNESS: Well, only in a sense that from sort of preliminary discussion where things are, then the subgroups go back and -- and look and evaluate and discuss, and that's what happened. I

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was not in the subgroup, so I have no idea what the discussion was.
BY MR. LASKER:
Q So sometime after this initial -- this plenary session on March 6, 2015, something happened over the next few days that led the subgroup to change its evaluation of the animal data with respect to glyphosate. Is that fair to say?
A You know, I'm not even sure I can say that, because what this says is "limited to inadequate." So if note-taking is messy, it could be limited or inadequate. Now it's a choice. So they haven't chosen. I have no idea. I really don't remember what went on at that time, other than this is saying they're exactly unsure where to put it. And I was not privy to discussions of that group at that time. So...
Q You are aware that the ultimate determination that appears in the final monograph is that the animal data was strong. Correct?
A Yeah.
Q And in fact, if the animal -- if the ultimate determination that the animal data was either limited or inadequate, the full working group would not have reached the determination that

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glyphosate was a probable carcinogen, correct?
MR. MILLER: Object to the form of the question.
THE WITNESS: Probably not.
BY MR. LASKER:
Q In fact, with that analysis and that evaluation of the animal data and the conclusion of your subgroup that the epidemiology data was limited, the highest classification that IARC working group could have come to is that glyphosate is a possible --
A That's correct.
Q -- carcinogen, right?
And in fact, with inadequate animal data, the IARC working group may have concluded that the size of the whole was inadequate to reach determination, and it would be a Group 3 substance, correct?
A They could have concluded that, yes.
Q And you discussed earlier that pursuant to the preamble for IARC, IARC only considers scientific literature that is peer-reviewed or made-publicly-available regulatory documents; is that correct?
A Not just regulatory. It's peer reviewed

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or publicly available is the key thing.
Q Understood. Prior to Monograph 112 -- the Monograph 112 working group meeting, you were aware of unpublished epidemiological data regarding glyphosate and hematopoietic cancers, correct?
A Well, I'm hesitating because it means were we working on the pooled analysis at that time, which I think was probably true.
Q Okay. And, in fact, we have some documents on that that I will show you about that.
So we -- you had some testimony earlier in question -- response to questions from Mr. Miller about the North American Pooled Project, correct?
A Yes.
Q That is a study that is pooling data that has been previously used for the Canadian McDuffie -- McDuffie study and the U.S. studies in that 2003 case-control study in the United States, correct?
A It's three different case-control studies in the United States.
Q Right. Yeah. So all of those studies were combined for the North American Pooled Project in this pooled analysis, correct?
A Yes.
Q And that was De Roos 2003 was the --

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A De Roos was the pooling of the American, the U.S. studies, and they were then pooled with the Canadian studies.
Q So let me mark as Exhibit 13 -- 14. I'm as good as Mr. Miller at this.
MR. MILLER: It's a high compliment.
MR. LASKER: I have to count the double digits. You were on the single digits. So I don't know. It's a little harder when you have to take off your shoe.
(Blair Exhibit No. 14 was marked for identification.)
BY MR. LASKER:
Q And this is a series of e-mails that we -- that you provided to us from your files.
And if -- am I correct that these are e-mails discussing some of the analyses that were being conducted for the North American Pooled Project in October of 2014?
A It looks like it, yeah.
Q So this would have been prior to the IARC working group meeting, which obviously was in March of 2015.
A Right.
Q Correct. In these e-mails, Dr. Pahwa --

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who is Dr. Pahwa?
A He's a scientist in Canada.
Q Is that a he or a she?
A A she.
Q And she is an epidemiologist like yourself?
A Yes.
Q And Dr. Pahwa and you are discussing the epidemial -- epidemiologic analysis that was being discussed as part of the North American Pooled Project in these e-mails, correct?
A Correct.
Q And in her October 23rd e-mail to you and others, I guess these -- am I correct these other individuals are other epidemiologists who are part of the North American Pooled Project study?
A Correct.
Q In this October 23rd e-mail, Dr. Pahwa provides a summary of a meeting you guys had on October 20 in which you discussed in part the possibility of getting some -- I will focus this because it's getting out of focus.
Dr. Pahwa is recounting a discussion that you had on October 20 about the possibility of getting some NAPP data on glyphosate published in

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time for consideration by the Monograph 112 working group, correct?
A Yes.
Q And during this meeting, you explained your role on the Monograph 112 working group and the deadline for getting data published for consideration by the working group in its evaluation of glyphosate, correct?
A Well, is it in here somewhere?
Q Yes.
A You're saying --
Q I'm sorry. It's the final bullet on the first page, and it's highlighted on the document, but it starts: "Aaron will be" -- the final bullet.
A Okay. Closing date. All right. Yes.
Q "Aaron will be on the IARC" --
A Yeah.
Q -- "Monograph 112 working group on March 3rd to 10 to help evaluate malathion, parathion" --
A Yeah, okay.
Q -- "diazinon, glyphosate," et cetera. "The closing date for data is February 3rd. Manisha has agreed to lead an analysis of glyphosate and NHL, MM and HL risks. She will submit her proposal to the

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NAPP executive committee by October 24th. Once approved, a progress check will be done in a month to determine if it's feasible to meet the February 3rd deadline. NHL is the priority cancer site."

You see that?

A Yeah.

Q And in your e-mail back to Manisha, you state: "Let me know if I can help in trying to meet the IARC manuscript deadline." Correct?

A Yeah.

Q So you were -- not only were you the chair of the working group, but in the months leading up to the working group, you were involved in investigating some data that might inform the decision of the working group but only if it was published, correct?

A Yes.

Q Now, let me mark the next document of mine.

(Blair Exhibit No. 15 as marked for identification.)

BY MR. LASKER:

Q And can you -- am I correct these are some further e-mails between you and other individuals, investigators for the North American

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Pooled Project, presenting some analysis of the data with respect to glyphosate and cancer risks, correct?

A Well, I can clearly read the names, so it's people in the North American Pooled Project. Yes, okay. Finally, I see glyphosate, so it appears to be so, yes.

Q And there are a series of communications reflected in this document between you and other NAPP investigators about, say, for certain analyses of glyphosate that could be published in time for the IARC working group deliberations, correct?

A I take your word for it. I --

Q Well, there is data on this -- there's data on this document with respect --

A I'm not disagreeing. I just mean you handed this to me, and these are e-mails of years ago, and you're saying this is correct. I'm just saying if it's in the document, I agree.

Q Okay. Well, just to be clear, this is an e-mail that was sent to you -- and these e-mails were sent to you in October of 2014, roughly four, four-and-a-half months before the IARC working group meeting, correct?

A Correct.

Q And these e-mails contain analyses of the

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North American Pooled Project data with respect to glyphosate, and in this case multiple myeloma, correct?

A Well, at least -- yes.

Q And if you could, because this is the way e-mails are, they always work this way when you print them out, they don't go in chronological order so it's hard to read them.

But if I could ask you to turn to the very last page, which is the first e-mail in this chain on October 27, 2014, from Dr. Pahwa, it starts: "Hi, John, Shelly and Laura." Do you see that?

A Yeah.

Q Now, in this -- on October 27 -- it's not focusing, so let me just read it, what the e-mail states.

Dr. Pahwa is discussing -- states: "I have prepared a research proposal for assessing glyphosate exposure and NHL risk in the NAPP. While we had discussed looking at glyphosate exposure and the risks of non-Hodgkin lymphoma, multiple myeloma and Hodgkin lymphoma in the NAPP, I thought to start off with non-Hodgkin lymphoma since it has been identified as a priority cancer type in general and has the largest sample size compared to the other

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cancer types."

Correct?

A You say this is the last page of this document you handed me?

Q Yes, the last page -- Dr. Pahwa is sending around a proposal for assessing glyphosate exposure in non-Hodgkin's lymphoma risk, correct?

A All right, here it is. You -- I just couldn't see this "I have prepared," but it's in a couple of words. Okay.

Q Right.

A All right.

Q So Dr. Pahwa, on October 27th, 2014, she sends around a proposal for assessing glyphosate exposure and non-Hodgkin lymphoma in the NAPP data, correct?

A Yes.

Q Now, in response to her e-mail, and again we have to go backwards in time, but Dr. Harris -- so it's on the bottom of the second to the last page, the e-mail that responds to Dr. Pahwa. In response, Dr. Harris, another NAPP investigator, suggests extending the analysis to include other cancers, correct?

A Okay. Yes.

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Q And then in response to Dr. Harris's e-mail, another NAPP investigator, Dr. Freeman, notes that there may already have been an investigation of the NAPP data to determine whether there was an association between glyphosate and multiple myeloma, correct?
A So tell me your interpretation of this sentence again.
Q That Dr. Beane-Freeman in the e-mail was asking whether or not -- hey, haven't we already looked at the NAPP data on glyphosate to determine if there is an association with multiple myeloma, correct? That's her question.
A Yes. Yes.
Q And then Dr. Pahwa comes back and says, You're right, we've already done this, but I'm not sure what we found. Correct?
A Yes.
Q And then Dr. Freeman in her e-mail, which is on the middle of this page, on October 28th, 2014, at 10:54, suggests that the group of NAPP investors, including yourself, have, quote: A strategic decision about whether to include multiple myeloma in the paper that was being considered for publication in time for the IARC Monograph review of glyphosate,

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correct?
A Yes.
Q We're not going to read that, but Dr. Freeman raises two factors for consideration: How far along the analysis is of glyphosate and multiple myeloma from the NAPP data; and whether there was, quote, any hint of an association, end quote. Correct?
A Yes.
Q And she states that the answers to those questions and probably others might affect how we think about the question, correct?
A Yes.
Q So the NAPP investigators, including yourself, wanted to find out first whether there was, quote, any hint of an association between glyphosate and multiple myeloma before deciding whether to make that data available for use in the IARC review, correct?
A Whether to complete the analysis.
Q In response to Dr. Freeman's e-mail, Dr. Harris took a look at the analysis that had been conducted from the North American Pooled Project data regarding glyphosate and multiple myeloma, correct?
A Where -- where is this? So I see --

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Q The first -- the first page now, the final e-mail, it's from Dr. Harris.
A Okay.
Q And she is going through --
A Okay.
Q -- and saying, Yes, we've done this analysis, and she presents the data from the North American Pooled Project on glyphosate and multiple myeloma, correct?
A Okay.
Q Correct?
A Yes.
Q Dr. Harris reports back to the group that the North American Pooled Project data did not show an elevated risk for multiple myeloma associated with glyphosate, correct?
A Yes.
Q The adjusted odds ratio for multiple myeloma for ever and never use of glyphosate was 1.23 with confidence intervals of 0.86 to 1.76, correct?
A Yes.
Q That's what epidemiologists refer to as a null finding, correct?
A No, that's not what they refer to as a null finding.

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Q Not the --
A That's what they refer to as an excess that isn't statistically significant.
Q A nonstatistically significant finding, correct?
A Nonstatistically significant excess.
Q Okay. So there was no statistically significant association between glyphosate exposure and multiple myeloma in the NAPP data, correct?
A Correct.
Q Dr. Harris also reports results with proxy respondents excluded, correct? The last three columns in her table?
A Yes.
Q A proxy is a next of kin or a spouse, not the actual individual who had the potential exposure, correct?
A Correct.
Q And generally speaking, self-reported data of the individual who had the exposure is considered more reliable than proxy reported exposure data, correct?
A Correct.
Q When proxy respondents were excluded, the NAP data -- NAPP data showed that the odds ratio for

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ever/never use of glyphosate and multiple myeloma was 0.97 with confidence intervals of 0.63 to 1.48, correct?
A Right.
Q So using the most reliable exposure data, there was no suggestion whatsoever of any increased risk of multiple myeloma with glyphosate exposure, correct?
A Correct.
Q So that was a null finding, correct?
A Yes.
Q Now, Dr. Harris notes that they could have a draft of this paper, including this glyphosate analysis, available for review in the next few weeks and that a paper could be submitted for publication early in the new year or before, correct?
And that's the very beginning of her e-mail, the second paragraph, the last sentence: "I expect you will have a draft to review in the next few weeks, and the paper could be submitted" --
A Well, if you're reading it, I don't find it, but okay, fine.
Q Well, no, I want you to be able to see it. In the very top of the e-mail, the first line is: "Hi, everyone. Thanks all for weighing in on

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this." Correct?
A Yeah.
Q And then the second paragraph, the last sentence, starting at the end of line 2: "I expect we will have a draft to review in the next few weeks and a paper could be submitted early in the new year or before." Correct?
A Okay. Yes.
Q And you were copied on obviously this e-mail that sets forth the NAPP data for glyphosate and multiple myeloma, correct?
A Correct.
Q But despite the fact that you had this data and it was in a form that could be submitted for review and submitted for publication in time for the IARC Monograph, this data was not in fact published in time for the IARC Monograph 112 review, was it?
A I think not.
Q In fact, the data was not published until June of 2016, some twenty months later and well after the IARC working group had conducted its review of glyphosate, correct?
A And I don't think it was submitted to -- it can be submitted to IARC if it's accepted for publication, but I don't think this was. So I think

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your answer -- your comments are correct.
Q Now, the June 2000 --
A And I just want to make the point that it doesn't have to be published, it has to be accepted, which means it's available from the journal.
Q Good clarification. So if you had -- you and the other NAPP investigators had submitted this data, it could have been considered by the IARC working group even if it hadn't been published yet?
A If it had been accepted by the journal and up on the journal's website, which happens to -- actually, one of the papers I got is the website version. It is the same thing as the published one.
Q But you guys didn't -- you guys didn't do that. You didn't get this data in a position that the IARC working group could consider it, correct?
A Correct.
Q And -- but you were obviously aware of this data during the IARC working group deliberations, right?
A Yes.
Q Did you mention the NAPP findings of no association between glyphosate and multiple myeloma to any of your fellow working group members during the Monograph 112 deliberations?

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A I don't think so. But I don't recall for sure. It wasn't published.
Q Just to be clear, it wasn't published because you guys decided not to publish it, correct?
A Because we didn't go through the process to get everything ready to send it off for publication. It's still not a sure thing, you understand. You make it sound like you decide, then it's done for sure. No, that's not the case. You work on it, you look at it, you revise, you send it to the journal to get reviews back from authors of -- the reviewers at the journal and so forth, and all that goes into the decision of whether you can make it, and we didn't do that. That is correct.
Q Dr. Harris in October of 2014 is suggesting, Hey, let's get this -- let's submit this to a journal and get it published so the IARC working group can consider it, but you didn't do that, correct?
A Did not do that.
Q Now, Dr. Pahwa had also discussed in these e-mails that she was looking at the North American Pooled Project data with respect to glyphosate and non-Hodgkin's lymphoma, correct?
A Right.

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Q And the NAPP investigators did not publish any findings with respect to glyphosate and non-Hodgkin's lymphoma prior to the monograph one -- IARC 112 meeting in March 2015, correct?
A I think that's correct, yeah.
Q Now, you have presented -- the NAPP investigators have presented data about glyphosate and non-Hodgkin's lymphoma at various scientific meetings, correct?
A At least two, I think.
Q Okay. Let me ask you about the first of those. What I believe is the first, and correct me if I'm wrong.
(Blair Exhibit No. 16 was marked for identification.)
MR. MILLER: 16?
MR. LASKER: 16.
BY MR. LASKER:
Q And, Dr. Blair, this is a presentation that the North American Pooled project investigators, including yourself, made with respect to what the NAPP data showed for glyphosate and non-Hodgkin lymphoma, correct?
A Yeah. Yes.
Q And this was presented on June 2015,

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which was after the IARC -- a few months after the IARC Monograph 112 meeting, correct?
A Right.
Q Now, if I can direct you to the first data table in this log deck, and it's a few pages in, and specifically -- so it would be this table right here (indicating). Okay. We will put it up on the screen.
MR. LASKER: Help me focus this. Zoom out, actually.
(Counsel conferring.)
BY MR. LASKER:
Q So the -- this table presents data on what the North American Pooled Project had found with respect to glyphosate use and non-Hodgkin lymphoma risks, correct?
A Yes.
Q And the first -- the overall odds ratio for ever/never use of glyphosate and non-Hodgkin lymphoma in the North American Pooled Project is 1.22 with confidence intervals of 0.91 to 1.63, correct?
A Correct.
Q So this is basically the same finding that the NAPP had made with respect to multiple myeloma back in October of 2014, almost exact same

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odds ratios, not statistically significant, correct?
A The odds ratio that are similar, right?
Q Yes.
A Is that your point?
Q Yes.
A Yes.
Q And not statistically significant, correct?
A Yes.
Q And just like with the multiple myeloma analysis we looked at before, we also have an analysis that breaks out proxies and looks only at the most reliable exposure data, and I think that is the table that looks like this (indicating). I apologize, there's not -- there are no page numbers here.
A Okay.
Q But in this analysis, proxy by self-respondents, just as with multiple myeloma finding, when you looked at the NAPP data and you looked at the most -- the more reliable self-respondent only data, you have an odds ratio for non-Hodgkin lymphoma and glyphosate in the North American Pooled Project of 1.04, with a confidence interval of 0.75 to 1.45, correct?

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A Correct.
Q So, again, this is a null finding from the North American Pooled Project with respect to whether or not glyphosate is associated with non-Hodgkin lymphoma, correct?
A Yes.
Q Did you mention these North American Pooled Project findings of no association between glyphosate and non-Hodgkin lymphoma to any of your fellow working group members during the Monograph 112 deliberations?
A I don't think so. And I want to say, actually I don't know whether these were available or not. So you -- I mean whether I even knew about them, because the analysis of multiple myeloma was going on, but I don't know whether this one was done or not. If it was, I'm sure you're going to show me, but I don't know whether this one was done or not.
Q Well, you certainly knew that you had the ability to look at that. You were --
A Well, that's a different thing than knowing what it is. We can look at a lot of things.
Q So in October of 2014, though, you and Dr. Pahwa and the others were talking about, Hey, let's look at the data from our North American Pooled

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Project with respect to glyphosate and non-Hodgkin lymphoma, correct?
A Yes.
Q Is it your testimony that you in fact, though, then didn't look at that data?
A I -- there were a bunch of things going on, and they were already analyzing, and I just don't remember the sequence that got to it. You make it sound like as if you can decide to look at it, and just it's over and done. These things take months and months and months. And so if you haven't looked at anything at all, the odds aren't good that you can complete it beforehand, before some date. And I think that was part of the thinking about non-Hodgkin lymphoma, that we couldn't get it ready in time.
Q You haven't published your findings with respect to glyphosate and non-Hodgkin lymphoma to this day, have you?
A No.
Q It's now three years later, correct?
A Scientific research takes time.
Q The -- and because of the fact that you had not published these results, including this finding of -- a null finding in the North American Pooled Project for glyphosate and non-Hodgkin

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lymphoma, that information was not available to IARC. Correct?
A No.
Q It was not available, correct?
A No.
Q I'm going to restate that.
It is correct that IARC did not have this information, right? Yes, IARC didn't have it?
A IARC did not have it.
Q IARC didn't have it.
A No.
Q And the various regulatory agencies, including the EPA and regulatory agencies around the world, also have not had this information that the -- that you've been aware of with respect to non-Hodgkin lymphoma?
A Yeah, except -- so, okay, I see you're pushing this hard now. So what if we look at frequency of days per year of use?
Q Okay.
A So now when you look at the people who used it more, they do have an excess of non-Hodgkin's lymphoma among the self-respondents.
Q That -- now, that's interesting you picked that one out. Why did you not look at

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duration or lifetime days?
A There's a lot --
Q There's a lot of analyses. You picked that one.
A There are a lot of them. You look at a lot of different things and you have to try to evaluate the whole thing. I picked out one and you picked out one.
Q Okay. But you didn't present any of the data so that the IARC working group could look --
A Because it wasn't -- I don't think it was available at the IARC working group time. If it --
Q But it was available to you.
A I'm not sure it was available to me. If you have information to show it's available, well, tell me, but I don't it was available. I remember this coming after the IARC working group stuff.
Q We just looked at October 28th, 2014 e-mails where you or the NAPP investigators were discussing --
A What to do. They didn't -- I don't remember it saying we had done it and this information was available. That's the issue.
Q Now, so that I understand, the NAPP analysis was based upon data that was already

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available to the IARC working group because it was pooling --
A Yes.
Q -- the McDuffie case report and the De Roos 2003 report.
A Correct.
Q Okay. Now, during the IARC Monograph -- during the IARC Monograph 112 deliberations, you were also -- strike that.
During the IARC Monograph 112 deliberations, you were also aware of unpublished data on glyphosate and non-Hodgkin lymphoma from the Agricultural Health Study, correct?
A You know, I -- I don't remember.
Q Okay. Well, we will go through this, but let me first refresh and let the jury understand because during Mr. Miller's questioning you didn't have the opportunity to talk about the findings from the Agricultural Health Study that has been published on glyphosate and non-Hodgkin lymphoma.
So let me provide for you, and we will mark this as Defense Exhibit 16 -- 17. 17. Sorry.
(Blair Exhibit No. 17 was marked for identification.)
MR. MILLER: Thank you. Exhibit 17.

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MR. LASKER: Exhibit 17.
MR. MILLER: We have a rule in the law, Doctor, it's called hungry break.
MR. LASKER: Oh, you want to take a break?
MR. MILLER: Whatever. It's not up to me. It's up to you, Doctor. You're the witness. So you can keep going or you can take a break. It's up to you.
THE WITNESS: It would be nice to take a break. It's sort of a physiological position. So is that --
MR. LASKER: Okay. That is -- we can take a break whenever you want. I just don't know if you mean now or later. Whenever you want to, just let me know.
THE WITNESS: I have no clue.
MR. LASKER: You have no clue whether you want to take a break?
THE WITNESS: No. I mean --
MR. LASKER: Well, we should have -- we should definitely have a lunch break. If you want to take it now, it's up to you.
THE WITNESS: Well, you're on a topic now. What I'm trying to find out is, are you going

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to go on this for a while and then switch to something else? I would prefer to get this done.
MR. LASKER: Okay.
THE WITNESS: But I don't know that.
MR. LASKER: Okay. Well, why --
THE WITNESS: Only you know that.
MR. LASKER: Okay. Well, why don't we get this done, and then we will switch to something else.
THE WITNESS: Okay.
MR. LASKER: Okay.
BY MR. LASKER:
Q So, with respect to the De Roos 2005 paper, this is a paper that you were -- a study that you were co-author on, correct?
A Yes.
Q And this is the cohort study we have been discussing before and the analysis of cancer incidence among glyphosate-exposed pesticide applicators, correct?
A Yeah. Yes.
Q And if you turn to page 49, the first page actually, on the "Materials and Methods" section, the De Roos 2005 paper was reporting out the findings from the AHS cohort based upon exposure data

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gathered between 1993 and 1997, and incidence of cancers identified as of December 31st, 2001, correct?
A Well, the '93 to '97 is correct. I guess the other is.
Q If you read down a little bit further along that same section, you will see --
A Yes.
Q -- cancers.
A Okay. Yes. Okay.
Q And if you go to page 51, Table 2, based on this data, De Roos 2005 identified 92 cases of non-Hodgkin lymphoma in farmers and the cohorts who had been -- who had reported exposure to glyphosate, correct?
A Yes.
Q And De Roos calculated and adjusted risk ratio for ever/never use of glyphosate and non-Hodgkin lymphoma of 1.1 with a confidence interval of 0.7 to 1.9, correct?
A Correct.
Q Which is showing no statistically significant association, correct?
A Yes.
Q And De Roos 2005 also presents data on

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non-Hodgkin lymphoma and glyphosate in association with the duration and intensity of exposure to glyphosate, correct?
A Yes.
Q That data was presented on page 52, Table 3?
A Yes.
Q And provides an analysis of 61 cases of non-Hodgkin lymphoma in farmers who had been exposed to glyphosate, correct? Towards the bottom of that chart, the non-Hodgkin lymphoma.
A Yes. Yes. Yes.
Q And for both -- let me do this so it's not in the -- actually, it's better to put it there.
A Which I found it in the table. Now you don't need to.
Q For both cumulative exposure days -- well, first of all, let me see if I understand this.
What is cumulative exposure days in the AHS evaluation?
A The number of days per year they say they applied a chemical multiplied by the number of years they said they used it.
Q And what is the intensity of exposure?
A It's those two factors weighted also by

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how they use protective equipment and things such as that that would influence exposure.
Q So in the De Roos 2005 paper for both cumulative exposure days, which is this data here (indicating), and for intensity weighted exposure dates, which is this data here (indicating), the relative risk for non-Hodgkin lymphoma was below 1.0 for higher exposures to glyphosate, correct?
A Correct.
Q So farmers who had either more days of exposure to glyphosate or had more intense exposure to glyphosate had a high -- had a lower --
A Lower.
Q -- lower incidence of non-Hodgkin lymphoma than farmers who had not used glyphosate, correct?
A That was not statistically significant.
Q So this would be a negative association. It wouldn't be a null finding, but it would not be statistically significant, correct?
A Correct.
Q Okay. And are you aware of some of the discussions that have taken place following the IARC classification of glyphosate about this AHS study and its strengths or weaknesses?

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A I mean I'm involved in the study, so if the answer is are there -- am I involved in discussions about it, well, yes.
Q Okay. Well, let me show you --
A But why don't you ask what you're interested in.
Q Let me show you specifically -- let me show you specifically a publication by Dr. Portier. I think you mentioned him earlier.
You know Dr. Portier, correct?
A I do.
(Blair Exhibit No. 18 was marked for identification.)
BY MR. LASKER:
Q And this is Defense Exhibit 18.
A You have two things there. Did you --
Q Oh, that has highlighting. Thank you.
A Actually, you have three things there.
MR. MILLER: Three things.
BY MR. LASKER:
Q Okay. And in this publication, Dr. Portier is -- well, first of all, it's entitled "Differences in carcinogenic evaluation of glyphosate between the IARC -- between the International Agency for Research on Cancer and the European Food Safety

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Authority," correct?
A Yes.
Q And in this publication, a variety of individuals are trying to address their views about the differences between what IARC concluded with respect to glyphosate and cancer and what the European Food Safety Authority concluded, correct?
A Yes.
Q And if we turn to the second page of this commentary, Dr. Portier is talking specifically about -- at the bottom of the first page and then turning over to the second page -- the Agricultural Health Study we were just looking at, the 2005 publication, correct?
A Okay. Yes.
Q And at page 2, on the top of that left column, Dr. Portier writes: "Despite potential advantages of cohort versus case-control studies, the AHS only had 92 NHL cases in the unadjusted analysis as compared to 650 cases in the case-control studies." Correct?
A Yes.
Q So he is pointing to the fact that there's only 92 NHLs found as of 2005?
A Yes.

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Q He also talks about the fact that the median follow-up time in AHS was 6.7 years, which is unlikely to be long enough to account for cancer latency, correct?
A Yes.
Q Now, in fact, the 6.7 years of follow-up to which Dr. Portier is referring to is not the amount of time between exposure and cancer, is it?
A No.
Q In fact, as we discussed earlier, at the time of entry into the Agricultural Health Study, the subject applicators, the farmers, had an average of about 15 years of pesticide use already, correct?
A Correct.
Q And glyphosates had been on the market since 1974 or about that time. I think Mr. Miller just read something about that in his questioning. Right?
A Yeah.
Q So on average, by the time the data collected for the 2005 De Roos study was analyzed, the farmers would have had -- more than 20 years had passed from the time of their first exposure to their cancer potentially, correct?
A More than twenty years' exposure to what?

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Q To glyphosate.
A Some may have. Right?
Q Correct.
A Some may have.
Q Certainly more than 6.7 years. That's not the correct year to be looking at for how much exposure they had had, correct?
A That's the person -- their follow-up time.
Q So that was the time from the questionnaire to follow-up, not exposure to follow-up?
A Correct.
Q So Dr. Portier's comment here in this publication is inaccurate, correct? There is something wrong with it?
A In --
MR. MILLER: Object to the form of the question, but it says "in addition to median follow-up time."
MR. LASKER: You can object. You can't testify. That's what the witness does.
THE WITNESS: Well, I -- I'm debating whether to answer your question or give you an epidemiology primer. I think I will just -- the

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length of time of follow-up has to be from the time you've followed people.
BY MR. LASKER:
Q Right.
A So if a person was exposed to anything 20 years before you started the study and died 19 years after -- before you started the study, they wouldn't be in it.
Q Understood.
A So there is that element in it, but it's correct that 6.7 is not the total amount of time that people would have -- some of the people would have been exposed in this study.
Q Well, the -- the median we talked about before for these farmers was that if they had 15 years of pesticide use prior to -- at the time of their questionnaire, correct?
A 15 years of pesticide use.
Q And you had data also on glyphosates, correct?
A But, again, it's a matter of how many people started using it and when they started using it.
I'm just saying your characterization is not fully descriptive. It goes on in the cohort

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study. There are staggered times --
Q Understood.
A -- going on and so forth. People have different amounts, but it could be -- some of them clearly have it more than 6.7 years.
Q And we're not -- to be clear, we're not talking about my characterization of the study. We're talking about Dr. Portier's characterization of the study.
MR. MILLER: Well, I object and move to strike that.
BY MR. LASKER:
Q And just so it's clear --
MR. MILLER: I just object and move to strike. Dr. Portier's characterization is follow-up, not exposure. You're interchanging those two terms intentionally to mislead, and I object.
BY MR. LASKER:
Q Just to be clear, the period of 6.7 years, which Dr. Portier says is unlikely to account for the cancer latency, is not the period of time from exposure to cancer that was assessed in the non -- in the AHS study, correct?
A That's correct. He says it's the median follow-up time.

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Q Right. So cancer latency, what's important is date of exposure to date of cancer, not date of questionnaire to date of cancer, correct?
A Yes, but he says follow-up time, not latency.
Q No, he mentions latency right there. That's what he talks about. He says, "Unlikely to be long enough to account for cancer latency," correct?
A But he says it's a median follow-up time.
Q Correct.
A Yeah.
Q But just we're clear, the median follow-up time doesn't tell you anything about the period of exposure to cancer. That's relating for -- to latency, correct?
A Yes.
Q Okay. Now, in fact, the AHS has conducted additional analyses of glyphosate following the 2005 paper -- published study with far larger -- a far larger number of incidence of NHL cases and longer follow-up, correct?
A There is a paper on that?
Q AHS has conducted analyses of glyphosate --
A Oh, okay. Okay.

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Q -- following the 2005 publication with a far larger number of NHL cases and a longer follow-up, correct?
A I think that's underway, yes.
Q Let me mark as next exhibit in line, and I will do this as Exhibit A and B. So 19-A and 19-B.
(Blair Exhibit Nos. 19-A and 19-B were marked for identification.)
BY MR. LASKER:
Q And let me represent that there is a printing date on this that is when this document was printed, somebody -- or maybe for public -- for production, but there is also a date on the document of when it was prepared. So we will have two dates on the document.
And this is yours.
A Oh, yes. I'm sorry. I was thinking you were talking about an analysis of just glyphosate people, but there is a -- this paper has been published actually for non-Hodgkin's lymphoma.
Q Okay. Well, we will talk about that.
A Yeah.
Q We will talk about what data was published and what data was not published.
But this is 19-B. And here you are.

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So I marked two versions of -- well, first of all, if you could just identify for the record what I've handed you as Exhibit 19-A and 19-B.
A Well, they look like documents, probably drafts that were prepared for the study of lymphoma and pesticide use in the Agricultural Health Study.
Q And these are drafts dated February 6, 2013, and March 15, 2013, correct?
A Well, mine says --
Q Well, there's a print --
A -- December 5th, 2016, and this one is November 30th, 2016.
Q And just -- that's why I want to clarify when we talk about -- that's when it was printed out by somebody, that's a Word -- something the Word program does, but if you look at the actual -- in the text --
A Oh, okay. Okay. Yes. Yes.
Q So these are drafts prepared in February 2013 and March of 2013, correct?
A Yes.
Q And if you look at the February '13 -- February 2013 -- strike that.
If you look at the February 2013 draft, there is -- in fact, starting on the very first page, a comment on the draft by an AEB, and that would be you, correct? Aaron Blair.
A On the first page?
Q Well, if you look on the right, you will see these little comment bubbles. And if you look throughout the document, you will see these comment bubbles.
A Yes. Yes.
Q And these -- this is your comment -- these are your comments on the document, correct?
A Yeah. Correct.
Q And if you look at the March 2013 draft, which is the next document, it also has various comments by you on the publication -- on the draft publication, correct?
A Yes.
Q Okay. Now, let's -- so it's fair to say that as of March 2013, you had reviewed at least two versions of this draft publication, correct?
A Yes.
Q Well, let's focus on the March 2013 draft. And if I could turn you first to page 6 in the discussion of the study population.
A We're at 2000 -- oh, March '13. Okay. Yes, got it.

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Q So I turn you to page 6.
A Six?
Q Yes. And this has a discussion of the study population about halfway through, correct?
A Yes.
Q And now we're looking at all -- I'm sorry, if you look at page 7, all incidence of primary non-Hodgkin lymphoma in the AHS cohort from enrollment through December 31st, 2008, correct? At the very top.
A Yes.
Q So this study includes an additional seven years of follow-up, an additional seven years of NHL cases beyond those that were reported and published in the De Roos 2005 paper, correct?
A Yes.
Q And if you look at page 9 of this 2013 draft paper, in the second paragraph on that page, it talks about the fact that this study also includes additional exposure data from a follow-up questionnaire.
So you have five years of additional exposure data that was not available for the 2005 study that was published, correct?
A Correct.

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Q Then the 2013 paper -- or 2013 study, I'm sorry, that includes a series of tables in the back that reports on the findings of various analyses of different exposures and the risks of non-Hodgkin lymphoma, correct? There's a whole bunch of tables back here.
A Okay.
Q Data tables?
A Yeah.
Q So how are these data tables prepared?
A I don't understand your question.
Q Okay, let me strike that.
This is the data that was available to the Agricultural Health Study and was to be presented in this publication, correct?
A Yes.
Q And this is -- these tables are showing the relative risks of non-Hodgkin lymphoma in farmers with various exposures based upon the additional data that had been generated in the AHS study, correct?
A Correct.
Q Now, I've looked through these tables, and the 2013 study does not appear to contain data on ever/never use. But I would like to have you turn to page 34.

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And on page -- on page 34 of the document, we have the AHS updated data on glyphosate and non-Hodgkin lymphoma, correct?
A Yes.
Q And we have -- this is the data for both duration and intensity-weighted duration of exposure to glyphosate, correct?
A Well, I think that's the case. I have to look at the -- not duration but total days of exposure and intensity-weighted days of exposure.
Q Okay. Well, isn't total days of exposure the duration of exposure?
A Not in normal epidemiologic parlance.
Q Okay.
A Duration is often measured in years, and that can be different than the total number of days.
Q But in the 2005 De Roos paper, De Roos was -- 2005 De Roos paper, duration was number of days and --
A Yes. And this is the same. It's the same.
Q It's the same analysis --
A Same analysis.
Q -- as the 2005 exposure -- 2005 publication, except in this analysis we have a

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category also of no exposure, correct?
A Yes.
Q And the De Roos 2005 analysis that we looked at was based upon -- the exposure analysis was based upon 61 cases of non-Hodgkin lymphoma in farmers who had reported exposure to glyphosate, correct?
A That sounds right to me.
Q The 2013 analysis includes data on 250 NHL cases among farmers who had reported exposure to glyphosate, correct? Just add up the three rows of exposure, about 250?
A About. I was looking, and say, Well, it's not going to add to 250, but it's about 250. I'm not quibbling.
Q I think it actually is, but it's about 250. That's fine.
And so this 2013 cohort study has results for glyphosate and non-Hodgkin lymphoma -- I'm sorry. Strike that.
This 2013 cohort study with results for glyphosate and non-Hodgkin lymphoma is more than four times larger than the De Roos 2005 study, correct?
A Yes.
Q It's gone from 61 -- or 62 to 250 cases.

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A Yes.
Q And the confidence intervals for the various analyses of NHL based upon the levels of glyphosate exposure, because it's a larger study, are much tighter than the confidence intervals were for De Roos 2005, correct?
A Correct.
Q Because this study now has more power, correct?
A Correct.
Q So this 2013 cohort study finds no association -- no evidence of association between exposure to glyphosate and non-Hodgkin lymphoma, correct?
A Correct.
Q And based upon the data that's set forth here, if you look at individuals who had no exposure to glyphosate, which is that first row, and you look at the three categories of individuals who did have exposure to glyphosate, if we were to do an ever/never analysis of glyphosate and non-Hodgkin lymphoma, the -- the relative risk here would be something below 1.0, correct? About 0.9?
A That's a reasonable guess, I think, yes.
Q So that means that the incidence of

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non-Hodgkin lymphoma in farmers exposed to glyphosate in the 2013 cohort study was lower than the incidence of non-Hodgkin lymphoma in farmers who were not exposed to glyphosate, correct?

A But not statistically significant.

Q So it's a negative association, but statistically --

A Not statistically significant.

Q Not a null result but a negative association.

A Correct.

Q And the applicators in the highest levels of exposure to glyphosate, both by lifetime days and intensity-weighted lifetime days, had the exact same incidence of non-Hodgkin lymphoma as applicators with no exposure to glyphosate whatsoever, correct?

A Correct.

Q So for the highest -- for each of these measures of exposure, for the relative risk for non-Hodgkin lymphoma at the highest level of exposure to glyphosate as compared to not exposed was a completely null result, correct?

A Yes.

Q The median lifetime use in days for the highest exposure group now is 172 days, correct?

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A Where do I see that?

Q Right here (indicating). The median days in the highest exposure group, 173 days. I apologize.

So the highest -- the highest exposure group for duration, we're looking at farmers with an average of 173 days of exposure to glyphosate, correct?

A I must be on the wrong table then.

Q If you look at the first column --

A Well, it's just not the ones I had. Maybe I've got the --

Q Are you on page 34?

A Page 34.

Q If you --

A The March 15th document.

Q Yep.

A Right? Glyphosate --

Q We have none, low, medium. Right here (indicating). You have the numbers in the brackets, right? Those numbers in the brackets are the median days of exposure, correct? Right here (indicating).

A Oh, 173. I'm sorry. I was hearing something else. It was there. I thought it's not the same number. Yeah, okay. Yes.

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Q So the median lifetime days of glyphosate exposure in this high exposure group where there was no finding of any increased risk of non-Hodgkin lymphoma whatsoever was 173 days, correct?

A Well, again, now I'm quibbling, because we've got two categories --

Q We have three.

A One is cumulative days, and the other is the intensity-weighted one. And so I think you're right that the judgment is this is the days, but that finding applies all across that row, and that can't be.

Q Okay.

A You know, but I think you're right, I think this is cumulative days, yes.

Q Got it. Okay.

A That's not your fault. That's --

Q And -- yes.

A -- the paper's fault.

Q And because of the fact that we now have longer follow-up, the exposure levels at each of these these three categories of low, medium and high exposure to glyphosate also are much higher than the exposure levels in the corresponding analysis in the 2005 published paper, correct?

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A The cumulative exposure is higher.

Q Now, these findings for glyphosate have never been published, have they?

A No. They haven't been published.

Q These findings, the AHS updated findings for glyphosate and non-Hodgkin lymphoma were not considered by IARC in its review of glyphosate, correct?

A No.

Q These findings also have not been available to any of the regulatory agencies that have been conducting reviews of glyphosate and cancer, correct?

A Correct.

Q Now, this obviously is data that you had in your possession and were aware of at the time of the IARC working group meeting, which is two years after you reviewed this paper, correct?

A Say again.

Q Well, you reviewed this data in March 2013, correct?

A Yes.

Q And then in March 2015, you were the chair of the IARC working group that was considering the question of --

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A Yes.
Q -- what the epidemiological data shows with respect to --
A Yeah, right.
Q -- glyphosate and non-Hodgkin --
A Right.
Q So you obviously knew about --
THE REPORTER: Excuse me. I need you to finish that question, please.
BY MR. LASKER:
Q I'll say it again. So in -- let me rephrase.
At the time that you were the chair of the IARC working group and a member of the epidemiology subgroup that was looking at the evidence of whether or not glyphosate was associated with non-Hodgkin lymphoma, you were aware of this updated data of a study four times larger than the published 2005 paper with respect to glyphosate and non-Hodgkin lymphoma, correct?
A That there were analyses of such data, but no published studies.
Q Correct. But you were aware of what the data showed, correct?
A Yes. But no published studies.

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Q Right. And did you alert any of your fellow working group members or any of the other members of the subgroup on epidemiology at IARC about the fact that this much larger AHS cohort study with larger follow -- a larger time of follow-up and higher levels of exposure had been conducted?
A No.
Q Now, the IARC working group also cited to a meta-analysis that IARC had prepared of the epidemiological studies regarding glyphosate and non-Hodgkin lymphoma. And Mr. Miller asked you about that earlier today. Correct?
A Yes.
Q Well, let me show you a copy of that meta-analysis, if I might.
(Blair Exhibit No. 20 was marked for identification.)
BY MR. LASKER:
Q This is Defense Exhibit 20.
And also let me just -- we have -- do you have the monograph working group which was a plaintiffs' exhibit? Oh, you have that. Okay.
This was marked previously as a plaintiffs' exhibit, I just don't remember what number it was, but this is the monograph.

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MR. LASKER: Do you remember what number this is, Mr. Miller?
MR. MILLER: This should be 20.
MR. LASKER: Four. Plaintiffs' 4? No, this is Plaintiffs' 4. It's the same -- you guys marked this.
MR. MILLER: Oh, I'm sorry.
MR. LASKER: I'm talking about the --
MR. MILLER: Well, we need to be more precise. Okay. 20 was the last exhibit you handed me. Now you're asking me what the original monograph was?
MR. LASKER: I believe it's Plaintiffs' Exhibit 4.
MR. MILLER: Four? Okay. Very well. On we go.
BY MR. LASKER:
Q I'm just going to hand you a copy of the monograph again. It's the same document. Mr. Miller can confirm.
But with respect to the meta-analysis that IARC conducted, that is mentioned on page 30 of the monograph. So if I could just turn you to page 30 of the monograph.
And do you see there is the discussion of

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a meta-analysis?
A Yes.
Q And the meta-analysis is identified as Schinasi and Leon. That is the publication, the paper I just handed to you, which we marked as exhibit -- Defense Exhibit 20, correct?
A Correct.
Q And it discusses the meta-analysis that was done by Schinasi and Leon, and then an adjustment that the working group made to that monograph -- I'm sorry, to that meta-analysis so as to use fully adjusted estimates of the risks with non-Hodgkin's lymphoma and glyphosate, correct?
A Yes.
Q And the IARC working group's conclusion was that the meta risk ratio of all the epidemiology was 1.3, which had a confidence interval of 1.03 to 1.65. So it just made barely that level of statistically significance, correct?
A Correct.
Q Now, the meta-analysis was based in part on the 2005 AHS publication, correct?
A Correct.
Q It was not based upon the data we've now just looked at of the 2013 AHS data, correct?

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A Right.
Q So if we look at Defense Exhibit 20, which is the Schinasi paper, and if you look at page 4505, this sets forth the various studies that IARC looked at with respect to glyphosate and non-Hodgkin lymphoma and the risk ratios from those studies, correct?
A Correct.
Q And the meta-analysis is a process of weighing these findings from these studies, correct?
A Right.
Q And the way that the meta-analysis works is it gives a different weight to different studies based upon the power of the study, which is reflected in the size of those confidence intervals, correct?
A Correct.
Q So the IARC meta-analysis weighing of the 2005 AHS study, which is listed here, is based upon the 71 cases of non-Hodgkin lymphoma that were available as of the time of that 2005 publication, correct?
A Correct.
Q Now, as we've already discussed, the 2013 data finds for a much larger number of NHL cases -- provides findings for a much larger number of NHL

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cases, we had like some four times, like 250 cases --
A Right.
Q -- in that data, correct?
A Right.
Q And the confidence intervals, because it's a much larger study, were much tighter in that 2013 data than the -- than the data we have here, correct?
A Correct.
Q And we already talked about the fact that the relative risk from the 2013 data of ever/never use was below 1.0, something like 0.9, so it was slightly below the 1.1 relative risk for the De Roos 2005 paper, correct?
A Correct.
Q So if the 2013 data, which you were aware of, had been available for IARC in its meta-analysis, the AHS data would have had significantly more weight in the meta-analysis than is reflected here --
A Yes.
Q -- and the relative risk data would have been lower than the 2005 study that's incorporated here, correct?
A The relative risk for the AHS study would have been lower.

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Q Right.
A Was lower. Yeah.
Q Yes, it would have been.
A Yeah.
Q So it's fair to say, given that IARC -- your meta-analysis was just barely statistically significant at 1.03 in the lower bound, if IARC had had the data from the 2013 study, much more -- a much larger study, much greater weight, lower relative risk -- that would have driven the meta-relative risk downward, correct?
A Correct.
Q And the meta-relative risk with that 2013 data from the AHS study that you were aware of would have not have been statistically significant, would it?
A I don't know, but probably not.
Q Probably not.
Now, during the Monograph 112 working group meeting, IARC provided the working group with this meta-analysis data, correct?
A Yes.
Q Did you mention to anyone at the meeting the likely impact that the more recent data from AHS would have in decreasing the meta -- meta-relative

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risk for glyphosate and non-Hodgkin lymphoma?
A No.
Q Now, the Schinasi meta-analysis also includes data from a case-control study, a pooled analysis in the U.S., the De Roos 2003 paper, and it includes relative risk from the McDuffie paper from Canada, correct? Those are also on this chart?
A Yes.
Q And Schinasi, IARC used an odds ratio of 2.1 for the Canadian -- I'm sorry, for the U.S. case-control data, correct? It's on the charts here, the De Roos 2003 with an odds ratio --
A You are --
Q We're still -- we're still on the Schinasi paper. Same --
A Oh, okay. Oh, okay.
Q So the De Roos 2003 is listed here. That's the U.S. case-control data, and that's an odds ratio of 2.1, correct?
A Yes.
MR. MILLER: What page are we on?
MR. LASKER: We're on page 4505.
MR. MILLER: 4505.
BY MR. LASKER:
Q And McDuffie, that's the Canadian

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case-control study, and that's 1.2, correct?
A Correct.
Q And now if -- there's a little bit different weighting of those two studies because McDuffie is a little bit larger, but if you were to sort of take those two studies in aggregate as considered by the meta-analysis, that works out to -- for those two studies an odds ratio of about 1.6 for purposes of meta-analysis if you combine those two studies, correct? 2.1, 1.2, it's going to be around that -- that area, right?
A Probably. I don't know. Sometimes you can't just put them together.
Q Roughly -- but roughly, roughly 1.6 or so, correct?
A Probably.
Q Okay. Now, the NAP data -- NAPP data that we were discussing earlier, that's actually a pooled analysis of the data from McDuffie 2001 and De Roos 2003, correct?
A Yes.
Q And the way that this meta-analysis works is IARC takes the most recent and most comprehensive pooled analysis and doesn't consider the earlier studies, correct?

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So, for example, Kantor 1992 is not in here because it was pooled into De Roos 2003, correct?
A They do -- unless the individual papers have information that isn't in the pooled analyses, which is often the case.
Q But with respect to this analysis, for example, De Roos 2003, they don't include Cantor -- the Cantor study. They include the most recent pooled data, correct?
A In this table.
Q Yes.
A Yes.
Q And in this meta-analysis.
A And in this meta-analysis.
Q So if we were then to use -- if the NAPP data had been available to IARC, the data we were looking at previously, you recall that the NAPP odds ratio, even including proxy respondents for ever/never use, for glyphosate and non-Hodgkin's lymphoma was 1.22, correct? We looked at that previously.
A Sounds right.
Q Okay. So if the NAPP data, again that you were aware of at the time, had been available to

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IARC and had been put into this analysis and replaced McDuffie 2001 and De Roos 2003, the odds ratio number for the U.S. and Canadian case-control studies would drop from probably somewhere around 1.6 to 1.2 or so, correct?
A I -- you know, I'm not comfortable making pronouncements about your combining of data from different studies without me seeing the data.
Q Okay. Well, just so we're clear, the NAPP data is your data. We looked at it earlier.
A It's not in front of me. I'm not comfortable --
Q Okay. Well, then --
A -- with combining --
Q -- let's go -- that's a good point.
A -- different things without seeing that.
Q Let's go back to that. That's a very good point.
So if we could refer -- okay. Look back to Defense Exhibit --
MS. SHIMADA: 16.
BY MR. LASKER:
Q -- 16. So it should be on that -- on the pile, probably in reverse order.
MR. MILLER: Well, while we look at that,

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we're calling a break. It's 1 o'clock. We've been going --
MR. LASKER: We're in the middle -- when we finish this line of questioning, we will take a break.
MR. MILLER: We said that a half an hour ago.
MR. LASKER: When I finish this line of questioning. I'm almost done. We'll be fine. I've got maybe five or ten more questions at most.
THE WITNESS: Is this the one you're --
BY MR. LASKER:
Q That's the one.
A Okay.
Q So this is the one that we looked at previously, and the first data table we looked at was the -- this table right here, right? This is the ever/never use. That's it.
So the ever/never use of this pooled analysis that's pooling the data from McDuffie and from De Roos 2003, the data that you had was 1.22 as the odds ratio, correct?
A Correct.
Q So that is a lower odds ratio than was used for purposes of the IARC meta-analysis because

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that meta-analysis was combining a 2.1 and a 1.2, correct?
A Yes.
Q So if that NAPP data had been available to IARC for its meta-analysis, that also would have lowered the meta-relative risk for glyphosate and non-Hodgkin lymphoma even further, correct?
A Probably.
MR. LASKER: We can take a break now.
THE VIDEOGRAPHER: The time is 12:56 p.m. We're off the record.
(Lunch Recess.)
THE VIDEOGRAPHER: The time is 1:47 p.m., on March 20th, 2017. And we are on the record with video 3.
MR. MILLER: I just wanted to make a short statement regards time management. Plaintiffs went about an hour and 30 something. I think the --
THE VIDEOGRAPHER: 1:34.
MR. MILLER: 1:34. So far defendants have gone --
THE VIDEOGRAPHER: Two hours.
MR. MILLER: -- two hours.
Counsel for Dr. Blair has been kind enough to say a total of eight hours, and that's time

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on record I wanted to clear up and we want our equal time on the record. So we think you would have two hours left then.
MR. LASKER: I don't have any problem with that.
MR. MILLER: Okay, great. Hopefully you will be done before then, and certainly I'm not going to go on just to hear myself talk either, believe me. Just -- all right, let's go.
BY MR. LASKER:
Q Okay, back on the record.
Dr. Blair, I would like to continue our discussion of the 2013 AHS data on glyphosate and -- or actually on pesticides and lymphoma risk or non-Hodgkin lymphoma risks, and particularly the glyphosate data.
If I could ask you to turn to page 84 of that document, Supplemental Table 7. And you had testified earlier this morning about the fact that the definition of non-Hodgkin lymphoma has changed over time. Do you recall that?
A Yes.
Q And in this 2013 study, the AHS data is actually presented with two different definitions of non-Hodgkin lymphoma, and Supplemental Table 7 is

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data that uses what is referred to as the old NHL definition.
Do you see that?
A Yes.
Q Okay. And do you recall how the definition changed from the old definition to the definition that's being used today?
MR. MILLER: Excuse me, Counsel. Page number?
MR. LASKER: 84.
THE WITNESS: Lymphoma -- non-Hodgkin lymphoma now includes multiple myeloma and chronic lymphocytic leukemia.
BY MR. LASKER:
Q Okay. So this data table, Supplemental Table 7 is defining non-Hodgkin lymphoma as not including multiple myeloma or CLL; is that correct?
A Correct.
Q Okay. So let's look at the data for glyphosate under the old definition, and that's on page 91.
And on the middle of the page, again we have glyphosate data, both the duration and intensity of use, correct?
A Yes.

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Q And again, we have data on no exposure and then low, medium and high exposure groups, correct?
A Correct.
Q Now, the total number of -- of farmers with non-Hodgkin lymphoma in this analysis is 72 plus 51 plus 60, that's about 183 farmers, correct?
A Correct.
Q So with using this data from the 2013 study, the study is about three times larger than the published data from the 2005 study, correct?
A Okay.
Q And the findings as far as the relative risks are concerned are pretty close to what the findings were with the new definition, correct?
A Correct.
Q As far as non-Hodgkin lymphoma risks?
A Yes.
Q So as we look at no exposures versus different levels of exposure, the ever/never risk ratio is again something like 0.9 or so, correct?
A Probably.
Q Okay. And the same discussion we had previously about how use of this updated data in the IARC meta-analysis would lower the meta-relative

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risk, that same answer would apply for this data as well, correct?
A Yes.
Q Now, I would like to take you to another part of the analysis in the 2013 -- in the 2013 AHS study with respect to different NHL subtypes.
Now, let me -- let's turn first to page 7 of the -- of the paper because they discuss the different subtypes there. And there are five different groups of subtypes discussed under tumor characteristics.
Do you see that?
A Yes.
Q So the -- this is looking at different types of non-Hodgkin lymphoma putting them into categories, correct?
A Correct.
Q And then there is a separate analysis conducted in this 2013 paper looking at the relative risks for the studied herbicides for each of the different NHL subtype categories, correct?
A Correct.
Q And that data -- that analysis starts on page 69. And specifically on page 69, we have data on glyphosate. Let's look first so we can get the

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categories correct -- on page 66 at the beginning of the table, so we can understand what is what.
So page 66 has the different categories of non-Hodgkin lymphoma on those columns on the top, right?
A Correct.
Q Okay. And then if you just keep your finger on that page just so you can remind yourself which categories are which, page 69 is where they have the findings for glyphosate, and I would like to ask you about the glyphosate finding with respect to -- on these different types of non-Hodgkin lymphoma.
So if you look at page 69, the AHS analysis in the first subtype grouping, which is chronic B-cell lymph -- lymphocytic lymphoma, small B-cell lymphocytic lymphomas, and mantle cell lymphomas, the 2013 AHS data analysis does not find any association between glyphosate and that NHL subtype, correct?
A Correct.
Q And if we look at -- in fact, for that subgroup -- oh, strike that.
If you look at the large B-cell lymphoma --

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MR. MILLER: I'm sorry. What page are we on?
MR. LASKER: We're on page 69.
MR. MILLER: Thank you.
BY MR. LASKER:
Q -- the second column is large B-cell lymphoma, correct?
A Diffuse large B-cell, yeah.
Q And the 2013 AHS data actually finds a statistically significant negative association between increased glyphosate exposure and -- and diffuse large B-cell lymphoma, correct?
A For days per year, yes.
Q Yeah. So, in other words, as a farmer has more days of exposure of glyphosate in this study population, the instance of large B-cell lymphoma actually decreases, correct?
A Correct.
Q And that's a statistically significant finding, correct?
A Yes. Trend test.
Q The 2013 AHS data also looks at follicular B-cell lymphomas, correct?
A Yes.
Q And the 2013 AHS analysis does not find

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any association between glyphosate exposure and follicular B-cell lymphomas, correct?
A Deficits that aren't statistically significant.
Q And when you say "deficits," what actually they found in this study, again, is as the level of -- as a farmer had more days of exposure to glyphosate, the incidence of follicular B-cell lymphomas went down, correct?
A No. It means that at any level of exposure, the level, the relative risk was less than 1.0.
Q Correct. Correct. Correct.
A It was 0.7 or 0.6. It does not go down.
Q So what with the 2013 AHS data reveals is that any level of exposure to glyphosate resulted in a lower incidence of follicular B-cell lymphomas, correct?
A Lower -- lower incidence or lower relative risk that isn't statistically significant.
Q And with respect to the category for --
A Other B-cell.
Q -- other B-cell type lymphomas, again we see that with any level of exposure to glyphosate, the incidence of B-cell type lymphomas, the relative

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risk goes down, correct?
A It's lower.
Q And if you look at the point estimate for relative risk, both for the other B-cell type lymphomas and the follicular B-cell lymphomas at the highest level of exposure, the relative risk is 30 to 40 percent lower for farmers with the highest level of glyphosate exposure compared to farmers with no exposure, correct?
A Correct.
Q Did you inform anyone at the IARC working group that the AHS -- that the Agricultural Health Study had conducted additional analyses of glyphosate for various NHL subtypes?
A No, because it wasn't published.
Q Now, let me ask you to turn to page 78 of this paper. And here we have a table that's looking at potential individual and joint effects of pesticide combinations and NHL risk, correct?
A Yes.
Q So now we're looking to see, well, what if you put two different types of pesticides together, what is that -- what is reflected in the data for that, correct?
A Correct.

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Q So let's turn to page 80 and 81. And here we have the data for glyphosate with -- in combination with other types of -- with other -- three other pesticides.
Do you see that?
A Yes.
Q So glyphosate and atrazine, glyphosate and 2,4-D, and glyphosate and chlordane, correct?
A Yes.
Q And the analysis, when you look at it this way for glyphosate only, and the atrazine -- glyphosate and atrazine analysis, glyphosate only is 0.96; for glyphosate only with the glyphosate and 2,4-D, it's 1.1; for glyphosate only and glyphosate and chlordane is 0.9.
So in the glyphosate-only portions of this, again we're not showing any increased risk of non-Hodgkin lymphoma, correct?
A Correct.
MR. MILLER: Object to the form of the question.
BY MR. LASKER:
Q And with respect to combinations, if you look at farmers exposed to glyphosate and atrazine together, there is no increased risk -- statistically

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significant increased risk of non-Hodgkin lymphoma, correct?
A Say again.
Q For farmers who are exposed to both glyphosate and atrazine, there is no statistically significant increased risk of non-Hodgkin lymphoma, correct?
A Correct.
Q For farmers exposed to both glyphosate and 2,4-D, there is no statistically significant increased risk of non-Hodgkin lymphoma, correct?
A Correct.
Q For farmers exposed to glyphosate and chlordane, there is no statistically significant increased risk of non-Hodgkin lymphoma, correct?
A Yes.
Q And this is also information that the IARC working group did not have at the time it made its analysis of glyphosate, correct?
A Correct.
Q Now, I want to show you another document that was from your production to us, and this is an e-mail between you and some of the other Agricultural Health Study investigators in February 2014.
First of all, who is Dr. Alavanha

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(phonetic)?
A Alavanja.
Q Alavanja.
A He was an investigator at the National Cancer Institute and was involved in the Agricultural Health Study.
Q Is he an epidemiologist as well --
A Yes.
Q -- as yourself?
Okay. Let's mark this as Defense Exhibit 21.
(Blair Exhibit No. 21 was marked for identification.)
BY MR. LASKER:
Q Well, first of all, do you recall when it was that the glyphosate data was removed from this AHS study that we've been talking about?
A Not exactly, but it went through many iterations after we decided to remove it because there really wasn't -- you couldn't put it all into one paper.
Q Let's look at an e-mail dated February 28, 2014, and this is an e-mail from Dr. Alavanja to other members of the AHS, including yourself, correct?

A This is the one you just handed me?
Q Yes.
A Yes.
Q Dr. Alavanja, he was the lead author, wasn't he -- was he not, on the 2013 paper that we were just looking at?
A The document, yes. Right.
Q In his February 14, 2014 e-mail, Dr. Alavanja is discussing the AHS team's efforts to get its updated NHL analysis published, correct?
A Yes, I guess so.
Q And I take it from your former answer, you're not -- you don't recall now whether or not the glyphosate data was still in the paper at this point in time or not, correct?
A No, it was not because it had been submitted to a journal, and we never submitted to a journal with that data in it.
Q Okay. So in this e-mail Dr. Alavanja is discussing the fact that the International Journal of Cancer had decided not to publish what was at that point the updated manuscript for non-Hodgkin lymphoma and other pesticides, correct?
A Yes. Insecticides.
Q Insecticides. And Dr. Alavanja

attributes the journal's decision not to publish the AHS paper on NHL and insecticides on the fact that the paper did not present conclusive evidence associating NHL with any of the pesticides examined, correct?
A That's what it says.
Q So Dr. Alavanja is referring to the fact that journals are sometimes less willing to publish epidemiologic studies if they don't find positive associations, correct?
A Yes.
Q This problem is sometimes referred to as publication bias, correct?
A Yes.
Q It's more difficult to get negative findings published, correct?
A Correct.
Q And as a result, sometimes negative findings and epidemiological studies are not published, correct?
A Yes. Right.
Q And Dr. Alavanja notes in the second paragraph of his e-mail -- and let's see, if it's working its way -- I was going to read it: "At the current time" -- and this is the second paragraph

starting at the very beginning: "At the current time IARC is making plans for a new monograph on pesticides."
And so, again, we're talking about the monograph that ultimately became Monograph 112 where you were the chair prior, correct?
A Well, it preceded that monograph certainly.
Q Right. So when he is talking about IARC is making plans for a new monograph on pesticides, he is referring to the monograph that was the one that you ultimately worked on, correct?
A Yes. Right.
Q And Dr. Alavanja states: "Concerning IARC's timetable for selecting candidates for the monograph, it would be irresponsible if we didn't seek publication of our NHL manuscript in time to influence IARC's decision."
Do you see that?
A Yeah.
Q And you would agree that the AHS provides important data regarding potential associations between pesticides and cancer, correct?
A Yes.
Q You would agree that the AHS data and the

most updated AHS data should be considered by IARC, correct?
A Yes.
Q You would agree that it would be --
A Well, wait, wait. If it's been published.
Q And you would agree with Dr. Alavanja that it would be irresponsible for the AHS -- Agricultural Health Study investigators not to publish the updated findings on pesticides and NHL in time to influence IARC's decision, correct?
A No. I don't agree with that. And the reason is because the timetable about when you have to have it published is arbitrary. And doing analyses and writing papers is not wedded to a timetable. And what is irresponsible is to rush something out that's not fully analyzed or thought out.
Q Let me ask you --
A That's irresponsible.
Q I'm sorry. Let me ask you then about the e-mails you were talking about previously with respect to the North American Pooled Project, and we can go back to those if you want. But as I remember, Dr. Pahwa was discussing the possibility of doing

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some analyses of NHL and multiple myeloma and glyphosate in time to get those published for the IARC analysis, right?

A Yeah.

Q And at that time you offered Dr. Pahwa whatever help she needed to see if you could get that data published, and this is before you saw what the data was, correct?

A I don't remember about that. Maybe. I -- I just don't remember about that.

Q So --

A I mean about whether I had seen the -- any data or not. I mean tables come out. There's -- none of this is listed in -- glistened down in your mind about where things are.

Q Well, if we can go back to Exhibit 14, and that should be in your pile there, but I can give you another copy if you want if that would be easier. Dr. Blair.

A Yeah.

Q So -- so this, just to refresh our jury's recollection, was prior to Dr. Pahwa going back and finding out what the data showed from NAPP for glyphosate and NHL or MM and -- or HL, Hodgkin lymphoma. You were offering Dr. Pahwa whatever help

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you could to try to get the data published in time for the IARC monograph meeting, correct?

A Yeah.

Q But then after we -- after you determined and found out what the data showed with respect to glyphosate and these cancers, the data wasn't published, correct?

A The paper wasn't finished, and you have to finish things in the analysis and the writing before you can publish it.

Q Okay. So let's go back then to what the IARC analysis was and what the working group did.

So the IARC working group then in its analysis of the epidemiology was relying upon -- was not relying upon the most up-to-date AHS data, correct?

A It was relying upon the most up-to-date published data, and that's always the standard at IARC.

Q I understand. But just so the record is clear, IARC was not relying upon the most updated analysis that you were aware of from the AHS data with respect to glyphosate and non-Hodgkin lymphoma, correct?

A Now you present it as if the analyses

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were completed. Analyses were done, manuscripts were in description, but the work wasn't finished, which means it's incomplete, and that you don't want to be reporting on. And we didn't.

Q So -- understood.

And because of the fact that you had not completed the manuscript that was in at least manuscript form in March of 2013 in time for it to be a publication by March 2015, IARC didn't have that information?

A That's correct.

Q Now, going back to this issue of publication bias, did the Agricultural Health Study decide not to include data regarding glyphosate and non-Hodgkin lymphoma in its updated publication because the data did not show a positive association?

A No. It decided to do pesticides first because we proceeded -- insecticides first, we sort of proceeded down that line early on and didn't think we had time to switch and do the other when IARC become clear that that's what they were going to look at.

Q Now, you and other AHS investigators are certainly aware, and we looked at some of this discussion previously, that questions have arisen

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about IARC's -- I won't say questions -- have arisen about IARC's classification of glyphosate, correct?

MR. MILLER: Objection to form.

Questions by whom, Monsanto?

BY MR. LASKER:

Q Well, let me put it this way: You're aware that Christopher Portier, we looked at one of his publications, has been defending the IARC classification of glyphosate by relying on the old data from the Agricultural Health Study to try and minimize the importance of that study, correct?

A Well, I guess as he reported about what IARC did, it was the -- there's no new published data from AHS to look at.

Q And --

A Is that what you're saying?

Q Well, Dr. Portier, though, as we looked at previously, in defending the IARC classification, has included arguments that the AHS data -- the AHS study in 2005 was of smaller numbers and limited follow-up. Remember we looked at that?

A Yes.

Q Okay. Nearly four years have passed now since you and the other AHS investigators looked at the updated and more robust AHS data and found no

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association between glyphosate and non-Hodgkin lymphoma, correct?
MR. MILLER: Object to the form of the question.
BY MR. LASKER:
Q You can answer.
MR. MILLER: You can answer.
BY MR. LASKER:
Q I will repeat the question.
A Yes.
Q Nearly four years have passed now since you and other AHS investigators looked at the updated data and saw that it did not show any association between glyphosate and non-Hodgkin lymphoma, correct?
MR. MILLER: And I object to the form of the question because you intentionally leave out that it's not statistical.
THE WITNESS: Yes, we -- we've looked at some data like that, but we haven't looked at a finished product.
BY MR. LASKER:
Q Now, the updated AHS data would directly answer the questions Dr. Portier raised about the size of the study and about the length of follow-up time, correct?

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A Yes.
Q But you and the other AHS investigators have, as of today's date in March 2017, not yet published this updated AHS data on glyphosate, correct?
A Correct.
Q In fact, the AHS has actively sought to prevent Monsanto from learning about this updated AHS data, hasn't it?
A I -- I -- I don't know about that.
Q Well, let me ask you -- let me show you another e-mail from your document production to us.
(Blair Exhibit No. 22 was marked for identification.)
BY MR. LASKER:
Q This is Defense Exhibit 22.
And this is an e-mail in which Mr. Sandler is responding to your e-mail to him attaching a copy of a subpoena we sent to you in this litigation, correct?
A Yes.
Q Mr. Sandler notes --
A It's a woman.
Q I'm sorry?
A It's a woman.

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Q Oh, Ms. Sandler. Dr. Sandler?
A Dr. Sandler.
Q Dr. Sandler. Thank you.
Dr. Sandler notes that our subpoena to you, and Dr. Sandler -- just so I understand, Dr. Sandler is with NIEHS?
A Correct.
Q The National Institute of Health?
A Environmental Health Sciences.
Q And Dr. Sandler notes in her e-mail back that our subpoena to you was seeking the same AHS papers and requests for data that Monsanto had separately sought from the AHS investigators affiliated with the National Institutes of Health through a FOIA request, correct?
MR. MILLER: Object to the form of the question. Intentionally misrepresenting the document. Read the document, Counsel.
BY MR. LASKER:
Q Dr. Blair?
A Apparently that's it.
Q And Dr. Sandler states, quote: We were hoping to make the Freedom of Information Act go away by offering data through a data sharing agreement.
Do you see that?

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A I do.
Q But -- and then Dr. Sandler says: "It's probably time to seek protection from NA -- NIH lawyers." Correct?
A Yes.
Q So the AHS investigators at the National Institutes of Health were seeking protection from National Institutes of Health lawyers to prevent Monsanto from getting access to the updated AHS data showing no association between glyphosate and non-Hodgkin lymphoma.
MR. MILLER: Object to the form of the question.
THE WITNESS: Maybe they did. I'm just -- I see the e-mail. It's the only thing I know about it.
BY MR. LASKER:
Q Okay. But you received this e-mail, correct? It's from your document production.
A Yes. But I'm saying I see this e-mail and that's the only thing I know about this.
Q You would agree that it's not appropriate for the National Institutes of Health to be seeking protection from its lawyers to prevent Monsanto from learning that the updated AHS data showed no

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association between glyphosate and non-Hodgkin lymphoma, don't you?
MR. MILLER: Objection. Calls for a legal conclusion. We already had one subpoena quashed.
THE WITNESS: I guess I don't see -- give me your question again, because I don't see it here. They're asking for data. That's the raw data.
BY MR. LASKER:
Q So do you believe -- well, strike that.
You would agree that it's not appropriate for the National Institutes of Health to turn to its lawyers to protect it from Monsanto's efforts to obtain updated Agricultural Health Study data with respect to glyphosate and non-Hodgkin lymphoma, don't you?
MR. MILLER: Objection to the question. It calls for a legal conclusion, when you've already lost before the court.
THE WITNESS: I don't think I can provide -- I mean there is a Freedom of Information Act that government employees follow, so I --
BY MR. LASKER:
Q Let me --
A -- I don't think I have any expertise in

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this.
Q Do you think it's appropriate for the National Institutes of Health to try and use legal means to avoid providing Monsanto with updated Agricultural Health Study data?
MR. MILLER: Object to the question. Requires a legal conclusion and on a motion to quash you've already lost, Counselor. And that's the third time you've asked the witness the same question. You're clearly harassing the witness.
BY MR. LASKER:
Q Do you think it's appropriate for the National Institutes of Health to use its lawyers to prevent Monsanto from getting updated AHS data that shows no association between glyphosate and non-Hodgkin lymphoma?
MR. MILLER: Objection to the question. Calls for a legal conclusion on a motion to quash you have already lost and will lose when you try again. You are harassing the witness. That is the fourth time you have asked the same question. You have only a certain amount of time left.
Ask it again and there will be a fifth objection.
MR. LASKER: Okay. So you are objecting

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to us finding out why the NIH has not given us the update from the Agricultural Health Study showing no association between glyphosate and cancer --
MR. MILLER: I'm referring to the National Institute of Health and their attorneys to find out what their legal rights might be, Counselor.
BY MR. LASKER:
Q And, Dr. Blair, perhaps counsel may try to prevent you from answering this question one more time, but I will ask you one more time.
MR. GREENE: Objection. I don't know if Dr. Blair --
MR. LASKER: He can answer that -- if that's his answer, that's fine. I just want an answer from him.
MR. GREENE: It's his position --
MR. LASKER: That's his -- if he has that answer, that's fine. I need to hear an answer from him, though. He's the witness.
MR. MILLER: What's the question, Counselor?
BY MR. LASKER:
Q Dr. Blair, do you think it's appropriate for the National Institutes of Health to use their lawyers to prevent Monsanto from getting updated

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Agricultural Health Study data showing no association between glyphosate and non-Hodgkin lymphoma?
MR. MILLER: And I object to the question. This calls for a legal conclusion on the harassing subpoenas that have been sent out by Monsanto and have been quashed by this court as recently as two weeks ago. You have now asked the witness the same question six times. Ask it of the National Institutes of Health attorneys. Ask it of Judge Chhabria, see if Judge Chhabria will give it to you.
BY MR. LASKER:
Q Dr. Blair, do you have an answer to my question?
MR. MILLER: You don't have to answer that.
MR. LASKER: He's not your witness.
MR. MILLER: He's not my witness, but --
BY MR. LASKER:
Q Dr. Blair, do you have an answer to my question?
A No.
Q All right. Dr. Blair, you have had the opportunity to discuss the IARC classification with various interested parties over the past three years,

correct?
A In general, yes. Right.
Q I would like to ask you about some of those communications.
(Blair Exhibit No. 23 was marked for identification.)
BY MR. LASKER:
Q Marked as Exhibit 23. And this is an e-mail string from March 23rd to March 25th of 2015 between you and a number of members of the IARC staff, including Kurt Straif, Dana Loomis and Kate Guyton, correct?
A Yeah.
Q And in the beginning of this e-mail chain, which again is at the end of the physical documents, or actually it's the third page in, you are advising IARC about a number of press interviews that you had conducted in the wake of the IARC classification of glyphosate, correct?
A Yes.
Q And you state here that the reporters questioned you about why the IARC evaluation of glyphosate was different than those done earlier elsewhere, correct?
A Yes.

Q You stated -- I'm sorry, you state that your answer to the question was that, quote: New information becomes available over time. Right?
A Yes.
Q In discussing this new information, did you inform any of these reporters about the updated Agricultural Health Study data finding no association between glyphosate and non-Hodgkin lymphoma based upon a study that was three to four times larger than the 2005 AHS paper?
MR. MILLER: Objection to the form of the question.
THE WITNESS: No, because we're talking about papers that are published.
BY MR. LASKER:
Q Is there any rule that reporters impose like IARC imposes that prevents you from informing them about scientific data if it's not published?
A There is when talking about the IARC data, which is based on published studies.
Q Well, did the reporters -- here you're saying new information becomes available over time. Did you tell those reporters, Listen, I'm only going to talk to you about the published data and not the unpublished data that I'm aware of?

A No, I certainly didn't do that.
Q You've also had a --
A Let me add to that, though. Yes, I didn't do that, but it's only prudent and appropriate to talk about studies that are finished before you start talking to the press about them.
Q And --
A Because things change.
Q And it's your decision with the AHS, as an AHS investigator, to determine and decide when you're going to try and submit things for them to be published, correct?
A Absolutely.
Q You've also had a number of discussions with a reporter named Carey Gillam, correct?
A Yes, I think so.
Q Did you ever tell Carey Gillam about the updated AHS data showing no association between glyphosate and non-Hodgkin lymphoma?
A No.
Q Now, Ms. Gillam reached out to you in September of 2016, and let me show you the document because I don't know if you will remember this.
And let's this -- we will mark this as Exhibit 24.

(Blair Exhibit No. 24 was marked for identification.)
BY MR. LASKER:
Q And this is an e-mail exchange between you and Carey Gillam, correct?
A Yes.
Q And in this e-mail she is reaching out to you in September 2016 after a phone call she had with Chris Portier, correct?
A Yes.
Q And again, we've discussed the fact that Chris Portier has been critical of the published 2005 AHS study because of what he viewed as limited numbers and limited use of follow-up, correct?
A Yes.
Q Did the issue of the AHS study come up during this conversation with Ms. Gillam?
A The issue of the AHS study?
Q Yes. And Dr. Portier's criticisms of that study.
A I -- I don't recall.
Q Do you recall if Ms. Gillam was following up on Chris Portier's observations about the 2005 AHS study?
A Well, she had talked to him, but I --

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nothing do I remember specific what was in the conversation she had with him.
Q But you do know that you did not tell her about the updated AHS data we've been discussing, correct?
A Correct.
Q You also contacted -- you were also contacted by someone named Marie-Monique Robin, correct?
Well, let me show you --
A Is there a document here somewhere?
Q There will be. It's the next one in line. Just wait a second.
A Doesn't ring a bell.
MR. LASKER: This will be Defense Exhibit 25.
(Blair Exhibit No. 25 was marked for identification.)
MR. MILLER: Thank you. 25.
MR. LASKER: 25.
BY MR. LASKER:
Q And so this is an e-mail in August of 2016 from Marie-Monique Robin to you, correct?
A Yes.
Q And in her e-mail to you, Ms. Robin

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explains that she is the author of a number of books that have been sharply critical of Monsanto and glyphosate, including, quote, Our Daily Poison, correct?
A I assume that is in there somewhere, but --
Q It's right at the beginning of her e-mail to you. "I am the author of documentaries and books, The World According to Monsanto, Our Daily Poison --
A Okay. Yes.
Q -- Crops of the Future, Good Old Growth.
A Yes.
Q And she also in that e-mail in the next paragraph accuses Monsanto of crimes against the environment and the ecosystem because of its sales of glyphosate, correct?
A Well, I don't see exactly the words you just read, but --
Q Well, she talks about submitting -- and about halfway through, she talks about making recommendations to the International Criminal Court in The Hague to recognize the crime of ecocide.
Do you see that?
A Okay.
Q So she is suggesting that Monsanto should

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be tried in the International Court -- Criminal Court in The Hague, correct?
A I -- I guess. I mean this is not something I -- I mean this sounds legal that I -- I can guess what the words say, but I have no idea what that means.
Q And Ms. Robin was referred to you by Kathryn Guyton of IARC, correct? That's what her subject line says.
A Yes.
Q Do you know why IARC suggested that Ms. Robin speak with you about glyphosate and her views about the International Criminal Court?
A No.
Q Do you believe --
A Other than I assume it's because I was on the IARC panel.
Q Do you believe that the sale of glyphosate amounts to a violation of international criminal law?
A I --
MR. MILLER: Calls for a legal conclusion.
THE WITNESS: Yeah, I --
BY MR. LASKER:

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Q You don't have an opinion one way or the other on that?
A No.
Q Did you --
MR. LASKER: Whoever is on the phone, if they could moot -- mute their line, please.
MR. MILLER: Is anyone on the phone?
MS. WAGSTAFF: Yeah, Aimee Wagstaff. I will put it back on mute.
MR. MILLER: Thank you. Thank you, Ms. Wagstaff.
BY MR. LASKER:
Q Did you tell Ms. Robin about the updated Agricultural Health Study data that showed no association between glyphosate and non-Hodgkin lymphoma?
A No.
Q Okay. You were also contacted on March 6th --
A I did not tell her about the incompleted AHS study --
Q Understood.
A -- that purports to show no -- yes. Let's use those words from now on.
Q And again, as an investigator for the

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AHS, it was your determination whether to submit that data for publication or not, correct?
A Yes. Not mine; authors.
Q You were one of --
A I'm just one of the authors.
Q -- the authors. Okay.
(Blair Exhibit No. 26 was marked for identification.)
THE WITNESS: Are we done with the one we just looked at?
MR. LASKER: Yes, we are.
BY MR. LASKER:
Q So Exhibit 26, now you have an inquiry from Mr. A Martin from Bloomberg News, correct? Andrew Martin?
A Yes.
Q And in his e-mail to you on March 24th, 2016, he states, quote: I wonder if you would be willing to talk about the pesticide -- pesticide industry's response to the IARC report on glyphosate, in particular criticism that was specific to you.
Do you see that?
A Yes.
Q And you in response to this reach out to IARC asked them what -- what this might be about,

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correct? You reach out to Kathryn Guyton and Kurt Straif of IARC.
You have to go backwards. It's the first page that has your response.
A Well, I certainly referred him to IARC. I --
Q Well, you reach out to IARC and say, any idea of what criticisms he is referring to --
A Okay, yes. I see it.
Q -- or any advice.
A Yes. Right.
Q So you asked IARC for advice as to how to respond to Andrew Martin from Bloomberg News.
A The -- actually, the decision was always who was going to talk to whom. IARC people talk to some, I talk to other people, and it was just a decision of who was going to talk to him.
Q So IARC in their response to you state that Mr. Martin might be talking about two potential criticisms, correct? There are two potential issues that come to mind?
A This is the top?
Q The top e-mail.
A Yes.
Q And the first potential criticism that

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IARC identifies is the issue of the negative AHS study outweighing the positive studies on non-Hodgkin lymphoma, correct?
A Okay. Yes.
Q And the second potential criticism is about experts reviewing their own work --
A Yes.
Q -- which is the issue that you had raised at the very beginning of this process, correct?
A Yes.
Q And Mr. Straif of IARC refers you to some IARC Q&A in response to those criticisms regarding IARC's treatment of the Agricultural Health Study, correct?
"We have posted additional material on our website responding to some criticisms." Do you see that?
A This is still in the top?
Q Yeah, the top e-mail, the third paragraph: After the latest invitation to the European Parliament, we have posted additional materials on our website" --
A Okay. Okay. Yes. All right.
Q -- "responding to some criticisms including the AHS issue." Correct?

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A Okay. Yes.
Q So let's take a look at that IARC Q&A document.
(Blair Exhibit No. 27 was marked for identification.)
BY MR. LASKER:
Q Exhibit 27. And this is from the IARC website dated March 1st, 2016. So this is a few weeks before the e-mail exchange we just looked at, correct?
A Yes.
Q So this is the Q&A on glyphosate that IARC refers you to with respect to the criticisms of the AHS study, correct?
A Yes.
Q Now, with respect to the Agricultural Health Study, if you can go to page 2, there is in the middle of the page in bold a discussion of the Agricultural Health Study and the criticisms of IARC's dealing with that study and then IARC's response. Correct?
A Yes.
Q And IARC in its Q&A states: "The Agricultural Health Study has been described as the most powerful study, but this is not correct. The

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AHS data on cancer and pesticides use in more than 50,000 farmers and pesticide applicators in two states in the U.S., the weakness of the study is that people were followed up for a short period of time, which means fewer cases of cancer would have had time to appear." Correct?

A Yes.

Q But as of this date, you were aware and had been for three years that there was more AHS data that had a longer follow-up and some four times more cases of NHL than had been discussed in the 2005 published paper, correct?

A Yes. For analyses that had not been completed.

Q Did you write back to Kurt Straif at IARC and point out that there is actually more updated data available from the AHS and that this criticism was no longer valid?

A No, because IARC works on papers that have been published.

Q And the IARC Q&A also refers in that last -- second paragraph, last paragraph in response to the questions about the Agricultural Health Study that the IARC working group had done an analysis -- statistical analysis of the results of all of the

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available studies on glyphosate and non-Hodgkin lymphoma, which includes the AHS and all the case-control studies, and that's referring to the meta-analysis, correct?

A Yes.

Q And the Q&A states that the data from all the studies combined showed a statistically significant association between non-Hodgkin lymphoma and exposure to glyphosate, correct?

A Correct.

Q And did you write back to Kurt Straif and point out that there was updated both from the Agricultural Health Study and through the NAPP that, if included, would result in that meta-analysis not showing a statistically significant increased risk of non-Hodgkin lymphoma?

A No, because those studies hadn't been published and weren't finished.

Q Now, you have also had conversations since the IARC glyphosate monograph with scientists at EPA, correct?

A Yeah, I guess. I --

MR. LASKER: Let's mark this as Exhibit 28.

(Blair Exhibit No. 28 was marked for identification.)

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BY MR. LASKER:

Q Now, Dr. Blair, does EPA have any rule that states that it will not look at data unless it's been published, to your knowledge?

A Not to my knowledge.

Q Okay. So this is an e-mail chain from May 2016 between you and a scientist at EPA named Natasha Henry. Did you in fact meet with EPA about glyphosate on or about May 2016?

A I'm trying to remember whether we met or just talked. I actually don't remember.

Q Okay. Do you recall if you've had more than one conversation with EPA about glyphosate?

A I had two conversations with this person. But two for sure.

Q Okay. And did you tell Dr. Henry or anyone else at EPA about the updated AHS findings of no association between glyphosate exposure and AH -- and non-Hodgkin lymphoma that are set forth in that 2013 study we just looked at?

A No, because the studies weren't finished and weren't published.

Q But we just talked about the fact that EPA does not limit its anal- -- analysis to published

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data, correct?

A But it makes a difference to scientists to not release things before you're finished with it. And that was the case here.

Q Did EPA ask you any questions about the AHS?

A I don't remember.

Q And you are aware that EPA has -- is in the process of -- of conducting its analysis and has issued some findings with respect to glyphosate and cancer, including non-Hodgkin lymphoma, correct?

A I've seen it in the press.

Q EPA, in reaching that determination, has not had the benefit that you have of having seen the updated Agricultural Health Study data showing no association between glyphosate and non-Hodgkin lymphoma, correct?

A Correct.

Q Now, you've also been contacted by plaintiffs' attorneys in this litigation, correct?

A Yes.

Q Let me mark as the next exhibit in line, Exhibit 29.

(Blair Exhibit No. 29 was marked for identification.)

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MR. MILLER: 28. I could be wrong.
MR. LASKER: This is 29.
THE WITNESS: This is 29.
MR. MILLER: Okay, 29 it is.
BY MR. LASKER:
Q And this is an e-mail exchange between you and Kathryn Forgie, who is sitting at the end of this table, at the Andrus Wagstaff law form -- law firm, correct?
A Yes.
Q And did you in fact meet with Ms. Forgie or any other plaintiffs' attorneys in December 2015?
A Well, I must admit I don't remember, but this sounds like I did. So I must have.
Q Well, let me ask you --
A I know I talked to her.
Q Separate from this document, you've had -- you've had a conversation with plaintiffs' counsel.
A Absolutely. Yes.
Q How many conversations have you had with plaintiffs' counsel in this litigation prior to today?
A Well, it -- I'm not sure I can give a precise answer, but not many.

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Q A half dozen?
A I don't think it was that many, but I don't know for sure.
Q Three or four?
A That would be my guess, three or four.
Q And what -- what did you and plaintiffs' counsel discuss during these conversations?
A Well, as I recall, they were asking about what went on at IARC and I think whether or not I would provide advice regarding this. And I said no.
Q Did they ask you any questions about your own scientific research including the Agricultural Health Study?
A I don't remember.
Q Do you recall if you shared with plaintiffs' attorneys any information about either the North American Pooled Project or the Agricultural Health Study analyses that were still going forward?
A I doubt it.
Q You said you had three or four conversations with plaintiffs' counsel.
A No, I said I guessed.
Q So the first conversation, was the issue of whether or not you would serve as an expert witness raised?

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A Well, I'm not sure whether it was the first conversation or which one. I --
Q So there were a series of conversations in which you guys were discussing the possibility, three to four conversations; is that fair?
A There was more than one. I don't actually know what the number was. But adding the numbers, it's more than one. That's all I know for sure.
Q Do you recall how long these conversation lasted?
A Not long.
Q Let me show you an e-mail from May of 2016. And this is an e-mail exchange between you and a Dr. Weisenburger. Do you who Dr. Weisenburger is?
A I do.
Q Who is Dr. Weisenburger?
A He is a cancer researcher.
MR. MILLER: May I have a copy, please. Exhibit 30? Maybe it is behind there.
MR. LASKER: I'm sorry. I did that. Just -- sorry.
MR. MILLER: Sure. Okay. Exhibit 30.
(Blair Exhibit 30 was marked for identification.)

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BY MR. LASKER:
Q Okay. So this is an e-mail that was forwarded to you from Dr. Weisenburger. Again, I'm sorry, I missed it. Who was Dr. Weisenburger?
A Pardon?
Q Who is Dr. Weisenburger?
A He's a pathologist who does epidemiologic studies like I do.
Q And he -- he actually is one of the other investigators with you on the North American Pooled Project?
A He is.
Q And so he also would be aware and would have been aware of this analysis of the NAPP data that we looked at earlier before the IARC monograph --
A Well, probably, but there's a lot of co-authors in that study and they get informed at different times, depending on where you are in the analysis, and I don't remember about this one. Eventually he would be informed if he wasn't then.
Q And so Dr. Weisenburger here -- Dr. Weisenburger, these e-mails reflect, is serving as an expert witness for plaintiffs' counsel, correct?

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A I think so.
Q You have had conversations --
A Yes.
Q -- with him where he's told you that, correct?
A Yes.
Q And in this e-mail he is passing on to you, he is letting you know that plaintiffs' counsel have contacted him about discussing his first case, correct?
A Yes.
Q What did Dr. Weisenburger tell you about his meetings with plaintiffs' counsel regarding this litigation?
MR. MILLER: Objection.
THE WITNESS: I -- I -- I don't remember.
BY MR. LASKER:
Q Do you recall having conversations with him about the NAPP data and how and when that might be published?
A I'm sure we had conversations about that.
Q Well --
A I don't remember details, but I'm sure we had conversations.
Q Okay. You had mentioned earlier with

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respect to the NAPP that there has been a number of -- more than one presentation of that data to date, correct?
A Well, two for sure. Maybe more than that.
Q And during that process, the NAPP investigators, you and Dr. Ferguson and other -- Dr. Weisenburger, I'm sorry, and others have been looking at the data in different ways, correct, and reporting it in different ways? Is that fair to say?
A We've been looking at the analyses that have been done trying to make judgments about what it says. Is that what you mean?
Q Well, in your presentation of the data, the data you're presenting had been changing over time, correct?
A I don't actually know whether that's true or not.
Q Okay. Well, let me show you an e-mail exchange between NAPP investigators -- actually, before we get to that, let's just refer back to Exhibit 29, which is the e-mail exchange between you and Ms. Forgie, plaintiffs' counsel.
And if you look at the first e-mail in that chain, it's dated -- again, it's the last page,

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so the second to the last page or the last page of the document. It's from Ms. Forgie to you, and it states: "Dear Dr. Blair" -- and this is dated on August 20, 2015, correct? Go to the last page.
So Ms. Forgie sent you this e-mail, plaintiffs' counsel, on August 20, 2015, correct?
A August 20. I thought you said August 15. August 20.
Q And in this e-mail, plaintiffs' counsel indicates that they have spoken to you twice with regard to pesticide exposure and cancer, and she notes that she is an attorney with Aimee Wagstaff, correct?
A Okay. Yes.
Q Okay. So I just want to put that in time.
If we can go back now to what has been marked as Exhibit 31. This is now an e-mail exchange on August 26, 2015, correct? I'm sorry.
A I don't have 31.
(Blair Exhibit No. 31 was marked for identification.)
MR. LASKER: I'm sorry, I need to give you one here. Let me finish this process.
MR. MILLER: 31?

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MR. LASKER: 31.
MR. MILLER: 31.
BY MR. LASKER:
Q So this is -- this e-mail is about a week after your e-mail exchange with plaintiffs' counsel, correct?
A Yes. Yes. August 20 -- 26th.
Q So if we can now look at the earliest e-mail in this string, Exhibit 31, so, again, you got to go back to the end and read forward, Dr. Pahwa is advising you and other NAPP investigators that she was going to be presenting findings about glyphosate use and NHL risk at the International Society for Environmental Epidemiology in August -- on August 31st, 2015, correct?
A Yes.
Q And she states in her e-mail, the very last line, that she is sharing her slide deck for that presentation with you all in advance, quote, given the sensitivity of the topic, correct?
A Yes.
Q And in your e-mail response, which is -- starts on the bottom of the first page of this document and then continues through the second page, you state that Dr. Pahwa will need to be prepared for

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questions after the presentation and that the -- the question is going to be, Do these data indicate that the IARC evaluation was wrong?
Do you see that?
A It's on the first page?
Q It's on the second page.
A Yes.
Q And you also suggest alerting IARC in advance of the meeting, correct?
A Yes.
Q Now, you do not suggest alerting Monsanto to the NAPP data, do you?
A No.
Q And if you look at page -- the first page of this e-mail chain, in fact, you were concerned that Monsanto might be, quote, scanning programs of meetings like ISEE and might find out about the NAPP findings, correct?
A Well, if you're presenting at a meeting, you can't be concerned about them finding it because, again --
Q Doctor --
A -- it's at the meeting.
Q Dr. Blair, do you see --
MR. MILLER: Don't. Stop. Let him -- I

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object.
Doctor, if you want to finish the answer, go right ahead.
MR. LASKER: I'm sorry.
MR. MILLER: He doesn't have the right to interrupt you.
BY MR. LASKER:
Q I'm sorry, did you have more to say? I thought you were finished.
A It's -- if you're presenting at a meeting, you would assume people might be able to get something, and you just want to be prepared to deal with questions that might come. It's known that this is pretty topical.
Q You state in your e-mail that, quote: I just suspect Monsanto has someone scanning programs of meetings like ISEE and would want to get press if they can. Correct?
A Yes. Yes.
Q And you were worried about that possibility, correct?
A Worried about the person presenting not being prepared to address questions that are relevant to them.
Q And for that reason, you decided -- you

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told Dr. Pahwa that she should alert IARC in advance, correct?
A Because it would affect what IARC gets, yeah.
Q Now, let me show you another e-mail that branches off in this e-mail chain of Exhibit 31, Exhibit 32.
(Blair Exhibit No. 32 was marked for identification.)
MR. MILLER: 32.
MR. LASKER: 32.
MR. MILLER: Gotcha.
BY MR. LASKER:
Q And this e-mail chain sort of branches off from the earlier e-mail chain, and the second e-mail in this chain starting from -- again, we've got to go to the back, so we have to read this backwards, I apologize -- but the second to the last page, there is an e-mail that was sent by you at 4:11 p.m. on August 26, 2015.
Do you see that?
A Yeah.
Q So that e-mail was sent -- and, I'm sorry, to make you do this, if you go back to Exhibit 31 -- this e-mail was sent roughly nine hours

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after you -- after you had raised the issue of the questions that Dr. Pahwa might receive about her presentation, correct?
A Okay.
Q And as set forth in this e-mail now at 4:11 p.m., and Dr. Pahwa's responding e-mail at 4:22, Dr. Pahwa had revised her slide presentation in response to comments she had received from you and from the other NAPP investigators, correct?
A Yes.
Q She also states that the abstract of the NAPP findings for glyphosate and non-Hodgkin lymphoma, quote: Does not appear on the ISEE website or in the conference program. Correct?
A Yes.
Q So she addressed your concern about the possibility that Monsanto might learn about these NAPP findings. Correct?
A Yes.
Q Dr. Pahwa agrees with you that it would be best for her not to deal with any potential press at the COP conference about her NAPP findings, correct?
A Yes.
Q She states, though, that she will prepare

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some talking points, and that she will share them with you and the rest of the group prior to the conference, correct?
A Yes.
Q In response, you again suggest that the abstract and the slide deck should be shared with IARC prior to the ISEE conference, correct?
A Yes.
Q So even though you now were sure that Monsanto was unlikely to learn about the NAPP findings, you still wanted IARC to be prepared in the event that the findings somehow got out to the press --
A Yes.
Q -- correct?
A Yes.
Q And then you prepared some talking points for Dr. Pahwa in case she was questioned about the NAPP findings and how they relate to the IARC evaluation, correct?
A Which -- where are you reading --
Q The first page now, the last e-mail: "I think we also should provide some suggested talking points in case" --
A Okay, yes. First page, yes.

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Q So you prepared some talking points for Dr. Pahwa just in case --
A Yes.
Q -- she was asked about IARC?
A Yes.
Q Now, Dr. Pahwa gave a subsequent presentation about the NAPP findings in connection with IARC's 50th anniversary conference in June 2016, correct?
A Yes.
Q Let me show you an e-mail chain with respect to that presentation. And this is going to be 33.
(Blair Exhibit No. 33 was marked for identification.)
BY MR. LASKER:
Q And this is the e-mail chain between various of the NAPP investigators, including Dr. Cantor, correct?
A Yes.
Q And you are on there as well.
A From Dr. Cantor, yes.
Q Who is Dr. Cantor?
A He is a retired epidemiologist from the National Cancer Institute.

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Q And Dr. Cantor actually was lead author on one of the first studies on -- that reported data on glyphosate and non-Hodgkin lymphoma, correct?
A Correct.
Q And in his original case-control study, he did not find any association between glyphosate and non-Hodgkin lymphoma, correct?
A That's what I remember.
Q But that data has now been pooled into the NAPP, correct?
A Yes.
Q Now, in this e-mail chain, there is a discussion of five abstracts that the NAPP was preparing for the IARC conference, correct?
A Yes.
Q And one of these abstracts addressed the NAPP findings that were going to be reported with respect to glyphosate and non-Hodgkin lymphoma, correct?
A Yes.
Q And Dr. Cantor in his e-mail talks specifically about that abstract with respect to glyphosate, correct?
A Yes.
Q And in his e-mail about the NAPP

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findings, Dr. Cantor states that the findings with respect to glyphosate and NHL, quote, are less than convincing given that control for other pesticides resulted in attenuated OR, which aren't in the abstract. Correct?
A Yes.
Q So we discussed earlier the NAPP data in June 2015 which showed no association between glyphosate and non-Hodgkin lymphoma when adjusted for other pesticides. You recall that, correct?
A Yes.
Q And Dr. Cantor is explaining in his e-mail now in January 2016 that the NAPP data still did not show any statistically significant association between glyphosate and non-Hodgkin lymphoma when the data was controlled for other pesticides, correct?
A Correct.
Q But in presenting the NAPP data for the IARC meeting, the abstract only reports odds ratios without controlling for other pesticide exposures, correct?
A I don't remember.
Q Well, Dr. Cantor is expressing that concern in this e-mail, correct, that the data on --

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the control data is not reported in the abstract?
A Well, he suggests the last sentence be removed.
Q He states that: "Results in the second abstract glyphosate -- about glyphosate are less than convincing given that control for other pesticides resulted in attenuated OR which aren't in the abstract."
So this concern is that the presentation of the NAPP data was not making clear that when the data was controlled for other exposures, there was no association between glyphosate and non-Hodgkin lymphoma?
A I understand all that. I don't -- but then he suggests it should be removed from the -- and so I'm not clear whether he is suggesting remove it from the abstract for this meeting or from some later publication. I'm not clear about that.
Q But his concern was that we were presenting -- the NAPP was presenting data without presenting the data on controlled --
A Clear --
Q -- exposures with glyphosate and other pesticides?
A Yes.

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Q Okay. So let's turn to the slide deck that the NAPP presented at that IARC conference.
(Blair Exhibit No. 34 was marked for identification.)
MR. MILLER: And this is Exhibit 34.
BY MR. LASKER:
Q So you could take a chance to look through it. This document Exhibit 34 is the presentation that was made -- strike that. Hold on a second. I'm not sure I have the right one. I don't know if this is the right one. This is June 2016 -- yeah, no, I'm sorry, this is right. Okay.
So this is the presentation that was made in June 2016 as part of the IARC @ 50 Conference, correct?
A I think so, yes.
Q And unlike the June 2015 data that we -- that we talked about earlier which presented only the controlled odds ratios accounting for other pesticide exposures, this June 16 presentation also presents odds ratios not controlled for those exposures, correct? So it's presenting the uncontrolled data.
A (Perusing document.)
Q Do see the reports that -- both for uncontrolled and for controlled for the pesticide

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exposures, have both those data in there?
And if you look at the tables -- on the bottom of those tables, they have ORA and ORB. So ORA is the unadjusted numbers and ORB is the adjusted numbers. Do you see that?
A Yes.
Q And so by presenting the unadjusted data, NAPP was able to present data that it could report as being statistically significant with respect to glyphosate and non-Hodgkin lymphoma, correct?
A Where on this table it says it's adjusted for --
Q Yes.
A -- 2,4-D, diazinon and malathion.
Q Right, that's ORB, correct?
There's ORA and there's ORB, and you present, unlike in June 2015 when you controlled for other exposures and just presented the controlled data, in this presentation you've now added in a presentation of the uncontrolled odds ratios, correct?
A Oh, yes. If that's your point, yes. I thought you were saying it was only presenting ORA. Well, it presents both.
Q It presents both. And by presenting the

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uncontrolled data, you therefore were able to present NAPP data to IARC that had a numerical number that was statistically significant, correct, with respect to glyphosate?
A That is the case, yes.
Q And unlike the June 2015 data we looked at, the June 2016 presentation does not provide any odds ratios that exclude proxy respondents and relied solely on the more reliable self-reported data, correct?
A Suggested for use of proxy respondents.
Q It does not -- it does not present data solely for self-respondent data, though, correct?
A It's suggested for use of proxy -- proxy respondents.
Q I understand. My question is, it does not present data solely from self-reported --
A That --
Q -- correct?
A That adjustment does literally the same thing.
Q Well, we know from the June 2015 data that when self-responded only data from the NAPP is used, the result is virtually null, with odds ratio of 1.04 for glyphosate and non-Hodgkin lymphoma,

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correct?
A Yes.
Q But that information is no longer in the presentation in 2016; that's been -- correct?
A It's adjusted for proxy respondents.
Q That data point, 1.04, showing a null result from the most reliable exposure data for glyphosate and non-Hodgkin lymphoma is no longer in the presentation.
MR. MILLER: Objection. Asked and answered. He said it's been adjusted.
MR. LASKER: Okay. Now we have two witnesses, but I will ask the question --
MR. MILLER: No, you don't have two witnesses.
THE WITNESS: Just say it again.
MR. MILLER: You have one lawyer who is harassing one witness. He said it had been adjusted.
BY MR. LASKER:
Q Dr. Blair --
A Say it again.
Q -- the data with the 1.04 odds ratio that was in the presentation in June 2015 that showed a complete null result of ever versus never use for glyphosate and non-Hodgkin lymphoma, is that 1.04

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data point in this presentation?
MR. MILLER: Objection. Asked and answered.
Go ahead, Doctor.
THE WITNESS: I don't actually know whether it is, but there are a lot of data points that are less than 1.0.
You know, so is the one you're mentioning in there, I -- I would have to pour through this. You may be right, but I'm saying there are a lot of others in here that are less than 1.0.
BY MR. LASKER:
Q It's fair to say, Dr. Blair, that the NAPP has presented different data, and presented different data now in June 2016 for this IARC meeting than it had presented in June 2015, correct?
A Yes. And that's because analyses move along and you do different things.
Q Okay. And this presentation in June 2016 was made -- and one of the authors, by the way, or one of the listed authors on this June 2016 presentation is Dr. Weisenburger, correct?
A Yes.
Q And Dr. Weisenburger as of this time we know was already serving as an expert witness for

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plaintiffs, correct?
A Probably, yeah.
Q Let's mark as the next exhibit in line an e-mail you received from Dr. Weisenburger on August -- in August 2016.
(Blair Exhibit No. 35 was marked for identification.)
BY MR. LASKER:
Q And this is Exhibit 35.
MR. MILLER: 35.
MR. LASKER: 35.
MR. MILLER: Got it.
BY MR. LASKER:
Q And again, so the record is clear, at the time Dr. Weisenburger wrote this e-mail to you in August 2016, he was serving as an expert witness for plaintiffs in this litigation, correct?
A I -- I don't know that, but you must have the dates.
Q Well, we can go back to this. He had sent you an e-mail in -- in May 2016. I think that was Exhibit 30 if you want to refer back.
A No, that's --
Q May 2016.
A I'm just saying you asked me point blank

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all these dates --
Q Okay.
A -- and immediately I do it, you start fumbling through the paper. Just say, No, we got an e-mail, and got it, and then we will move on. Okay?
Q Well, I was trying to find the e-mail to help refresh your recollection.
A No, you weren't.
Q Dr. Blair -- Dr. Blair, in May of 2016, you had an e-mail that made it clear to you that Dr. Weisenburger was serving as an expert for plaintiffs in this litigation, correct?
A Yes.
Q Okay. So in August of -- let me get my dates correct -- in August of 2016, you certainly were aware of the fact that Dr. Weisenburger was serving as an expert witness for the plaintiffs in this litigation, correct?
A Yes.
Q And in his e-mail to you, he is pressing for publication of the NAPP data as it had been most recently presented at the IARC meeting, correct?
A Yes.
Q Dr. Weisenburger says, quote: It is important to get our U.S.-Canadian paper on this

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submitted soon as to be considered by the European authorities in their review of glyphosate. Correct?
A Yes. To be --
MR. MILLER: You read the quote wrong.
MR. LASKER: I'm sorry. I will read it again.
THE WITNESS: Yeah.
BY MR. LASKER:
Q I will read it again. The earlier e-mail, and that's --
A Yes. Okay. I'm sorry.
No, it's okay, it's down in the bottom. Only just "European authorities" was not in the line you were reading and I was trying to follow.
Q To be fair --
A But it's down below. It's okay.
Q To be fair, the e-mails below are between Christopher Portier and Dr. Weisenburger, correct?
A Yes. Yes.
Q And Christopher Portier is also an expert witness for plaintiffs, correct?
A I don't -- maybe I know that. But I don't know.
Q I will represent to you that he has because he's subpoenaed already for plaintiffs in

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this litigation.
A Okay.
Q So the first e-mail is between Chris Portier and Dennis Weisenburger, two plaintiffs' experts in the litigation, talking about the EU's review of glyphosate, correct?
A Yes.
Q And then Dr. Weisenburger turns to you and sends an e-mail saying, quote: It seems important to get our U.S.-Canadian paper on this submitted soon so it can be considered in this review. Correct?
A Correct.
Q And he is talking about the NAPP paper that was now being --
A I -- I assume so. I'm sure that's the case, yeah.
Q So -- and again, as one of the investigators on the NAPP, you and Dr. Weisenburger have the ability to publish data or not publish data as you -- as you choose, correct?
A No. Dr. Weisenburger and I and the many other authors on the paper make the decision when papers are ready for submission for publication.
Q So you certainly have the ability to try

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and get data published at --
A Absolutely.
Q -- whatever time when you decide to do so.
A Absolutely.
Q And prior to the IARC working group meeting, you had data from the North American Pooled Project, you had data from the Agricultural Health Study, and you decided, for whatever reason, that that data was not going to be published at that time, and therefore was not considered by IARC, correct?
A No. Again, you foul up the process. What we decided was the work that we were doing on these different studies were not yet -- were not yet ready to submit to journals. Even after you decide to submit them to journals for review, you don't decide when it gets published.
Q You submit --
A But first you have to decide is it ready for submission; that the -- all the authors are satisfied with the analysis and interpretation, and that's the process these papers are in.
Q You submitted AHS data for pesticides in 2014, correct?
A I -- again, I don't know what you're

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referring to AHS data on. Many AHS data on pesticides are submitted.
Q Okay. There's an updated data -- updated study on the Agricultural Health Study data on non-Hodgkin lymphoma and pesticides, and you decided to submit that data in 2014, and in fact, that study was published in 2014, correct?
A Yes.
Q All right. And you decided not to submit data that had been included in a draft with that same pesticide data for publication, correct?
A Yes.
Q And you to this day have not submitted that data for publication, correct?
A Correct.
Q But in this exchange in August 2016, we have two plaintiffs' counsel discussing how they can get certain data published so that it could be considered, correct?
MR. MILLER: Object to the form of the question.
BY MR. LASKER:
Q That is Chris Portier and Dennis Weisenburger trying to figure out, now that the NAPP data has been reviewed and altered from August of --

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from 2015 to 2016, they're now talking about how can we get this published, aren't they?
MR. MILLER: Object to the form of the question.
THE WITNESS: Well, that's not the words I would use to describe what they're trying to do, but that is okay.
MR. LASKER: Let's take a brief break. I may be done.
THE VIDEOGRAPHER: Okay. The time is 3:10 p.m. We're going off the record.
(Recess.)
THE VIDEOGRAPHER: The time is 3:16 p.m., and we're back on the record.
BY MR. LASKER:
Q Dr. Blair, I need you to turn to another issue briefly. What is the Ramazzini Institute?
A It's not an institute. It's an association, a professional association.
Q Have you ever done work for the Ramazzini association?
A No.
Q Have you ever collaborated with the Ramazzini association with respect to any scientific research that you can recall?

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A Not that I -- I don't think so. I -- I'm a member of it. I don't think I've ever done anything with them.
Q So you're -- you're a member. Does that mean you've gone to meetings?
A I've been to one meeting.
Q Okay. Have you had any discussions with anyone at Ramazzini regarding glyphosate?
A I don't remember it, but I guess it's possible.
MR. LASKER: Thank you, Doctor. I have no further questions.
I do have to -- just before I forget, there was one document that -- and we can do this after you are done, but I am remembering now, so I want to do it. There was one document that you used in your direct examination that was an e-mail that's confidential and under the protective order. So just that document, and it was really like maybe two or three questions about that document, we will designate as "Confidential" under the protective order.
MR. MILLER: That is fair. Okay.
MR. LASKER: And that's that.
MR. MILLER: Great. Let's switch seats

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and keep this moving.
THE VIDEOGRAPHER: The time is 3:18 p.m. We're going off the record.
(Recess.)
THE VIDEOGRAPHER: The time is 3:22 p.m., March 20th, 2017, and we are on the record with video 4.
REDIRECT EXAMINATION
BY MR. MILLER:
Q Good afternoon, Dr. Blair.
A Afternoon.
Q Again, I'm Michael Miller, and I started out today asking questions, and I'm going to follow up in response to the questions from Monsanto's attorneys, okay?
A Okay.
Q Okay. Now, you and I never met each before today, have we?
A I don't think so.
Q No. I'm about your age. I'm not sure -- yeah, our memories are what they are. But we've never met each other, right?
A Right.
Q Okay. And we've never talked on the phone, right?

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A No, I don't think so.
Q Okay. And to the extent you talked to one lady lawyer out of Denver that asked you to be an expert for plaintiffs, you said you would rather not do that, right?
A Right.
Q You wanted to stay impartial and neutral, didn't you?
A That's the way I look at it, yes.
Q Your science is what's important to you?
A Yes.
Q Okay. Now, let's get over some of the substance that was brought up by Monsanto's attorneys.
One of the issues that he talked about, and he showed you Exhibit 26, was an issue that someone at IARC had e-mailed you about after -- is it fair to say after IARC issued its report that probably -- that glyphosate probably caused non-Hodgkin lymphoma, there was quite a bit of ruckus, if you will, about all that, wasn't there?
MR. LASKER: Objection to form.
THE WITNESS: Yes.
BY MR. MILLER:
Q Okay. And one of the issues was that

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there was this negative AHS study that you've been talking about a lot with Monsanto's lawyers, right?
A Yes.
Q And there were the -- the positive studies on non-Hodgkin lymphoma, right?
A Yes.
Q So the issue is we're weighing the positive case-control studies, more than a few of them that the jury has heard of by now, that show the association statistically significant between glyphosate and non-Hodgkin lymphoma, and the negative study, AHS, which really didn't show a statistically significant association, right?
A Correct.
Q And you, Dr. Blair, are one of the authors of that AHS study, right?
A Yes.
Q Yet when it came time to vote as a volunteer scientist on the International Agency for the Research for Cancer, you voted unanimously with 16 of your peers that there was a probable association between glyphosate and non-Hodgkin lymphoma, right?
A Well, I voted that way. I think it was unanimous. I don't actually remember.

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Q I understand. I understand.
And you're not the only author of the AHS study that -- that thinks there is an association between glyphosate and non-Hodgkin lymphoma, are you, sir?
MR. LASKER: Objection to form.
THE WITNESS: I actually don't know the answer to that.
MR. MILLER: What's our next number exhibit?
MR. LASKER: 36.
MR. MILLER: Thank you.
All right. 36.
(Blair Exhibit No. 36 was marked for identification.)
BY MR. MILLER:
Q And I might not be pronouncing this right, but Michael Alavanja?
A Alavanya (phonetic).
Q Excuse me. Michael Alavanja is one of the authors of the AHS study, isn't he?
A He is.
Q No. 36. All right. Here is an article that Dr. Alavanja wrote that came out -- let's make sure we get the date right -- in 2013? Yes, okay.

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Which was about -- well, which was the same year as you had your AHS data, right, that you talked about so much --
MR. MILLER: Excuse me, here's a copy for counsel.
MR. LASKER: Thank you.
BY MR. MILLER:
Q And here's a copy for you, Dr. Blair.
-- the same year that you had that -- that AHS study, right?
A Yes, this paper is in the same time frame, '13.
MR. LASKER: And I'm going to object to form. Questioning a fact witness about a paper that he is not an author of. Lack of foundation.
BY MR. MILLER:
Q And here's what he says on page 5 in his table about glyphosate --
MR. LASKER: Where are you?
MR. MILLER: Table 5.
MR. LASKER: What page is it?
MR. MILLER: Let's count them out. Let's count them out. One, two --
MR. LASKER: That's not going to work. I thought there was a page number on the bottom.

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MR. MILLER: No, sir, I don't have one. When you have -- when you have Table 5, let me know, and we will get back to work here.
MR. LASKER: Table 5?
BY MR. MILLER:
Q But this author of the AHS study in the same year that you have --
MR. LASKER: I'm sorry. Is this the glyphosate on the middle of the page?
MR. MILLER: Table 5. Are you -- when you've found Table 5, I'm going to ask my question. Are you ready, Counsel?
MR. LASKER: Okay.
MR. MILLER: Okay.
BY MR. MILLER:
Q Table 5, this author of the AHS in the same year that this so-called new data comes out in 2013 says: "Glyphosate is positively associated with non-Hodgkin lymphoma. That's the epidemiologic evidence."
Do you see that, sir?
MR. LASKER: Objection to form. Incomplete reading of the exact line that you're looking at.
BY MR. MILLER:

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Q You can answer, Doctor.
A All right. I'm actually trying to find it. Is it on the first page of the table or the second?
Q I tell you what, it's easier if we all look at the screen.
A Oh, oh, sorry. All right.
Q I said Table 5, Dr. Alavanja says "epidemiologic evidence." Do you see that, sir?
A Yes.
Q And he lists --
A Yeah. Okay.
MR. LASKER: 47. Reference Windstar.
BY MR. MILLER:
Q And he says: "Glyphosate positively associated with non-Hodgkin lymphoma."
MR. LASKER: Objection to form.
THE WITNESS: That's what he says.
BY MR. MILLER:
Q Yes, sir. And following up on counsel's questions, you certainly never wrote a letter to Dr. Alavanja, your co-author, and said, Gee, you're wrong when you say that glyphosate is positively associated with non-Hodgkin lymphoma, right?
MR. LASKER: Misrepresenting a document.

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Objection to form.
BY MR. MILLER:
Q You can answer.
A I did not.
Q Okay. And I think -- well, the jury is going to hear a lot about this, but I want to ask you, this AHS study was a cohort study, right?
A Yes.
Q And these other studies, the case-control studies upon which the positive association with non-Hodgkin lymphoma, it's a different kind of epidemiological study, right, as compared to a cohort study?
A Yes.
Q And that one of the problems -- all studies have problems and no studies are perfect. Is that fair?
A Fair.
Q Okay. One of the problems of cohort studies is they've got to be powered up enough to find statistically significant information that we as scientists can rely upon, right?
A True for all studies, yes.
Q Sure. But if they're not powered up enough, the information comes back and it's not statistically significant, right?
A Yes.
MR. LASKER: Objection to form.
THE WITNESS: It's harder to find statistical significance, yes.
BY MR. MILLER:
Q Sure. And a responsible scientist is not going to rely upon information that is not statistically significant when he has statistically significant information he can look at, right?
MR. LASKER: Objection to form.
THE WITNESS: Yes.
BY MR. MILLER:
Q Sure. And one of the other problems with cohort studies like the AHS study is loss to follow-up. You've heard that phrase before, haven't you?
A Yes.
Q Tell the jury what "loss to follow-up" means, Doctor.
MR. LASKER: Objection to form. Calling for expert opinion now.
BY MR. MILLER:
Q You can answer.
A The --

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MR. LASKER: Beyond the scope.
THE WITNESS: In the cohort studies, that you have to keep following people, and in an open society, it's hard to do.
BY MR. MILLER:
Q And, look, we know you and Dr. Alavanja are hard-working scientists that are working on this issue when you prepared that cohort study, the AHS study, but the truth is you had loss to follow-up.
A We did.
Q Yeah. And the truth is the information that counsel kept asking about in a hundred different ways for the last several hours was not statistically significant, was it?
We can go back and look at a lot of numbers, but that 2013 data was, by and large, not statistically significant.
A It was no excess, but it wasn't a statistically significant deficit, I think.
Q Sure.
A Is that correct.
Q I think. I think that's a fair way to put it, Doctor.
Let's look at the NAPP study. Now, the NAPP study is the North American Pooled Project which

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is looking again scientifically at this issue of glyphosate and non-Hodgkin lymphoma, right?
A It's one of the pesticides that can be looked at, yes.
Q And unlike the voluminous data in the AHS study that had the problems of loss to follow-up that was not statistically significant, the abstract for the NAPP study shows statistically significant information, right, sir?
MR. LASKER: Objection to form, misstates the document.
THE WITNESS: I -- I've seen a lot of stuff. I sort of generally know what studies I've been involved with show. I feel uncomfortable giving a "yes" or "no" answer without the evidence in front of me to look at. I think that's correct.
BY MR. MILLER:
Q Totally fair, Doctor. And let me then show you that statistically significant information, and we can look at it together, and I have a --
MR. LASKER: May I have a document?
MR. MILLER: Of course. Of course, you can.
MR. LASKER: What's the date of --
MR. MILLER: 37.

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MR. LASKER: What is the date on this one?
(Exhibit No. 37 was marked for identification.)
BY MR. MILLER:
Q All right. So here we are, Doctor. Statistically significant information from a study that you authored with others. And this is an abstract, right, sir?
A Yes.
Q Explain to the jury what an abstract is.
A Different scientific associations have meetings of their members, and at those meetings there will be verbal presentations, and you get accepted to be on the program by submitting an abstract to decide who gets to be on the program. And these are the abstracts. This is one of those abstracts.
Q Sure.
A It's not a full paper, but it's a -- a synopsis of some work someone has done they're willing to talk about.
Q All right, sir. And it's presented at the International Society for Environmental Epidemiology. Right, sir?

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A Yes.
Q And that was at their 2015 conference, right, sir?
A I think so, yes.
Q All right, sir. And so the jury understands, it was an evaluation of glyphosate, which is the active ingredient in Roundup, right?
A Yes.
Q And the risk of non-Hodgkin lymphoma --
A Yes.
Q -- major histological subtypes in the North American Pooled Project, right?
A Correct.
Q And you are one of the authors, Aaron Blair from the United States Cancer Institute, right?
A Yes.
Q And Dennis Weinberger -- I'm sorry, Weisenburger from the City of Hope Hospital. Right?
A Yes.
Q And among many others, right?
A A number of others.
Q Yes, sir.
And what you scientists found statistically significant and presented to the International Society for Environmental Epidemiology

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was several findings, results. Cases who ever use glyphosate had elevated non-Hodgkin lymphoma risk overall, with an odds ratio of 1.51 statistically significant. Right?
A Yes.
Q And as a scientist, statistical significance is important, isn't it?
A Yes.
Q The highest risks were found for other subtypes, "other" meaning other types of non-Hodgkin lymphoma?
A It means if we looked at several different subtypes, and the one that's sort of the catchall category was the one that had a statistically significant elevation.
Q An odds ratio of 1.9 are almost a doubling of the risk, right?
A Correct.
Q Statistically significant?
A Yes.
Q All right. Subjects who used glyphosate for greater than five years had an increased odds ratio that was higher, 2.58, right?
A Yes.
Q And that shows as dose-dependent

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response, right?
A That is -- you did say "subtype," right?
Q Yes, sir.
A Yeah, okay. Yes.
Q And dose-dependant response is strong evidence of causality is what the preamble to the IARC tells us, right?
A Yes.
MR. LASKER: Objection to form. Objection to the line of questioning to the extent that plaintiffs now apparently are using or trying to use Dr. Blair as an expert witness. Beyond the scope of the litigation.
MR. MILLER: Did you get the answer?
THE REPORTER: Yes.
BY MR. MILLER:
Q Okay. "Compared to non-handlers, those who handled glyphosate for greater than two days/year had significantly elevated odds of non-Hodgkin lymphoma overall, odds ratio of 2.66."
Was that statistically significant, Doctor?
A Yes.
Q And it goes on to tell us about various subtypes of non-Hodgkin lymphoma, right?

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A Correct.
Q What's FL?
A Follicular lymphoma.
Q Okay. And that odds ratio was 2.36?
A Correct.
Q And that's statistically significant?
A Yes.
Q And DLBCL, what's that?
A Diffuse B-cell chronic leukemia.
Q Trip -- triple the risk of diffuse B-cell non-Hodgkin lymph --
A Lymphoma, yeah.
Q Right, sir?
Statistically significant?
A Yes.
Q As a result of exposure to glyphosate?
A Yes.
Q And this is information that was reported out after IARC found the positive association between glyphosate and non-Hodgkin lymphoma, right?
A Yes.
Q Okay. But you couldn't tell IARC about this positive finding from this NAPP study because it hadn't been published in March when you were in your IARC meetings in Lyon, France, correct?

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A Correct.
Q Scientists follow protocols, right?
A Correct.
Q Do what you say, say what you do.
MR. LASKER: Object to form.
THE WITNESS: Well, you want to make sure that the analysis is complete and the interpretation is the best you can make it.
BY MR. MILLER:
Q You are not as quite as old as I, but do you remember Paul Harvey?
A I do.
Q "The rest of the story," as he liked to say.
Monsanto's lawyer showed you Exhibit 34, a PowerPoint by Dr. -- is it Patchwa?
MR. LASKER: Pahwa.
THE WITNESS: Pahwa.
BY MR. MILLER:
Q I'm sorry, I didn't mean to mispronounce it. My apologies.
We will get this thing where you can look at it.
(Counsel conferring.)
BY MR. MILLER:

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Q So he showed you this, which is Exhibit 34, from the doctor --
MR. MILLER: Well, I know it is. I know it is.
(Counsel conferring.
BY MR. MILLER:
Q Exhibit 16 is a detailed evaluation of glyphosate using the risk of non-Hodgkin lymphoma in the North American Pooled Project presented in June of 2015. Do you see that?
A Yes.
Q Okay. What counsel didn't show you was in that PowerPoint there was in fact a statistically significant increased risk for non-Hodgkin lymphoma with use of glyphosate, right, sir?
MR. LASKER: Objection to form.
THE WITNESS: For some subtypes.
BY MR. MILLER:
Q And that's for the diffuse B-cell --
A Yep.
Q -- and others?
A And other.
Q Okay. For others, it was over double the risk and statistically significant, right?
MR. LASKER: Objection to form,

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mischaracterizes the document.
THE WITNESS: Yes.
BY MR. MILLER:
Q Also in that PowerPoint about this North American Pooled Project was the frequency, that is the number of days a year, of glyphosate handling and NHL risk. Do you see that, sir?
A Yes.
Q And what they're telling us is here that there was overall almost a doubling of the risk statistically significant if you handled a glyphosate for greater than two days; is that right, sir?
A Yes.
Q And for diffuse B-cell, it was 2.49 statistically significant, right?
A Correct.
Q What does the trend test tell us?
A It's a measurement across the different exposure categories and whether or not that trend line is statistically significant.
Q Okay. What is the difference between proxy and self-respondents?
A Proxy would be someone else reporting for the subject in the study where it's often the spouse or child or brother or sister.

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Q Because the person who got non-Hodgkin lymphoma may not be alive to report.
A May not be alive or may be incapacitated and can't report.
Q Sure. So what would be the significance in comparing in the North American Pooled Project proxy information versus self-respondent information?
A Well, the general assumption -- in fact, the data supported it -- that proxy respondents tend to make more errors and so would tend to drive the risk down, where you get more accurate reporting and more accurate analyses based on information from the individuals themselves.
Q And so when proxies were compared to self-respondents for frequency of greater than two days use, we had a statistical doubling of the risk from proxy and self-respondents, right?
A Yes.
Q At one point --
A Actually, sorry. Let me --
Q Sure, go ahead.
A That's one -- one component is proxies can't tell you as much, which means more exposure misclassification, which drives the risk down. The other is the worry that proxies will remember things

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that aren't correct, and seize upon the topic of the day and falsely report things in such numbers that gives you a false positive. But the thing about case-control studies is it can go in both directions.
Q And you did not find a problem with self-reporting in the case-control studies when you reviewed this for IARC. Fair enough?
MR. LASKER: Objection to form.
THE WITNESS: Well, we did some methodologic aspects to our studies to see if there was case response bias.
BY MR. MILLER:
Q And what did you find?
A We did not find case response bias.
Q You did not find a problem. Right?
A With case response bias.
Q Okay. So -- and case response bias was the allegation of bias against the case-control studies, isn't it?
MR. LASKER: Objection to form.
THE WITNESS: It's one of them.
BY MR. MILLER:
Q And you didn't find it?
A We did not find it.
Q And this PowerPoint supports the position

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of not finding that bias because in fact when you compared self-respondents only, you got remarkably similar to proxy and self-respondents, 1.98 and 2.05, right?
MR. LASKER: Objection to form, incomplete discussion of the document.
THE WITNESS: Yes.
BY MR. MILLER:
Q Okay. I want to -- I want to go back to Exhibit 27 that -- that Monsanto's counsel showed you. It was a question and answer that was prepared by IARC.
Do you remember generally speaking to him about this document?
A (No response.)
Q Sir?
A Yeah.
Q Do you generally remember speaking to Monsanto's lawyer about this document?
A Yeah.
Q Okay.
A Sorry.
Q That's all right. It's a long day. We're doing the best we can.
Let's go to page 2 of this document

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prepared by IARC in response to the allegations that this -- well, let's just ask about it.

This question and answer: "Several of the epidemiological studies considered by the IARC expert working group showed increased cancer rates in occupational settings after exposure to glyphosate in herbicides. Can this be attributed to glyphosate as a single ingredient or could it be due to other -- other chemicals in the formulations? And that was the question.

And the answer that IARC --

MR. LASKER: Objection to form, beyond the scope.

BY MR. MILLER:

Q And the answer that IARC was, quote: Real world exposures that people experience are to glyphosate in formulated products. Studies of humans exposed to different formulations in different regions at different times reported similar increases on the same type of cancer, non-Hodgkin lymphoma.

That's what you saw, right, Doctor?

MR. LASKER: Objection to form.

THE WITNESS: Yes.

BY MR. MILLER:

Q And one of the questions that IARC wanted

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a formal answer to was the question posed by Monsanto's attorneys as to whether the Agricultural Health Study was the most powerful study, and IARC said no. Isn't that right, Doctor?

MR. LASKER: Objection to form.

THE WITNESS: It's -- it's a powerful study. And it has advantages. I'm not sure I would say it was the most powerful, but it is a powerful study.

BY MR. MILLER:

Q Sure. Unfortunately, not powered up enough to get statistically significant information in 2013.

MR. LASKER: Objection to form. In 2005 or 2013?

MR. MILLER: I said 2013.

MR. LASKER: 2013. Okay. Well, that's --

THE WITNESS: I would not say it in that way because it assumes that if you make the study bigger, you will get the same answer. And that's not --

BY MR. MILLER:

Q Oh.

A -- scientific.

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Q Oh, I --

A Whatever you find now with some study, you make it bigger, the relative risk may go in either direction.

Q Understood.

A So it's --

Q I understand.

A Power is power, but it doesn't direct where it's going to fall.

Q Absolutely. And what you're looking to get is enough power to get statistically significant information --

A Absolutely.

MR. LASKER: Objection to form.

THE WITNESS: Yes.

BY MR. MILLER:

Q Okay. Let's go back to see what IARC's official position is on whether the AHS was the most powerful study, and the answer provided is: "The Agricultural Health Study has been described as the most powerful study, but this is not correct."

That's --

MR. LASKER: Objection to form. Can we clarify which study you're talking about now?

BY MR. MILLER:

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Q The official position of IARC, isn't it, Doctor?

A You're asking me if that is the official position --

Q Yes, sir.

A -- of IARC?

MR. LASKER: Objection to form.

THE WITNESS: Yes, apparently so.

MR. MILLER: All right, sir. All right.

(Counsel conferring.)

BY MR. MILLER:

Q Remember counsel for Monsanto spent a long time talking to you about the draft of the AHS study that you have not released because -- you explained to us, I guess, why. It -- it's still -- this still hasn't been published, has it?

A Well, we published half of it. We published on the insecticides.

Q Sure.

A But not on the herbicides.

Q I understand. But in this -- yes, sir. I understand.

In this draft that counsel talked to you about, he didn't show you the sentence, you write in there --

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MR. LASKER: Where are you?
MR. MILLER: On page 20, bottom of the page.
BY MR. MILLER:
Q -- quote: Cautious interpretation of these results is advised. Since the number of exposed cases for each subgroup of NHL --
MR. LASKER: Objection to form. Where are you?
BY MR. MILLER:
Q -- for each subgroup of NHL in the AHS is still relatively small.
MR. MILLER: It's pages 20 and 21.
BY MR. MILLER:
Q That's what you --
MR. LASKER: Objection to form.
BY MR. MILLER:
Q That's what you wrote, right, Doctor?
MR. LASKER: Objection to form, mischaracterizing the document.
THE WITNESS: Well, this was in -- this is in the document.
BY MR. MILLER:
Q Yes, sir.
A Right, it was in the document.

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Q That's right.
A That's what that non-finished document says.
Q Yes, I understand.
A Yes.
Q And the reason you caution people because this is a draft document, isn't it, sir?
A Yes. Yeah.
MR. LASKER: Objection.
BY MR. MILLER:
Q And the data in this document only goes to 2008, right, sir?
A I think that's correct.
Q I understand.
A I don't remember for sure.
Q And I think you've -- I think you've already said as much, but we're looking at an old interview that you did --
MR. LASKER: Do you have a document for me?
MR. MILLER: In a minute when I use one.
MR. LASKER: Okay.
BY MR. MILLER:
Q Recall by -- recall bias, it doesn't add up to much. Isn't that basically your experience?

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MR. LASKER: Objection to form, beyond the scope, calling for expert opinion.
THE WITNESS: In our evaluation of it, it doesn't occur very often.
BY MR. MILLER:
Q Okay. And when it -- when it does happen, it can cause the association between the agent and the disease to actually look smaller than it really is or look a little larger than it really is. It can go in either direction.
A It can go in either direction.
MR. LASKER: Objection to form, calling for an expert opinion, beyond the scope of the deposition.
BY MR. MILLER:
Q You know what SEER data is, right?
A Yes.
Q In SEER data, since 1975 to present, the number of cases of death by non-Hodgkin lymphoma in this country have doubled, haven't they?
MR. LASKER: Objection to form. Objection, beyond the scope --
BY MR. MILLER:
Q You can answer.
MR. LASKER: -- of the deposition as

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noticed, beyond the scope of my direct examination and without a document.
BY MR. MILLER:
Q You can answer.
A Both mortality and incidence has gone up.
Q This, I believe, was Exhibit 13. Counsel marked some notes from some other fellow that was on -- invited to be a member of IARC.
Do you remember that general line of questions?
A Yes.
Q Okay. So without any lawyers around, this fellow made some notes. What was his name again?
A It was Ross, I think.
Q He said --
A Last name Ross.
Q He said: "Case-control glyphosate, non-Hodgkin lymphoma." Right?
A Yes.
Q That wraps it up, doesn't it really?
MR. LASKER: Object to form.
THE WITNESS: Well, that's what he thought.
BY MR. MILLER:

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Q That's what the panel unanimously thought, right?
MR. LASKER: Objection to form.
THE WITNESS: Yes.
BY MR. MILLER:
Q Okay. Has anything you've been shown by Monsanto's lawyers in the 3 hours and 40 minutes that he questioned you changed the opinions that you had at the IARC meeting about glyphosate and non-Hodgkin lymphoma?
MR. LASKER: Objection to form, beyond the scope.
BY MR. MILLER:
Q You can answer.
A No.
MR. MILLER: I didn't even use an hour. Thank you for your time.
MR. LASKER: I have like three questions, but I will ask them from here. We don't have to go off.
MR. MILLER: Sure. Sure. If the doctor is okay with it, I'm okay with it.
THE WITNESS: That's fine.
RECROSS-EXAMINATION
BY MR. LASKER:

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Q Dr. Blair. I just want to clarify something. I believe you said in response to one of the questions from Mr. Miller that you don't look at nonsignificant data. Is that what you said?
A Well, if I did, it's wrong.
Q Okay. Clearly, you do look at nonsignificant data in evaluating the scientific evidence, correct?
A Absolutely.
Q And epidemiological studies that do not find a significant association are important studies to consider in evaluating whether or not a substance can cause or is associated with an illness, correct?
A Absolutely. They're -- all data are useful to some extent.
Q And you were shown -- strike that.
Mr. Miller asked you about the case-control studies and whether or not they found a positive association. And just so the record is clear, the North American Pooled Project analysis that we've discussed a fair amount today is a pooling of case-control studies, correct?
A Correct.
Q In fact, it's a pooling of all the case-control studies in North America, correct?

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A I think so.
Q And as we discussed in our presentation -- in our questions --
A Of non-Hodgkin lymphoma.
Q Exactly.
As we discussed in our questions and your answers earlier, when the pooled data is looked at for all the case-control studies in North America for non-Hodgkin lymphoma and that data is controlled for exposures to other pesticides, there is no statistically significant positive association between glyphosate and non-Hodgkin lymphoma, correct?
A Well, it depends on what you actually look at. Overall, yes. Now, whether you look at categories, whether you look at subgroups, it's not that simplistic.
Q The yes/no, ever exposed versus exposed analysis that was used in the meta-analyses, for example, that you relied upon that I prepared show that for all the case-control data in North America, when it's controlled for exposures to other pesticides, there is no statistically significant positive association between glyphosate and non-Hodgkin lymphoma, correct?
A I think that's right for ever/never

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exposure.
Q And Mr. Miller on redirect showed you some presentation from the North American Pooled Project, and the data that he showed you -- and let me absolutely just go to this. This was plaintiffs' exhibit -- or Exhibit 16, I'm sorry, and he went through and showed certain data on -- he pointed out certain numbers that were statistically significant among the various evaluations that were presented in this -- I'm sorry -- June 10, 2016 presentation. Do you recall that?
A Yes.
Q And those data points that he was pointing to you was of the analysis that was not controlled for exposures to other pesticides, correct?
A If you say so. I don't remember.
Q Okay. So you don't know -- when you were looking at it, you didn't know if that data was controlled or not controlled. You were just reading what the numbers were on the page.
A Absolutely.
MR. LASKER: I have no further questions.
MR. MILLER: Just --
MR. LASKER: Oh, that's the document.

MR. MILLER: Just one.

REDIRECT EXAMINATION

BY MR. MILLER:

Q So a person who ever used Roundup for one time would be in the ever exposed group.

THE WITNESS: Yes.

MR. MILLER: Okay. Thank you for your time.

MR. LASKER: No further questions. Thank you, Dr. Blair.

MR. GREENE: Before we stop. Doctor, you have the right to read your deposition, and even though I know that the reporter does a very good job as far as taking down everything that was said and all the questions asked, knowing how you are with respect to accuracy, I would suggest in this case you may want to read.

THE WITNESS: I think I would like that.

MR. MILLER: Yeah, we'll send you a copy. We'll send it to your counsel and --

MR. LASKER: The court reporter can send it to him.

MR. MILLER: There is a certain amount of time involved.

THE WITNESS: Sure.

MR. MILLER: Sure, absolutely, we'll --

THE WITNESS: I have one other request. Can I have a card from everybody in this room?

MR. MILLER: Sure. Absolutely.

THE VIDEOGRAPHER: The time is 3:58 p.m., March 20th, 2017. Going off the record, concluding the videotaped deposition.

(Whereupon, at 3:58 p.m. the deposition of AARON EARL BLAIR, Ph.D. was concluded.)

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ACKNOWLEDGMENT OF DEPONENT

I, _____, do hereby certify that I have read the foregoing pages, and that the same is a correct transcription of the answers given by me to the questions therein propounded, except for the corrections or changes in form or substance, if any, noted in the attached Errata Sheet.

_____

AARON EARL BLAIR, PH.D. DATE

Subscribed and sworn to before me this

_____ day of _____, 20____.

My commission expires:_____

_____

Notary Public

CERTIFICATE OF NOTARY PUBLIC

I, LESLIE ANNE TODD, the officer before whom the foregoing deposition was taken, do hereby certify that the witness whose testimony appears in the foregoing deposition was duly sworn by me in stenotype and thereafter reduced to typewriting under my direction; that said deposition is a true record of the testimony given by said witness; that I am neither counsel for, related to, nor employed by and the parties to the action in which this deposition was taken; and, further, that I am not a relative or employee of any counsel or attorney employed by the parties hereto, nor financially or otherwise interested in the outcome of this action.

LESLIE ANNE TODD
Notary Public in and for the
District of Columbia
My commission expires:
November 14, 2017

Int. J. Cancer: **123,** 1657–1663 (2008)

Pesticide exposure as risk factor for non-Hodgkin lymphoma including histopathological subgroup analysis

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We report a population based case–control study of exposure to pesticides as risk factor for non-Hodgkin lymphoma (NHL). Male and female subjects aged 18–74 years living in Sweden were included during December 1, 1999, to April 30, 2002. Controls were selected from the national population registry. Exposure to different agents was assessed by questionnaire. In total 910 (91%) cases and 1016 (92%) controls participated. Exposure to herbicides gave odds ratio (OR) 1.72, 95% confidence interval (CI) 1.18–2.51. Regarding phenoxyacetic acids highest risk was calculated for MCPA; OR 2.81, 95% CI 1.27–6.22, all these cases had a latency period >10 years. Exposure to glyphosate gave OR 2.02, 95% CI 1.10–3.71 and with >10 years latency period OR 2.26, 95% CI 1.16–4.40. Insecticides overall gave OR 1.28, 95% CI 0.96–1.72 and impregnating agents OR 1.57, 95% CI 1.07–2.30. Results are also presented for different entities of NHL. In conclusion our study confirmed an association between exposure to phenoxyacetic acids and NHL and the association with glyphosate was considerably strengthened.

Key words: phenoxyacetic acids; MCPA; glyphosate; insecticides; impreganting agents; non-Hodgkin lymphoma

Non-Hodgkin lymphoma (NHL) is a heterogeneous group of lymphoid malignancies, where new classification systems based on immunohistochemistry, cytogenetics and evolving knowledge in clinical presentation and course has lead to modern classification systems.[1] Today, it is therefore more adequate to discuss NHL as many different diseases, which share some features but also differ in several aspects.

Interest in the etiology of NHL has been strengthened by an observed substantial increase in the incidence of the disease from the 1960's to the 1980's as reported from most countries with reliable cancer registries. However, this increase has clearly leveled off in many countries since the early 1990's, *i.e.*, in Sweden, Denmark and the USA.[2] The established risk factors for development of NHL include different immunosuppressive states, *e.g.*, human immunodeficiency virus (HIV), autoimmune diseases as Sjögren's syndrome and systemic lupus erythematosus (SLE), immunodepressants used after organ transplantation and some inherited conditions, for review see *e.g.*, Ref. 3. However, these causes may only explain a minority of cases, with a possible exception for HIV-related increases among younger persons in certain areas.[4]

It has been shown that Epstein-Barr virus (EBV) plays an essential role in the pathogenesis of lymphomas after organ transplantation.[5] A relation between lymphoma and elevated EBV-titers has been reported in a cohort.[6] Normally, EBV-production is held back by active cellular and humoral immune mechanisms. In immunodeficiency states this balance is disrupted and EBV-infected B-cells begin to proliferate.[7]

During the last decades, research on the etiology of NHL has been directed towards other potential causes such as pesticides, which may explain the impressive increase in the incidence. Today, it is also reasonable to consider the leveling off in incidence as a probable consequence of a reduced carcinogenic influence related to NHL. Furthermore, our emerging knowledge concerning the spectrum of NHL subgroups makes it reasonable to investigate causative agents for these different types of disease.

In 1981, we published results from a case–control study from Sweden, indicating statistically significant increased odds ratios for NHL and Hodgkin lymphoma (HL) in persons who had been exposed to phenoxyacetic herbicides or impregnating chlorophenols.[8] Our study was initiated by a case report.[9] Some of these chemicals were contaminated by dioxins, of which 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) has been recognised as a complete carcinogen by IARC.[10] Furthermore, these and several other related chemicals are immunotoxic.[11–15] Our results have been confirmed in some other studies, regarding phenoxyacetic herbicides from *e.g.*, Kansas[16] and Nebraska.[17]

Furthermore, in 1999 we reported a new case–control study performed to evaluate more recent exposure to pesticides and other chemicals, and we could thereby confirm our earlier findings regarding a relation with phenoxyacetic herbicides that was related to latency period.[18]

In that study, however, some newer compounds that are widely used today, such as the herbicide glyphosate, were still not very common. During the 1970's certain chemicals, *e.g.*, the phenoxy herbicide 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), chlorophenols, and the insecticide dichlorodiphenyltrichloroethane (DDT), were prohibited due to health concerns. Later also the phenoxy herbicide 2,4-dichlorophenoxyacetic acid (2,4-D) was banned in Sweden. Reporting of these agents is therefore nowadays much less likely. It is also probable that the risk pattern has been influenced by protective measures during the last decades.

To further evaluate the relation between exposure to pesticides and other chemicals, focusing also on newer types of compounds, we have performed a new case–control study in Sweden. In our study we have also evaluated exposures in relation to different histopathological subtypes according to the most recent classification.[1]

Material and methods

The study covered 4 out of 7 health service regions in Sweden, associated with the University Hospitals in Lund, Linköping, Örebro and Umeå, and was approved by the ethics committees. Data were collected during December 1, 1999, to April 30, 2002, which was the time period for diagnosis of the cases. Regarding recruitment of cases and controls collaboration was established with another research group, which at the same time performed a parallel study on NHL in Sweden and Denmark.

Cases

All consecutive patients aged 18–74 years with newly diagnosed NHL, identified through physicians treating lymphoma and through pathologists diagnosing the disease, were approached if their physician did not judge this as less appropriate by ethical rea-

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sons. This was done regardless of whether the person had accepted to participate in the parallel study with which we collaborated in the recruitment procedure. If they accepted to participate they were included as potential cases, and went through the data assessment procedure described below. No cases were excluded because of specific conditions potentially associated with NHL, but no cases with *e.g.*, HIV or postransplantation NHL occurred. All the diagnostic pathological specimens were scrutinised by 1 out of 5 Swedish expert lymphoma reference pathologists, if they had not been initially judged by one of these 5. About 70% of all included cases were reviewed, whereas the remaining had been previously classified by one of the reference pathologists. If there was a disagreement from the original report the sample was reviewed by a panel of these pathologists. Therefore, some potential cases could later be excluded if a NHL diagnosis was not verified, and in those occasions all collected exposure information was disregarded. The pathologists also subdivided all NHL cases according to the WHO classification,[1] to enable etiological analyses also for the different diagnostic NHL entities. Since all lymphoma treating clinics and all lymphoma pathologists in the involved regions were covered by the study, it may well be regarded as population based, although the possibility of some individuals not reported through the case ascertainment system used.

Controls

From the population registry covering whole Sweden, randomly chosen controls living in the same health service regions as the cases were recruited during several occasions within the study period. The controls were frequency-matched in 10 years age and sex groups to mirror the age and sex distribution of the included cases, and to increase efficacy in the adjusted analyses. If they accepted to participate, they were included as controls.

Assessment of exposure

All subjects who accepted to participate received a comprehensive questionnaire, which was sent out shortly after the subjects had been telephone interviewed by the other research group we had collaboration with as stated earlier. Their interview, however, did not focus on work environment or chemical exposure, but rather dealt with other life style factors and diseases. Our questionnaire included a total work history with in depth questions regarding exposure to pesticides, organic solvents and several other chemicals. For all pesticides not only numbers of years and numbers of days per year, but also approximate length of exposure per day were questioned. Since most work with pesticides was performed in an individualized manner, no job-exposure matrix was judged to be applicable. Furthermore, the questionnaire also included questions on *e.g.*, smoking habits, medications, leisure time activities and proximity from home to certain industrial installations, but data on these factors are not included in this article.

Specially trained interviewers scrutinized the answers and collected additional exposure information by phone if important data were lacking, incomplete or unclear. These interviewers were blinded with regard to case/control status. All exposures during the same calendar year as the diagnosis and the year before were disregarded in the cases. Correspondingly, the year of enrolment and the year before were disregarded for the controls. As in our previous lymphoma studies we used a minimum criterion of one full day exposure to be categorized as exposed.[8,18]

Statistical methods

Unconditional logistic regression analysis (Stata/SE 8.2 for Windows; StataCorp, College Station, TX) was used to calculate odds ratios (OR) and 95% confidence intervals (CI). Adjustment was made for age, sex and year of diagnosis (cases) or enrolment (controls). In the univariate analysis, different pesticides were analyzed separately and the unexposed category consisted of subjects that were unexposed to all included pesticides. When analyzing subgroups of NHL all controls were used in the separate analyses. In the dose-response calculations made for agents with at least 20 exposed subjects, median number of days of exposure among controls was used as cut-off. Latency period calculations and multivariate analyses included agents with statistically significant increased OR, or with an OR > 1.50 and at least 10 exposed subjects.

TABLE I – NON-HODGKIN LYMPHOMA CASES DIVIDED ON HISTOPATHOLOGICAL SUBTYPES ACCORDING TO WHO CLASSIFICATION.

WHO diagnosis	Number of cases
B-cell lymphomas, total	819
Lymphocytic lymphoma/B-CLL (SLL/CLL)	195
Follicular, grade I–III (FL)	165
Diffuse large B-cell lymphoma (DLBCL)	239
Other specified B-cell lymphoma	131
Unspecified B-cell lymphoma	89
T-cell lymphomas	53
Unspecified non-Hodgkin lymphoma	38
Total	910

Results

In total, 1,163 cases were reported from the participating clinics. Of these, 46 could not participate because of medical conditions, 88 died before they could be interviewed. Since these were primarily excluded by the reporting physicians we had no information on *e.g.*, final WHO categories on these cases. Three NHL cases were not diagnosed during the study period, 1 lived outside the study area and 30 were excluded not being NHL (HL 20, acute lymphoblastic leukaemia 1, other malignancy 7 and unclear diagnosis 2). Of the finally included 995 cases with NHL, 910 (91%) accepted to participate and answered the questionnaire. Of these, 819 were B-cell, 53 T-cell and 38 unspecified lymphomas, Table I.

Among the 1,108 initially enrolled controls 92 did not respond to the mail questionnaire, resulting in 1,016 (92%) controls to be included in the analyses.

The medium and median age in cases was 60 and 62 years, and in controls it was 58 and 60 years, respectively. Of the cases, 534 were males and 376 females, and of the controls the corresponding numbers were 592 and 424.

This report presents exposure data regarding different types of pesticides.

Herbicides

Exposure to herbicides gave for all NHL OR 1.72 (95% CI 1.18–2.51), Table II. Exposure to phenoxyacetic acids yielded OR 2.04 (95% CI 1.24–3.36). This group was further subdivided in 3 categories; (*i*) 4-chloro-2-methyl phenoxyacetic acid (MCPA), which is still on the market and not known to be contaminated by dioxins; (*ii*) 2,4,5-T and/or 2,4-D which often were used together and were potentially contaminated with different dioxin isomers; (*iii*) other types. MCPA seemed to give the most pronounced increase in OR. Exposure to other herbicides, regardless if they also had been exposed to phenoxyacetic acids or not, also gave a statistically significant OR 1.82 (95% CI 1.08–3.06). In this category the dominating agent was glyphosate, which was reported by 29 cases and 18 controls, which produced OR 2.02 (95% CI 1.10–3.71). If both phenoxyacetic acids and glyphosate were excluded, exposure to other herbicides (37 different agents reported, but no one by more than 6 subjects at most) gave a nonsignificant OR of 1.22 (95 % CI 0.63–2.39).

Dose-response analyses regarding herbicides in total and glyphosate yielded an increased OR in the higher exposed group, Table II. For phenoxyacetic acids, however, no such association was demonstrated.

Regarding phenoxy herbicides and glyphosate an analysis was made taken the latency period for exposure into account. For the

latency period 1–10 years no exposed cases were found for MCPA and 2,4,5-T and/or 2,4-D. Regarding glyphosate OR 1.11 (95% CI 0.24–5.08) was obtained. Latency period >10 years yielded for MCPA OR 2.81 (95% CI 1.27–6.22), for 2,4,5-T and/or 2,4,-D OR 1.72 (95% CI 0.98–3.19), and for glyphosate OR 2.26 (95% CI 1.16–4.40).

When different NHL entities were analysed separately, the OR for the subtype small lymphocytic lymphoma/chronic lymphocytic leukaemia (SLL/CLL) was increased for both phenoxy herbicides and, especially, glyphosate, Table III. The entity diffuse large B-cell lymphoma (DLBCL) was significantly associated with exposure to phenoxyacetic acids, but not to other herbicides. On the other hand, the group follicular lymphoma was not clearly associated with phenoxyacetic acids, and only nonsignificantly with glyphosate. The category "other specified B-cell lymphoma" (*e.g.*, mantle cell lymphoma, marginal zone lymphoma) was significantly associated with exposure to phenoxyacetic acids, and an increased risk was also indicated for glyphosate. T-cell lymphomas seemed to be associated with all types of herbicides, but no statistically significant ORs were found due to relatively few exposed subjects. The least numerous categories ("unspecified NHL") yielded high and statistically significant ORs for phenoxy herbicides and glyphosate.

TABLE II – EXPOSURE TO VARIOUS HERBICIDES

Agents	Cases/controls	OR	CI
Herbicides, total	74/51	1.72	1.18–2.51
≤20 days	36/27	1.58	0.95–2.65
>20 days	38/24	1.87	1.10–3.18
Phenoxyacetic acids	47/26	2.04	1.24–3.36
≤45 days	32/13	2.83	1.47–5.47
>45 days	15/13	1.27	0.59–2.70
MCPA	21/9	2.81	1.27–6.22
≤32 days	15/5	3.76	1.35–10.5
>32 days	6/4	1.66	0.46–5.96
2,4,5-T and/or 2,4-D	33/21	1.61	0.87–2.97
≤29 days	21/11	2.08	0.99–4.38
>29 days	12/10	1.33	0.57–3.13
Other	7/7	1.21	0.42–3.48
Herbicides except phenoxyacetic acids	38/26	1.82	1.08–3.06
≤24 days	20/13	1.91	0.93–3.89
>24 days	18/13	1.73	0.84–3.60
Glyphosate	29/18	2.02	1.10–3.71
≤10 days	12/9	1.69	0.70–4.07
>10 days	17/9	2.36	1.04–5.37
Other herbicides	18/18	1.22	0.63–2.39
≤32 days	12/9	1.64	0.68–3.96
>32 days	6/9	0.80	0.28–2.29

Number of exposed cases/controls, odds ratios (OR) and 95% confidence intervals (CI). Agents with more than 20 exposed subjects were also divided in two groups based on median number of days among exposed controls. Adjustment was made for age, sex and year of diagnosis or enrolment.

Insecticides

In our study no overall increased OR was demonstrated for exposure to insecticides, OR 1.28 (95% CI 0.96–1.72), Table IV. The most reported insecticide DDT yielded OR 1.46 (95% CI 0.94–2.28). Increased risk was shown for mercurial seed dressing, OR 2.03 (95% CI 0.97–4.28).

In the dose-response analysis, OR 1.47 (95% CI 0.99–2.16) was found for the high category of insecticide exposure, Table IV. Similar trends were found for DDT and mercurial seed dressing.

Different NHL entities were analysed separately, Table V. Hereby, certain exposures seemed to be associated with subtypes of NHL. Thus, the group follicular lymphoma was associated with DDT, OR 2.14 (95% CI 1.05–4.40) and mercurial seed dressing, OR 3.61 (95% CI 1.20–10.9). Furthermore, exposure to DDT increased the risk also for T-cell lymphoma, OR 2.88 (95% CI 1.05–7.95).

Fungicides and rodenticides

Exposure to fungicides was not a risk factor in our study, neither in total, OR 1.11 (95% CI 0.56–2.23), Table IV, nor for different subtypes of NHL, Table VI. Furthermore, there were no single substances among 24 reported that significantly differed between cases and controls. Also for rodenticides no increased risk was found, Table IV.

Impregnating agents

Exposure to impregnating agents yielded a statistically significant OR 1.57 (95% CI 1.07–2.30), Table IV. In a dose-response calculation OR increased further in the high exposure group. Creosote showed a statistically significant OR for high exposure, OR 3.33 (95% CI 1.20–9.27).

Table VI presents results for different NHL entities. An increased risk for SLL/CLL was associated with exposure to impregnating agents in total, and most pronounced for creosote,

TABLE III – EXPOSURE TO VARIOUS HERBICIDES DIVIDED ACCORDING TO DIFFERENT LYMPHOMA ENTITIES

Lymphoma entities	Herbicides, total	Phenoxyacetic acids (ph)	MCPA	2,4,5-T and/or 2,4-D	Herbicides except ph	Glyphosate	Other
B-cell lymphomas, total (n = 819)	1.68 1.14–2.48	1.99 1.20–3.32	2.59 1.14–5.91	1.69 0.94–3.01	1.72 1.003–2.94	1.87 0.998–3.51	1.14 0.57–2.31
Lymphocytic lymphoma/B-CLL (n = 195) (SLL/CLL)	2.27 1.28–4.01	2.11 0.995–4.47	2.57 0.74–8.97	1.93 0.85–4.41	2.56 1.17–5.60	3.35 1.42–7.89	1.39 0.45–4.31
Follicular, grade I–III (n = 165) (FL)	1.78 0.88–3.59	1.26 0.42–3.75	–[1]	1.21 0.35–4.22	2.32 0.96–5.60	1.89 0.62–5.79	1.48 0.42–5.23
Diffuse large B-cell lymphoma (n = 239) (DLBCL)	1.44 0.81–2.59	2.16 1.08–4.33	3.94 1.48–10.5	1.65 0.71–3.82	1.20 0.51–2.83	1.22 0.44–3.35	1.00 0.33–3.03
Other specified B-cell lymphoma (n = 131)	1.62 0.82–3.19	2.60 1.20–5.64	3.20 0.95–10.7	2.21 0.90–5.44	1.38 0.51–3.73	1.63 0.53–4.96	1.15 0.33–4.03
Unspecified B-cell lymphoma (n = 89)	1.09 0.41–2.89	1.14 0.33–3.95	1.35 0.16–11.2	0.88 0.20–3.92	1.52 0.44–5.27	1.47 0.33–6.61	0.71 0.09–5.53
T-cell lymphomas (n = 53)	1.64 0.55–4.90	1.62 0.36–7.25	2.40 0.29–20.0	1.02 0.13–7.95	1.57 0.35–6.99	2.29 0.51–10.4	2.24 0.49–10.3
Unspecified non-Hodgkin lymphoma (n = 38)	2.86 1.001–8.18	3.75 1.16–12.1	9.31 2.11–41.2	3.21 0.85–12.1	5.29 1.60–17.5	5.63 1.44–22.0	1.88 0.23–15.4

Odds ratios (OR) and 95% confidence intervals (CI). Adjustment was made for age, sex and year of diagnosis or enrolment.
[1]No exposed cases

OR 2.91 (95% CI 1.01–8.33). Regarding follicular lymphomas and DLBCL, increased risks were also noted after creosote exposure, and for the latter subtype this was also the case for all impregnating agents together. T-cell lymphomas were also associated with impregnating agents, and it seemed to be specifically chlorophenols. In the group of patients whose lymphomas were not possible to classify histopathologically, increased risks were indicated for all types of impregnating agents.

TABLE IV – EXPOSURE TO VARIOUS OTHER PESTICIDES

Agents	Cases/controls	OR	CI
Insecticides, total	112/101	1.28	0.96–1.72
≤40 days	44/51	1.03	0.68–1.57
>40 days	65/50	1.47	0.99–2.16
DDT	50/37	1.46	0.94–2.28
≤37 days	20/19	1.17	0.62–2.22
>37 days	30/18	1.76	0.97–3.20
Mercurial seed dressing	21/11	2.03	0.97–4.28
≤12 days	7/6	1.27	0.42–3.83
>12 days	14/5	2.93	1.04–8.25
Pyretrine	15/10	1.74	0.78–3.91
≤25 days	8/5	1.86	0.60–5.75
>25 days	6/5	1.36	0.41–4.51
Permetrine	9/9	1.23	0.48–3.14
Other insecticides	28/26	1.25	0.72–2.16
≤33 days	9/14	0.79	0.34–1.85
>33 days	18/12	1.67	0.79–3.51
Fungicides	16/18	1.11	0.56–2.23
≤37 days	9/9	1.29	0.51–3.31
>37 days	7/9	0.94	0.35–2.57
Impregnating agents	70/51	1.57	1.07–2.30
≤45 days	27/25	1.23	0.71–2.16
>45 days	43/24	2.04	1.21–3.42
Chlorophenols	40/36	1.24	0.77–1.98
≤33 days	23/18	1.46	0.78–2.74
>33 days	17/17	1.08	0.54–2.15
Arsenic	7/5	1.63	0.51–5.20
Creosote	19/10	2.10	0.96–4.58
≤39 days	4/5	0.87	0.23–3.29
>39 days	15/5	3.33	1.20–9.27
Tar	8/5	1.84	0.59–5.69
Other impregnating agents	27/20	1.55	0.85–2.81
≤7 days	4/10	0.44	0.14–1.42
>7 days	22/10	2.55	1.19–5.47
Rodenticides	5/4	1.67	0.44–6.29

Number of exposed cases/controls, odds ratios (OR) and 95% confidence intervals (CI). Agents with more than 20 exposed subjects were also divided in two groups based on median number of days among exposed controls. In some subjects, number of days was not known (excluded in dose-response calculations). Adjustment was made for age, sex and year of diagnosis or enrolment.

Multivariate analysis

Since mixed exposure to several pesticides was more a rule than an exception, and all single agents were analyzed without adjusting for other exposure, a multivariate analysis was made to elucidate the relative importance of different pesticides. Criteria for agents to be included in this analysis are defined in Statistical Methods above. As seen in Table VII increased ORs were found but in general lower than in the univariate analysis.

Discussion

This was a population based case–control study on NHL, which is a strength of the investigation. Only living cases and controls were included, which was of advantage in comparison with interviewing next-of-kins. The study covered all new cases of NHL during a specified time. Pathologists in Sweden that were experts in lymphoma diagnosis confirmed all diagnoses. Thus, a main advantage compared with the earlier studies was the possibility to study the different NHL entities, classified according to the recently developed WHO classification system. The histopathological subgroups may well be regarded as separate in etiology and pathogenesis, as well as they are known to be different regarding course, prognosis and best treatment.

The frequency matching on age groups, gender and health service regions increased the efficacy of the study and ensured exposure conditions for the controls representative for the population in the included geographical areas. We achieved a high response rate among cases and controls, which is another advantage. A motivating introduction letter that was sent out with the questionnaire and with reminders if needed may explain this.

Exposures were assessed by questionnaires with information supplemented over the phone. Thereby use of different pesticides could be checked by information in *e.g.*, receipts and bookkeeping. However, no registries exist in Sweden on such individual use, which is a weakness in the assessment of exposure. Exposure to pesticides may be difficult to assess, and some misclassification regarding quantity of exposure has probably occurred, but such misclassification would most probably be nondependent of case/control status, and therefore only weaken any true risks. Use of protective equipment was not asked for which might have been a disadvantage of the study. However, such use would dilute the exposure and thus bias the result towards unity.

We have earlier published the results from 2 Swedish case–control studies on lymphomas, the first one on NHL and HL[8,19] and later on NHL.[18] These studies showed an increased risk for lymphomas as a result of exposure to herbicides belonging to the class phenoxyacetic acids. In the first study we also found correlation with chlorophenols and organic solvents. Several other studies,

TABLE V – EXPOSURE TO VARIOUS INSECTICIDES DIVIDED ACCORDING TO DIFFERENT LYMPHOMA ENTITIES

Lymphoma entities	Insecticides, total	DDT	Mercurial seed dressing	Pyretrine	Other
B-cell lymphomas, total (n = 819)	1.19	1.32	1.81	1.68	1.08
	0.88–1.61	0.83–2.10	0.84–3.93	0.73–3.86	0.60–1.94
Lymphocytic lymphoma/B-CLL (n = 195) (SLL/CLL)	1.46	1.39	0.75	2.40	1.57
	0.91–2.35	0.69–2.83	0.16–3.47	0.73–7.89	0.66–3.75
Follicular, grade I–III (n = 165) (FL)	1.37	2.14	3.61	2.60	0.28
	0.79–2.38	1.05–4.40	1.20–10.9	0.79–8.51	0.04–2.11
Diffuse large B-cell lymphoma (n = 239) (DLBCL)	1.23	1.24	2.20	1.25	1.31
	0.78–1.93	0.61–2.49	0.79–6.12	0.34–4.61	0.58–2.97
Other specified B-cell lymphoma (n = 131)	1.32	1.33	2.39	1.49	1.42
	0.77–2.27	0.57–3.10	0.73–7.81	0.32–6.94	0.53–3.80
Unspecified B-cell lymphoma (n = 89)	0.42	0.23	–[1]	–[1]	0.42
	0.15–1.18	0.03–1.75			0.06–3.18
T-cell lymphomas (n = 53)	1.61	2.88	2.08	2.20	1.59
	0.72–3.60	1.05–7.95	0.25–17.1	0.27–17.8	0.36–7.02
Unspecified non-Hodgkin lymphoma (n = 38)	1.91	2.39	5.43	3.14	4.70
	0.79–4.62	0.77–7.42	1.34–22.0	0.37–26.3	1.48–14.9

Odds ratios (OR) and 95% confidence intervals (CI). Adjustment was made for age, sex and year of diagnosis or enrolment.
[1]No exposed cases.

TABLE VI – EXPOSURE TO FUNGICIDES AND IMPREGNATING AGENTS DIVIDED ACCORDING TO DIFFERENT LYMPHOMA ENTITIES

Lymphoma entities	Fungicides	Impregnating agents, total	Chlorophenols	Creosote	Other
B-cell lymphomas, total (n = 819)	1.01	1.41	1.12	2.09	1.51
	0.48–2.09	0.95–2.11	0.69–1.84	0.94–4.64	0.82–2.78
Lymphocytic lymphoma/B-CLL (n = 195)	1.33	1.71	1.35	2.91	2.23
	0.43–4.12	0.94–3.11	0.64–2.85	1.01–8.33	0.97–5.13
Follicular, grade I–III (n = 165)	–[1]	1.49	0.91	2.56	1.80
		0.70–3.19	0.31–2.66	0.68–9.68	0.59–5.48
Diffuse large B-cell lymphoma (n = 239)	1.26	1.70	1.40	1.75	1.51
	0.45–3.47	0.97–2.96	0.70–2.78	0.54–5.74	0.62–3.67
Other specified B-cell lymphoma (n = 131)	1.56	1.24	0.95	2.58	1.09
	0.51–4.76	0.58–2.63	0.36–2.51	0.78–8.55	0.31–3.78
Unspecified B-cell lymphoma (n = 89)	–[1]	0.41	0.54	–[1]	0.54
		0.10–1.75	0.12–2.32		0.07–4.19
T-cell lymphomas (n = 53)	1.10	3.26	2.39	–[1]	2.07
	0.14–8.70	1.39–7.63	0.78–7.28		0.45–9.53
Unspecified non-Hodgkin lymphoma (n = 38)	3.73	2.52	2.02	4.94	1.40
	0.77–18.0	0.88–7.19	0.56–7.31	0.97–25.2	0.17–11.2

Odds ratios (OR) and 95% confidence intervals (CI). Adjustment was made for age, sex, and year of diagnosis or enrolment.
[1]No exposed cases.

TABLE VII – MULTIVARIATE ANALYSES INCLUDING AGENTS ACCORDING TO SPECIFIED CRITERIA, SEE TEXT

Agents	Univariate		Multivariate	
	OR	CI	OR	CI
MCPA	2.81	1.27–6.22	1.88	0.77–4.63
2,4,5-T and/or 2,4-D	1.61	0.87–2.97	1.24	0.68–2.26
Glyphosate	2.02	1.10–3.71	1.51	0.77–2.94
Mercurial seed dressing	2.03	0.97–4.28	1.58	0.74–3.40
Arsenic	1.63	0.51–5.20	1.17	0.34–4.02
Creosote	2.10	0.96–4.58	1.70	0.73–3.98
Tar	1.84	0.59–5.69	1.39	0.43–4.48

Odds ratios (OR) and 95% confidence intervals (CI). Adjustment was made for age, sex and year of diagnosis or enrolment.

but not all, from different research groups have supported our results, as reviewed,[20] and also confirmed later, *e.g.*, Ref. 21.

Furthermore, other groups have demonstrated associations between NHL and other classes of pesticides, especially different types of insecticides, *e.g.*, organophosphates,[22] carbamate,[23] lindane[24] and chlordane,[25] but also other groups of herbicides as atrazine.[26] Some case–control studies have found associations between several classes of pesticides, *e.g.*, Ref. 27 or merged groups of pesticides as in one recent study,[28] which demonstrate a significantly increased risk for NHL associated with exposure to "nonarsenic pesticides." These authors discuss the fact that several pesticides are chemically related and may exert their effects on humans through a similar mechanism of action, which may explain the wide range of pesticides that have been related to NHL over time in different countries and with different exposure conditions.

Several factors urged for a third Swedish study on the relation between pesticides, other chemicals and NHL, and the present study also used a somewhat changed methodology, which also may be of interest.

Thus, the use of phenoxyacetic herbicides, which earlier were dominating both as weed killers in agriculture and against hard wood in forestry, have substantially decreased during the last decades. 2,4,5-T, which was contaminated by TCDD, was prohibited in Sweden 1977, and 2,4-D was withdrawn from the market in 1990. MCPA, even if still used, has been largely substituted by other agents, among which glyphosate has been clearly dominating. This change of herbicide practice along with successively strengthened protection instructions has prompted our new study, reflecting also later years of exposure.

Furthermore, the changing trend of the incidence of NHL in many countries with reliable cancer registries, *e.g.*, Sweden, with a substantial and steady increase during the 1960's through 1980's but a leveling off or even slight decrease after that, makes it important to find etiological factors contributing to this shift in trend. Chlorinated compounds in the environment, which have been regulated during the 1970's and 1980's, may at least partly explain this trend, as discussed by us.[2] Phenoxyacetic herbicides with potential contaminating dioxins are examples of such substances. However, the prohibition of common environmental pollutants as polychlorinated biphenyls (PCB) and the following decline in the environment is probably more important to explain the leveling off of the incidence.[2]

In contrast to our 2 former case–control studies on NHL, this study included both genders and only consecutive living cases and living controls. In our earlier studies we have only studied male lymphoma cases, making the results of this study more representative for the whole population. To facilitate comparisons with our earlier results we also made additional analyses of herbicide exposure by gender. Only few women were exposed and separate analyses for both sexes still yielded an increased risk for NHL. Thus, in the total material herbicide exposure gave OR = 1.72, 95% CI 1.18–2.51 (n = 74 cases, 51 controls), whereas for men only OR = 1.71, 95% CI = 1.15–2.55 (n = 68 cases, 47 controls) and for women only OR = 1.82, 95% CI = 0.51–6.53 (n = 6 cases, 4 controls) were calculated.

In our study lymphocytic lymphoma/B-CLL was significantly associated with herbicides with highest OR for glyphosate but also creosote. Follicular lymphoma was significantly associated with DDT and mercurial seed dressing, diffuse large B-cell lymphoma with MCPA, and T-cell lymphoma with DDT and impregnating agents overall. Unspecified NHL was significantly associated with MCPA, glyphosate and mercurial seed dressing. It should be noted that several ORs were increased for herbicides; insecticides and impregnating agents but the calculations were hampered by low numbers of exposed cases and controls.

Our earlier results of exposure to phenoxyacetic herbicides as a risk factor for NHL were confirmed in our study. As in our previous lymphoma studies exposure to MCPA seemed to yield the highest OR among the different phenoxyacetic acids. This is of interest because MCPA is known not to be contaminated by dioxins, as 2,4-D and 2,4,5-T. At the same time MCPA is the only phenoxyacetic acid still in wider use in Sweden and many other countries.

Glyphosate is a broad-spectrum herbicide, which inhibits the formation of amino acids in plants.[29] The US Environmental Protection Agency[30] and the World Health Organization[31] have concluded that glyphosate is not mutagenic or carcinogenic. Since then, however, some experimental studies indicate genotoxic, hormonal and enzymatic effect in mammals, as reviewed.[32] Of particular interest is that glyphosate treatment of human lymphocytes *in vitro* resulted in increased sister chromatid exchanges,[33] chromosomal aberrations and oxidative stress.[34,35]

Glyphosate was associated with a statistically significant increased OR for lymphoma in our study, and the result was strengthened by a tendency to dose-response effect as shown in Table II. In our former study[18] very few subjects were exposed to glyphosate, but a nonsignificant OR of 2.3 was found. Furthermore, a meta-analysis combining that study with an investigation on hairy-cell leukaemia, a rare NHL variant, showed an OR for glyphosate of 3.04 (95% CI 1.08–8.52).[36] Recent findings from other groups also associate glyphosate with different B-cell malignancies such as lymphomas and myeloma.[32,37,38]

Glyphosate has succeeded MCPA as one of the most used herbicides in agriculture, and many individuals that used MCPA earlier are now also exposed to glyphosate. This probably explains why the multivariate analysis does not show any significant ORs for these compounds.

Exposure to insecticides was associated with a slightly increased OR, Table IV. In some other studies on the relation between pesticides and NHL, insecticides seem to be of some importance as causative agents.[27,37,38] Especially, different organophosphates were indicated as risk factors in those studies, with a Canadian study[37] showing statistical significant ORs for malathion and diazinon. In our study, only few subjects were exposed to different organophosphates, but we found a nonsignificant OR of 2.81 (95% CI 0.54–14.7) for malathion based on 5 exposed cases and 2 controls, not shown in Table.

The organochlorine DDT has shown suggestive but rarely significant association with NHL in some studies.[8,19,38–40] Our study showed a moderately but not significant increased OR for exposure to DDT.

Fungicides were not associated with the risk for NHL in our study, but few subjects were exposed to a wide range of different agents. In some earlier studies increased risks have also been noted for this group of pesticides.[16,18]

Exposure to impregnating agents produced a significant OR with a dose-response relation, Table IV. The highest risk was found for high exposure to creosote, which gave a significant OR. This finding was in contrast to our previous results on NHL,[18] but another Swedish study also found an association between creosote and NHL.[41] Chlorophenols have been the most common group of impregnating agents in Sweden, but were banned in 1977. In our first NHL study, reflecting exposures mainly during the time these substances were used, we found a strong association with NHL. As in the present study, however, no association was found in our second study on NHL.[18]

In conclusion, this study, which mirrors pesticide exposure during later years than in our previous studies, confirmed results of an association between exposure to phenoxyacetic herbicides and NHL. Furthermore, our earlier indication of an association between glyphosate and NHL has been considerably strengthened.

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References

1. Jaffe ES, Harris NL, Stein H, Vardiman JW. World Health Organization classification of tumours. Pathology and genetics. Tumours of haematopoetic and lymphoid tissues. Lyon: IARC Press, 2001.
2. Hardell L, Eriksson M. Is the decline of the increasing incidence of non-Hodgkin lymphoma in Sweden and other countries a result of cancer preventive measures? Environ Health Perspect 2003;111: 1704–6.
3. Hardell L, Axelson O. Environmental and occupational aspects on the etiology of non-Hodgkin's lymphoma. Oncol Res 1998;10:1–5.
4. Pluda JM, Venzon DJ, Tosato G, Lietzau J, Wyvill K, Nelson DL, Jaffe ES, Karp JE, Broder S, Yarchoan R. Parameters affecting the development of non-Hodgkin's lymphoma in patients with severe human immunodeficiency virus infection receiving antiretroviral therapy. J Clin Oncol 1993;11:1099–107.
5. Patton DF, Wilkowski CW, Hanson CA, Shapiro R, Gajl-Peczalska KJ, Filipovich AH, McClain KL. Epstein-Barr virus–determined clonality in posttransplant lymphoproliferative disease. Transplantation 1990;49:1080–4.
6. Lehtinen T, Lumio J, Dillner J, Hakama M, Knekt P, Lehtinen M, Teppo L, Leinikki P. Increased risk of malignant lymphoma indicated by elevated Epstein-Barr virus antibodies—a prospective study. Cancer Causes Control 1993;4:187–93.
7. Potter M. Pathogenetic mechanisms in B-cell non-Hodgkin's lymphomas in humans. Cancer Res 1992;52:5522S–5528S.
8. Hardell L, Eriksson M, Lenner P, Lundgren E. Malignant lymphoma and exposure to chemicals, especially organic solvents, chlorophenols and phenoxy acids: a case-control study. Br J Cancer 1981;43:169–76.
9. Hardell L. Malignant lymphoma of histiocytic type and exposure to phenoxyacetic acids or chlorophenols. Lancet 1979;1:55–6.
10. International Agency for Research on Cancer. Polychlorinated dibenzo-para-dioxins. IARC Monogr Eval Carcinog Risks Hum 1997;69:333–343.
11. Vos JG, Moore JA, Zinkl JG. Effect of 2,3,7,8-tetrachlorodibenzo-*p*-dioxin on the immune system of laboratory animals. Environ Health Perspect 1973;5:149–62.
12. Exon JH, Talcott PA, Koller LD. Effect of lead, polychlorinated biphenyls, and cyclophosphamide on rat natural killer cells, interleukin 2, and antibody synthesis. Fundam Appl Toxicol 1985;5:158–64.
13. Lu YC, Wu YC. Clinical findings and immunological abnormalities in Yu-Cheng patients. Environ Health Perspect 1985;59:17–29.
14. Kerkvliet NI, Brauner JA. Mechanisms of 1,2,3,4,6,7,8-heptachlorodibenzo-p-dioxin (HpCDD)-induced humoral immune suppression: evidence of primary defect in T-cell regulation. Toxicol Appl Pharmacol 1987;87:18–31.
15. Faustini A, Settimi L, Pacifici R, Fano V, Zuccaro P, Forastiere F. Immunological changes among farmers exposed to phenoxy herbicides: preliminary observations. Occup Environ Med 1996;53: 583–5.
16. Hoar SK, Blair A, Holmes FF, Boysen CD, Robel RJ, Hoover R, Fraumeni JF, Jr. Agricultural herbicide use and risk of lymphoma and soft-tissue sarcoma. JAMA 1986;256:1141–7.
17. Zahm SH, Weisenburger DD, Babbitt PA, Saal RC, Vaught JB, Cantor KP, Blair A. A case-control study of non-Hodgkin's lymphoma and the herbicide 2,4-dichlorophenoxyacetic acid (2,4-D) in eastern Nebraska. Epidemiology 1990;1:349–56.
18. Hardell L, Eriksson M. A case-control study of non-Hodgkin lymphoma and exposure to pesticides. Cancer 1999;85:1353–60.
19. Hardell L, Eriksson M, Degerman A. Exposure to phenoxyacetic acids, chlorophenols, or organic solvents in relation to histopathology, stage, and anatomical localization of non-Hodgkin's lymphoma. Cancer Res 1994;54:2386–9.
20. Hardell L, Eriksson M, Axelson O, Flesch-Janys D. Epidemiological studies on cancer and exposure to dioxins and related compounds. In: Schecter A, Gasiewicz T, eds. Dioxins and health. Hoboken, NJ: John Wiley & Sons, 2003. p 729–64.
21. Miligi L, Costantini AS, Veraldi A, Benvenuti A, Vineis P. Cancer and pesticides: an overview and some results of the Italian multicenter case-control study on hematolymphopoietic malignancies. Ann N Y Acad Sci 2006;1076:366–77.
22. Waddell BL, Zahm SH, Baris D, Weisenburger DD, Holmes F, Burmeister LF, Cantor KP, Blair A. Agricultural use of organophosphate pesticides and the risk of non-Hodgkin's lymphoma among male farmers (United States). Cancer Causes Control 2001;12:509–17.
23. Zheng T, Zahm SH, Cantor KP, Weisenburger DD, Zhang Y, Blair A. Agricultural exposure to carbamate pesticides and risk of non-Hodgkin lymphoma. J Occup Environ Med 2001;43:641–9.
24. Purdue MP, Hoppin JA, Blair A, Dosemeci M, Alavanja MC. Occupational exposure to organochlorine insecticides and cancer incidence in the agricultural health study. Int J Cancer 2007;120:642–9.
25. Colt JS, Davis S, Severson RK, Lynch CF, Cozen W, Camann D, Engels EA, Blair A, Hartge P. Residential insecticide use and risk of non-Hodgkin's lymphoma. Cancer Epidemiol Biomarkers Prev 2006;15:251–7.
26. Rusiecki JA, De Roos A, Lee WJ, Dosemeci M, Lubin JH, Hoppin JA, Blair A, Alavanja MC. Cancer incidence among pesticide applicators exposed to atrazine in the Agricultural Health Study. J Natl Cancer Inst 2004;96:1375–82.
27. Fritschi L, Benke G, Hughes AM, Kricker A, Turner J, Vajdic CM, Grulich A, Milliken S, Kaldor J, Armstrong BK. Occupational exposure to pesticides and risk of non-Hodgkin's lymphoma. Am J Epidemiol 2005;162:849–57.

28. van Balen E, Font R, Cavalle N, Font L, Garcia-Villanueva M, Benavente Y, Brennan P, de Sanjose S. Exposure to non-arsenic pesticides is associated with lymphoma among farmers in Spain. Occup Environ Med 2006;63:663–8.
29. Steinrucken HC, Amrhein N. The herbicide glyphosate is a potent inhibitor of 5-enolpyruvyl-shikimic acid-3-phosphate synthase. Biochem Biophys Res Commun 1980;94:1207–12.
30. US EPA. U.S. Environmental Protection Agency Registration Eligibility Decision (RED) Glyphosate. EPA-R-93-014. Washington DC: US Environmental Protection Agency, 1993.
31. World Health Organization. International programme on chemical safety. Glyphosate. Environmental health criteria 159. Geneva: WHO, 1994.
32. De Roos AJ, Blair A, Rusiecki JA, Hoppin JA, Svec M, Dosemeci M, Sandler DP, Alavanja MC. Cancer incidence among glyphosate-exposed pesticide applicators in the Agricultural Health Study. Environ Health Perspect 2005;113:49–54.
33. Bolognesi C, Bonatti S, Degan P, Gallerani E, Peluso M, Rabboni R, Roggieri P, Abbondandolo A. Genotoxic activity of glyphosate and its technical formulation Roundup. J Agric Food Chem 1997;45:1957–62.
34. Lioi MB, Scarfi MR, Santoro A, Barbieri R, Zeni O, Di Berardino D, Ursini MV. Genotoxicity and oxidative stress induced by pesticide exposure in bovine lymphocyte cultures in vitro. Mutat Res 1998; 403:13–20.
35. Lioi MB, Scarfi MR, Santoro A, Barbieri R, Zeni O, Salvemini F, Di Berardino D, Ursini MV. Cytogenetic damage and induction of pro-oxidant state in human lymphocytes exposed in vitro to gliphosate, vinclozolin, atrazine, and DPX-E9636. Environ Mol Mutagen 1998;32:39–46.
36. Hardell L, Eriksson M, Nordstrom M. Exposure to pesticides as risk factor for non-Hodgkin's lymphoma and hairy cell leukemia: pooled analysis of two Swedish case-control studies. Leuk Lymphoma 2002; 43:1043–9.
37. McDuffie HH, Pahwa P, McLaughlin JR, Spinelli JJ, Fincham S, Dosman JA, Robson D, Skinnider LF, Choi NW. Non-Hodgkin's lymphoma and specific pesticide exposures in men: cross-Canada study of pesticides and health. Cancer Epidemiol Biomarkers Prev 2001;10: 1155–63.
38. De Roos AJ, Zahm SH, Cantor KP, Weisenburger DD, Holmes FF, Burmeister LF, Blair A. Integrative assessment of multiple pesticides as risk factors for non-Hodgkin's lymphoma among men. Occup Environ Med 2003;60:E11.
39. Tatham L, Tolbert P, Kjeldsberg C. Occupational risk factors for subgroups of non-Hodgkin's lymphoma. Epidemiology 1997;8:551–8.
40. Rothman N, Cantor KP, Blair A, Bush D, Brock JW, Helzlsouer K, Zahm SH, Needham LL, Pearson GR, Hoover RN, Comstock GW, Strickland PT. A nested case-control study of non-Hodgkin lymphoma and serum organochlorine residues. Lancet 1997;350:240–4.
41. Persson B, Dahlander AM, Fredriksson M, Brage HN, Ohlson CG, Axelson O. Malignant lymphomas and occupational exposures. Br J Ind Med 1989;46:516–20.

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Exposure to Pesticides as Risk Factor for Non-Hodgkin's Lymphoma and Hairy Cell Leukemia: Pooled Analysis of Two Swedish Case-control Studies

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Increased risk for non-Hodgkin's lymphoma (NHL) following exposure to certain pesticides has previously been reported. To further elucidate the importance of phenoxyacetic acids and other pesticides in the etiology of NHL a pooled analysis was performed on two case-control studies, one on NHL and another on hairy cell leukemia (HCL), a rare subtype of NHL. The studies were population based with cases identified from cancer registry and controls from population registry. Data assessment was ascertained by questionnaires supplemented over the telephone by specially trained interviewers. The pooled analysis of NHL and HCL was based on 515 cases and 1141 controls. Increased risks in univariate analysis were found for subjects exposed to herbicides (OR 1.75, CI 95% 1.26–2.42), insecticides (OR 1.43, CI 95% 1.08–1.87), fungicides (OR 3.11, CI 95% 1.56–6.27) and impregnating agents (OR 1.48, CI 95% 1.11–1.96). Among herbicides, significant associations were found for glyphosate (OR 3.04, CI 95% 1.08–8.52) and 4-chloro-2-methyl phenoxyacetic acid (MCPA) (OR 2.62, CI 95% 1.40–4.88). For several categories of pesticides the highest risk was found for exposure during the latest decades before diagnosis. However, in multivariate analyses the only significantly increased risk was for a heterogeneous category of other herbicides than above.

Keywords: Non-Hodgkin's lymphoma; Hairy cell leukemia; Pesticides; Phenoxyacetic acids; Glyphosate; Impregnating agents

INTRODUCTION

Non-Hodgkin's lymphoma (NHL) is one of the malignant diseases with the most rapidly increasing incidence in the western world [1]. In Sweden, the mean age-adjusted incidence increased yearly by 3.6% in men and 2.9% in women during the time period 1958–1992 [2]. Hairy cell leukemia (HCL) was first described in 1958 and is regarded as a rare subgroup of NHL. HCL is more common in men with 23 male and 9 female patients reported to the Swedish Cancer Register in 1999 for the whole country [3].

The etiology of NHL is regarded to be multifactorial with different environmental exposures being part of it. Certain immunodefective conditions are established risk factors such as immunosuppressive medication after organ transplantation [4,5] and HIV-infection [6]. Also viral genesis, especially regarding Epstein–Barr virus (EBV) and endemic African Burkitt lymphoma has been indicated [7].

Regarding chemicals, exposure to phenoxyacetic acids, chlorophenols and organic solvents were associated with increased risk for NHL in Swedish studies [8–10]. In subsequent studies exposure to phenoxyacetic acids, particularly 2,4-dichlorophenoxyacetic acid (2,4-D), was associated with an increased risk for NHL [11,12]. These associations have been reviewed by us giving reference also to other studies [13].

We have now performed one case-control study on NHL, which did not include HCL [14], and another on HCL, specifically [15]. Both these studies focused interest especially on exposure to pesticides. In the NHL study, we found increased risks for subjects exposed to herbicides or fungicides. Among herbicides, phenoxyacetic acids

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TABLE I Number of exposed cases and controls, odds ratio (OR) and 95% confidence interval (CI) for exposure to pesticides and organic solvents

Agent	Number of exposed cases/controls	OR	CI
Herbicides	77/103	1.75	1.26–2.42
Phenoxyacetic acids	64/90	1.65	1.16–2.34
MCPA	21/23	2.62	1.40–4.88
2,4-D + 2,4,5-T	48/70	1.48	0.99–2.20
Glyphosate	8/8	3.04	1.08–8.52
Other	15/13	2.90	1.34–6.37
Insecticides	112/184	1.43	1.08–1.87
DDT	77/138	1.27	0.92–1.73
Mercurial seed dressing	20/33	1.40	0.77–2.47
Pyrethrins	13/27	1.16	0.57–2.25
Fungicides	18/17	3.11	1.56–6.27
Impregnating agents	104/162	1.48	1.11–1.96
Chlorophenols	66/106	1.37	0.98–1.92
Pentachlorophenol	64/101	1.40	0.99–1.98
Arsenic	8/10	1.75	0.66–4.54
Creosote	22/35	1.54	0.87–2.66
Other	40/67	1.35	0.88–2.04
Organic solvents	250/492	1.16	0.93–1.44

dominated. One subclass of these, 4-chloro-2-methyl phenoxyacetic acid (MCPA), turned out to be significantly associated with NHL. For several categories of herbicides, we observed that only exposure during the latest decades before diagnosis of NHL was associated with an increased risk for NHL. In the HCL study, we found increased risk for exposure to different categories of pesticides [15]. However, due to comparatively low number of study subjects, it was not meaningful to make further analyses of the tumor induction period.

Thus, the risk patterns for NHL and HCL in these studies, performed by the same methodology, showed similarities with respect to pesticides. Since the NHL study included patients with many different variants of NHL, it seemed motivated also to include HCL, as nowadays being regarded as a NHL subgroup, in a pooled analysis regarding risks in relation to pesticide exposure. The purpose was to enlarge the study size thereby allowing more precise risk estimates.

MATERIALS AND METHODS

Cases

The NHL study encompassed male cases aged ≥25 years with NHL diagnosed during 1987–1990 and living in the four most northern counties of Sweden and three counties in mid-Sweden [14]. They were recruited from the regional cancer registries and only cases with histopathologically verified NHL were included, in total 442 cases. Of these cases 192 were deceased.

From the national Swedish Cancer Registry, 121 male patients with HCL diagnosed during 1987–1992 were identified from the whole country [15]. One case later turned out to have been diagnosed in 1993, but was included in the study. Only living cases were included.

Controls

For living NHL cases two male controls matched for age and county were recruited from the National Population Registry.

For each deceased case two deceased controls matched also for year of death were identified from the National Registry for Causes of Death. For deceased subjects interviews were performed with the next-of-kin.

Similarly, four male controls matched for age and county were drawn to each case of HCL from the National Population Registry.

Assessment of Exposure

In both studies a similar questionnaire was mailed to the study subjects or next-of-kin for deceased individuals. A complete working history was asked for as well as exposure to different chemicals. If the information was unclear a trained interviewer supplemented the answers over the phone, thereby using written instructions. Years and total number of days for exposure to various agents were assessed. Also names of different agents were carefully asked for. If necessary, the Swedish Chemical Inspectorate was contacted to obtain information on the chemical composition of different brands of pesticides and other agents. A minimum exposure of one working day (8 h) and a tumor induction period of at least one year were used in the coding of chemicals. Thus, total exposure less than one day as well as exposure within one year prior to diagnosis (corresponding time for the matched control) were disregarded. The questionnaires were blinded as to case or control status during the interviews and coding of data.

Statistical Analysis

Conditional logistic regression analysis for matched studies was performed with the SAS statistical program (SAS Institute, Cary, NC). Thereby odds ratios (OR) and

TABLE II Exposure to different types of herbicides with dose-response calculations. High exposure is defined as > median number of days for exposed subjects. Range of exposure in days given within parenthesis

Agent	Total OR (CI)	Median number of days	OR (CI)	
			Low	High
Herbicides	1.75 (1.26–2.42)	33 (1–709)	1.74 (1.10–2.71)	1.79 (1.15–2.79)
Phenoxyacetic acids	1.65 (1.16–2.34)	33 (1–709)	1.65 (1.01–2.66)	1.67 (1.02–2.69)
MCPA	2.62 (1.40–4.88)	25 (1–491)	1.94 (0.79–4.55)	3.61 (1.49–9.05)
2,4-D + 2,4,5-T	1.48 (0.99–2.20)	30 (1–709)	1.87 (1.08–3.20)	1.20 (0.68–2.08)
Other	2.90 (1.34–6.37)	11 (1–220)	2.26 (0.76–6.77)	3.37 (1.08–11)

95% confidence intervals (CI) were obtained. Both univariate and multivariate analyses were done. In this pooled analysis adjustment was made for study, study area and vital status. When risk estimates for different pesticides were analyzed only subjects with no pesticide exposure were taken as unexposed, whereas subjects exposed to other pesticides were disregarded.

RESULTS

The questionnaire was answered by 404 cases (91%) and 741 controls (84%) in the NHL study. Regarding HCL 111 cases (91%) and 400 controls (83%) participated. In the following results are given for the pooled analysis containing 515 cases and 1141 controls.

An increased risk was found for exposure to herbicides, insecticides, fungicides and impregnating agents, Table I. Regarding specific agents OR was highest for glyphosate and MCPA.

For herbicides dose-response calculations were also performed by comparing high and low dose exposures divided by the median exposure time in days, Table II. Exposure to MCPA gave a dose-response effect. Also for the group constituting of other herbicides than phenoxyacetic acids the risk was highest in the group with high exposure.

For herbicides in total and phenoxyacetic acids as a group the highest risks were seen when first exposure occurred 10–20 years before diagnosis, Table III. This was also the case for insecticides and impregnating agents. Within the latter group, however, an induction period of 20–30 years gave the highest risk for both creosote and pentachlorophenol.

Time to diagnosis from last exposure to different agents was also used in the calculation of risk estimates, Table IV. For phenoxyacetic acids the OR was highest for exposure 1–10 years prior to diagnosis whereas no increased risk was seen for those with last exposure >20 years from the time of diagnosis.

TABLE III Exposure to phenoxyacetic acids, insecticides, impregnating agents and organic solvents. Calculations are made with exposure divided according to time span from first exposure to diagnosis (induction period)

Agent	Induction period, years			
	1–10 OR (CI)	>10–20 OR (CI)	>20–30 OR (CI)	>30 OR (CI)
Herbicides	1.00 (0.05–11)	2.32 (1.04–5.16)	1.63 (0.87–2.98)	1.70 (1.12–2.58)
Phenoxyacetic acids	–*	2.88 (1.11–7.72)	1.54 (0.85–2.76)	1.50 (0.94–2.37)
MCPA	–*	5.36 (1.57–21)	0.89 (0.20–3.03)	3.77 (1.49–9.99)
2,4-D + 2,4,5-T	–†	2.87 (0.81–11)	1.87 (0.98–3.53)	1.15 (0.67–1.93)
Insecticides	1.20 (0.25–4.70)	2.84 (0.95–8.54)	2.19 (1.14–4.17)	1.31 (0.96–1.77)
DDT	–†	2.64 (0.61–11)	1.63 (0.80–3.26)	1.17 (0.82–1.65)
Impregnating agents	1.20 (0.37–3.49)	2.27 (1.15–4.49)	1.89 (1.07–3.30)	1.23 (0.85–1.75)
Chlorophenols	–†	1.91 (0.82–4.44)	1.90 (0.98–3.65)	1.13 (0.73–1.71)
Pentachlorophenol	–†	1.91 (0.82–4.44)	2.13 (1.07–4.25)	1.13 (0.73–1.72)
Creosote	–*	0.88 (0.04–7.27)	5.33 (1.26–27)	1.34 (0.69–2.49)
Organic solvents	1.51 (0.65–3.37)	1.38 (0.84–2.24)	1.46 (1.00–2.12)	1.02 (0.79–1.30)

* No exposed cases, one exposed control.
† No exposed subjects.

TABLE IV Exposure to phenoxyacetic acids, impregnating agents and organic solvents. Calculations are made with exposure divided according to time span from last exposure to diagnosis

Agent	Time span, last exposure-diagnosis, years			
	1–10 OR (CI)	>10–20 OR (CI)	>20–30 OR (CI)	>30 OR (CI)
Herbicides	2.53 (1.38–4.64)	1.68 (0.88–3.14)	1.22 (0.66–2.19)	1.84 (0.95–3.51)
Phenoxyacetic acids	3.22 (1.59–6.65)	2.06 (1.03–4.09)	1.01 (0.54–1.81)	1.26 (0.57–2.62)
MCPA	3.52 (1.58–7.99)	2.33 (0.56–9.09)	0.92 (0.13–4.39)	–*
2,4-D + 2,4,5-T	4.31 (1.12–21)	1.85 (0.90–3.78)	1.04 (0.54–1.94)	1.41 (0.65–2.92)
Insecticides	2.37 (1.40–4.02)	0.87 (0.48–1.53)	1.45 (0.85–2.41)	1.46 (0.94–2.24)
DDT	1.45 (0.65–3.10)	1.13 (0.62–1.97)	1.46 (0.83–2.50)	1.20 (0.69–2.02)
Impregnating agents	1.92 (1.30–2.82)	0.79 (0.40–1.46)	1.67 (0.88–3.11)	1.19 (0.61–2.21)
Chlorophenols	–†	1.52 (1.02–2.25)	1.36 (0.61–2.86)	0.84 (0.32–1.96)
Pentachlorophenol	–†	1.59 (1.06–2.37)	1.28 (0.58–2.67)	0.81 (0.29–2.01)
Creosote	2.56 (0.85–7.67)	0.93 (0.13–4.17)	1.17 (0.36–3.43)	1.54 (0.60–3.75)
Organic solvents	1.17 (0.91–1.50)	1.00 (0.66–1.50)	1.39 (0.84–2.25)	0.99 (0.56–1.69)

* one exposed case, one exposed control.
† No exposed case or control.

Furthermore, exposure to phenoxyacetic acids during different decades from the 1940s was analyzed. Increased risk was found during recent decades, Table V.

No statistically significant increased risk was found for the whole group of organic solvents in this pooled analysis, but when the solvents were subgrouped according to specific substances there were increased risks for vanolen (OR = 1.91, CI = 1.03–3.49; $n = 20$ cases) and aviation fuel (OR = 3.56, CI = 1.03–12; $n = 6$ cases).

Multivariate analysis of exposure to phenoxyacetic acids, insecticides, fungicides and impregnating agents is presented in Table VI. An increased risk persisted for exposure to herbicides, fungicides and impregnating agents, however not statistically significant.

A separate multivariate analysis was performed on exposure to herbicides. Lower risk estimates were obtained although all herbicides still constituted risk factors for NHL, Table VII.

DISCUSSION

The cases in this study were identified by using the Swedish Cancer Registry, which is composed by six regional registries. In Sweden, the reporting of malignant diseases to the Cancer Registry is compulsory, which makes it likely that most incident cases in the study area were identified. Controls were selected from the National Population Registry and, in order to minimize recall bias, deceased controls were used for deceased cases in one of the studies [14] which were the basis for this analysis. In the other only living cases were included [15]. Recall bias is always a matter of concern in a case-control study with self-reported exposures. Farmer as occupation did not increase the risk in this pooled analysis (OR = 1.19, CI = 0.95–1.49) which indicates that the risk increase for pesticides was not explained merely by misclassification of exposure. All interviews and coding of data were performed blinded as to case or control status in order to minimize observational bias.

TABLE V Exposure to phenoxyacetic acids during different decades. Note that one subject may occur during several decades

Decade	Cases/controls	OR	CI
1940s	4/6	1.46	0.37–5.23
1950s	35/53	1.44	0.91–2.26
1960s	43/58	1.68	1.10–2.55
1970s	32/33	2.37	1.42–3.95
1980s	16/33	3.25	1.53–7.07

TABLE VI Multivariate analysis of exposure to pesticides

Agent	Univariate		Multivariate	
	OR	CI	OR	CI
Herbicides	1.75	1.26–2.42	1.39	0.96–2.02
Insecticides	1.43	1.08–1.87	1.07	0.78–1.45
Fungicides	3.11	1.56–6.27	2.02	0.97–4.23
Impregnating agents	1.48	1.11–1.96	1.30	0.98–1.72

TABLE VII Multivariate analysis of exposure to herbicides. Odds ratios (OR) and 95% confidence intervals (CI) are given

	Univariate		Multivariate	
Agent	OR	CI	OR	CI
MCPA	2.62	1.40–4.88	1.67	0.77–3.57
2,4-D + 2,4,5-T	1.48	0.99–2.20	1.32	0.88–1.96
Glyphosate	3.04	1.08–8.52	1.85	0.55–6.20
Other herbicides	2.90	1.34–6.37	2.28	1.02–5.15

This study was a pooled analysis of two case-control studies, one on NHL [14] and the other on HCL [15] to provide larger numbers, which would allow more detailed analyses regarding the timing of exposure and adjustment of multiple exposures. This method was justified since HCL is a type of NHL and similar methods and questionnaires were used in both studies. Also the findings regarding pesticide exposure were relatively homogenous for both studies. The smaller HCL study had a somewhat higher prevalence of exposure and therefore has in this pooled analysis more weight than one would expect.

Conditional logistic regression analysis was performed since both studies in this pooled analysis were matched. Heterogeneity in findings was averaged after stratification by study. Since the NHL study included also deceased cases and controls adjustment was made for vital status. Finally, in the HCL study the whole Sweden was included as study base whereas in the NHL study only parts of Sweden were included. Thus, adjustment was made for geographical area for cases and controls, i.e. county.

In the multivariate analysis exposure to herbicides, fungicides and impregnating agents increased the risk although OR was lower than in the univariate analysis. Significantly increased risk remained only for the heterogeneous group of "other herbicides". The results in multivariate analysis must be interpreted with caution since exposure to different types of pesticides correlate. Multivariate analysis is mainly useful to estimate the risk factors that seem to be most important.

Several previous studies have associated exposure to phenoxyacetic acids, primarily 2,4-D and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), with an increased risk for NHL [8–12,16–18]. Concerning MCPA data are sparse although in our first study on NHL, we found an increased risk [9,10].

In this pooled analysis, most subjects were regarding herbicides exposed to phenoxyacetic acids, mostly the combination of 2,4-D and 2,4,5-T. 2,4-D was withdrawn from the Swedish market in 1990 and 2,4,5-T was prohibited in 1977. Also MCPA, the phenoxy herbicide still commonly used in Sweden, increased the risk for NHL. Glyphosate is the herbicide now mostly used in Sweden. In this study, exposure to glyphosate was a risk factor for NHL. Thus, regarding herbicides lymphomagenesis seems not to be depending on contaminating dioxins, i.e. 2,3,7,8-TCDD in 2,4,5-T. A contributing effect of such exposure cannot be excluded, although not supported by mortality results in a cohort of workers exposed to 2,3,7,8-TCDD [19]. IARC classified recently 2,3,7,8-TCDD as a human carcinogen, Group I [20].

In the univariate analysis exposure to insecticides, mostly DDT, increased the risk for NHL. In the multivariate analysis no risk was found. This is in accordance with our previous results [9,10] and a pooled analysis of three case-control studies concluded that DDT is not a risk factor for NHL [21]. Furthermore, analysis of serum DDT/DDE has not given a clear association with NHL [22,24,25].

Regarding fungicides an increased risk for NHL has previously been reported from USA [11]. Our result with increased risk for NHL needs to be further studied since the finding was based on few subjects exposed to several types of fungicides.

Chlorophenols, which are chemically related to phenoxyacetic acids and have been used as e.g. wood preservatives, were banned in Sweden in 1978. An increased risk for NHL was found in this pooled analysis, but also for exposure to arsenic and creosote. Both chlorophenols and creosote have been associated with NHL [26,27].

An association between exposure to organic solvents and NHL has been described [9,10,28–30]. However, such an association was not confirmed now although an influence of tumor induction period can not be ruled out, *c.f.*, below. Another possibility might be that solvents used during later years are less toxic than previously, e.g. water based, and that they are more cautiously handled [31].

To further elucidate mechanisms in lymphomagenesis analysis of tumor-induction period (latency) and also time from last exposure to diagnosis was performed. Thereby the corresponding year for diagnosis was used for the matched control. For 2,4-D, 2,4,5-T and chlorophenols no subject had first exposure during 1–10 years prior to diagnosis due to restrictions in the use of these chemicals in Sweden during that time period. For fungicides such calculations were not meaningful due to low number of exposed subjects.

The highest risk for exposure to herbicides, insecticides and impregnating substances was found for last exposure 1–10 years prior to diagnosis. Correspondingly, in general the lowest risks were found for the longest tumor induction periods.

Do these results cast further light on the etiology of NHL? Certainly, exposure to some chemicals is of significance in lymphomagenesis. Furthermore, bearing in mind that several of these chemicals are immunotoxic, e.g. certain pesticides and chlorophenols [27,32,33] and immunosuppression is an established risk factor for NHL [34] such toxicity might be of importance for chemical agents.

Viruses have been associated with lymphomas in animals [35,36] and more specifically EBV for humans [7,37]. Virus proliferation in lymphocytes is held back by the immune system and immunosuppression may be followed by development of both B-cell and T-cell

lymphoma in animals [38–39]. For renal transplant patients treated with immunosuppressive drugs the risk for NHL is highest during the first years after transplantation and then declines [40].

Timing of exposure in relation to risk of NHL, particularly in regard to higher risk for recent exposures, seemed to be an interesting result regarding lymphomagenesis. Several interpretations are possible such as chance finding, late stage in lymphomagenesis, type of exposure or interaction with other factors. Certainly immunmodulation by pesticides [32,33] is one hypothesis which should be more elaborated on, possibly with interaction with latent virus infection such as EBV. This might explain the short tumor induction period. In fact, results from the included HCL-study showed interaction between EBV-infection and exposure to such chemicals [41,42]. Additionally, polychlorinated biphenyls [22,24,25] and chlordanes [23,24], chemicals that are immunotoxic [43,44], have been associated with an increased risk for NHL.

The etiology of NHL is multifactorial and further studies should consider immunotoxic effects by the studied chemicals as well as tumor induction period and interaction with virus infection, e.g. EBV.

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References

[1] Rabkin, C.S., Devesa, S.S., Hoar Zahm, S. and Gail, M.H. (1993) "Increasing incidence of non-Hodgkin's lymphoma", *Semin. Hematol.* **30**, 286–296.

[2] Nordström, M. (1996) "Increasing incidence of non-Hodgkin's lymphomas in Sweden 1958–1992", *Oncol. Rep.* **3**, 645–649.

[3] Anonymous (2001). Cancer Incidence in Sweden 1999. The National Board of Health and Welfare. Stockholm, Sweden.

[4] Penn, I., Hammond, W., Brettschneider, I. and Startzl, T.E. (1969) "Malignant lymphomas in transplantation patients", *Transplant. Proc.* **1**, 106–112.

[5] Kinlen, L.J., Sheil, A.G.R., Peto, J. and Doll, R. (1979) "Colloborative United Kingdom–Australiasian study of cancer in patients treated with immunosuppressive drugs", *Br. Med. J.* **2**, 1461–1466.

[6] Ziegler, J.L., Beckstead, J.A., Volberding, P.A., Abrams, D.J., Levine, A.M., Lukes, R.J., Gill, P.S., Burkes, R.L., Meyer, P.R., Metroka, C.E., Mouradian, J., Moore, A., Riggs, S.A., Butler, J.J., Cabanillas, F.C., Hersh, E., Newell, G.R., Laubenstein, L.J., Knowles, D., Odanjnyk, C., Raphael, B., Koziner, B., Urmacher, C. and Clarkson, B. (1984) "Non-Hodgkin's lymphoma in 90 homosexual men: relationship to generalized lymphadenopathy and acquired immunodeficiency syndrome", *N. Engl. J. Med.* **311**, 565–570.

[7] Evans, A.S. and Mueller, N.E. (1990) "Viruses and cancer: causal associations", *Ann. Epidemiol.* **1**, 71–92.

[8] Hardell, L. (1979) "Malignant lymphoma of histiocytic type and exposure to phenxoyacetic acids or chlorophenols", *Lancet* **1**, 55–56.

[9] Hardell, L., Eriksson, M., Lenner, P. and Lundgren, E. (1981) "Malignant lymphoma and exposure to chemicals, especially organic solvents, chlorophenols and phenoxy acids: a case-control study", *Br. J. Cancer* **43**, 169–176.

[10] Hardell, L., Eriksson, M. and Degerman, A. (1994) "Exposure to phenoxyacetic acids, chlorophenols, or organic solvents in relation to histopathology, stage, and anatomical localization of non-Hodgkin's lymphoma", *Cancer Res.* **54**, 2386–2389.

[11] Hoar, S.K., Blair, A., Holmes, F.F., Boysen, C.D., Robel, R.J., Hoover, R. and Fraumeni, Jr. J.F. (1986) "Agricultural herbicide use and risk of lymphoma and soft-tissue sarcoma", *JAMA* **256**, 1141–1147.

[12] Hoar Zahm, S., Weisenburger, D.D., Babbitt, P.A., Saal, R.C., Vaught, J.B., Cantor, K.P. and Blair, A. (1990) "A case-control study of non-Hodgkin's lymphoma and the herbicide 2,4-dichlorophenoxyacetic acid (2,4-D) in Eastern Nebraska", *Epidemiology* **1**, 349–356.

[13] Hardell, L., Eriksson, M., Axelson, O. and Hoar Zahm, S. (1994) "Cancer epidemiology", In: Schecter, A., ed, Dioxins and Health (Plenum Press, New York), pp 525–547.

[14] Hardell, L. and Eriksson, M. (1999) "A case-control study of non-Hodgkin lymphoma and exposure to pesticides", *Cancer* **85**, 1353–1360.

[15] Nordström, M., Hardell, L., Magnuson, A., Hagberg, H. and Rask-Andersen, A. (1998) "Occupational exposures, animal exposure and smoking as risk factors for hairy cell leukaemia evaluated in a case-control study", *Br. J. Cancer* **77**, 2048–2052.

[16] Kogevinas, M., Kauppinen, T., Winkelmann, R., Johnson, E.S., Bertazzi, P.A. and Buneo de Mesquita, B.H. (1995) "Soft tissue sarcoma and non-Hodgkin's lymphoma in workers exposed to phenoxy herbicides, chlorophenols, and dioxins: two nested case-controls studies", *Epidemiology* **6**, 396–402.

[17] Becher, H., Flesch-Janys, D., Kauppinen, T., Kogevinas, M., Steindorf, K., Manz, A. and Wahrendorf, J. (1996) "Cancer mortality in German male workers exposed to phenoxy herbicides and dioxins", *Cancer Causes Control* **7**, 312–321.

[18] Fontana, A., Picoco, C., Masala, G., Prastaro, C. and Vineis, P. (1998) "Incidence rates of lymphomas and environmental measurements of phenoxy herbicides: ecological analysis and case-control study", *Arch. Environ. Health* **53**, 384–387.

[19] Steenland, K., Piacitelli, L., Deddens, J., Fingerhut, M. and Chang, L.I. (1999) "Cancer, heart disease, and diabetes in workers exposed to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin", *J. Natl Cancer Inst.* **91**, 779–786.

[20] International Agency for Research on Cancer (1997). IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Vol. 69, Polychlorinated Dibenzo-para-Dioxins and Polychlorinated Dibenzofurans. Lyon, France.

[21] Baris, D., Hoar Zahm, S., Cantor, K. and Blair, A. (1998) "Agricultural use of DDT and risk of non-Hodgkin's lymphoma: pooled analyses of three case-control studies in the United States", *Occup. Environ. Med.* **55**, 522–527.

[22] Hardell, L., van Bavel, B., Lindström, G., Fredrikson, M., Hagberg, H., Liljegren, G., Nordström, M. and Johansson, B. (1996) "Higher concentrations of specific polychlorinated biphenyl congeners in adipose tissue from non-Hodgkin's lymphoma patients compared with controls without a malignant disease", *Int. J. Oncol.* **9**, 603–608.

[23] Hardell, L., Liljegren, G., Lindström, G., Van Bavel, B., Broman, K., Fredrikson, M., Hagberg, H., Nordström, M. and Johansson, B. (1996) "Increased concentrations of chlordane in adipose tissue from non-Hodgkin's lymphoma patients compared with controls without a malignant disease", *Int. J. Oncol.* **9**, 1139–1142.

[24] Hardell, L., Eriksson, M., Lindström, G., van Bavel, B., Linde, A., Carlberg, M. and Liljegren, G. (2001) "Case-control study on concentrations of organohalogen compounds and titers of antibodies to Epstein–Barr virus antigens in the etiology of non-Hodgkin lymphoma", *Leuk. Lymph.* **42**(4), 619–629.

[25] Rothman, N., Cantor, K.P., Blair, A., Bush, D., Brock, J.W., Helzlsouer, K., Zahm, S.H., Needham, L.L., Pearson, G.R., Hoover, R.N., Comstock, G.W. and Strickland, P.T. (1997) "A nested case-control study of non-Hodgkin lymphoma and serum organochlorine residues", *Lancet* **350**, 240–244.

[26] Persson, B., Dahlander, A.M., Fredriksson, M., Noordlind-Brage, H., Ohlson, C.G. and Axelson, O. (1989) "Malignant lymphomas and occupational exposures", *Br. J. Ind. Med.* **46**, 516–520.

[27] Hardell, L. and Axelson, O. (1998) "Environmental and occupational aspects on the etiology of non-Hodgkin's lymphoma", *Oncol. Res.* **10**, 1–5.
[28] Vianna, N.J. and Polan, A. (1979) "Lymphomas and occupational benzene exposure", *Lancet* **ii**, 1394–1395.
[29] Olsson, H. and Brandt, L. (1988) "Risk of non-Hodgkin's lymphoma among men occupationally exposed to organic solvents", *Scand. J. Work. Environ. Health* **14**, 246–251.
[30] Yin, S.N., Hayes, R.B., Linet, M.S., Le, G.L., Dosemeci, M., Travis, L.B., Zhang, Z.N., Li, D.G., Chow, W.H., Wacholder, S. and Blot, W.J. (1996) "An expanded cohort study of cancer among benzene-exposed workers in China", *Environ. Health Perspect.* **104**(Suppl. 6), 1339–1341.
[31] Axelson, O. and Hogstedt, C. (1994) "The health effects of solvents", In: Zenz, C., Dickerson, O.B. and Horvath, Jr, E.P., eds, Occupational Medicine (St Louis, Mosby), pp 764–778.
[32] Faustini, A., Settimi, L., Pacifici, R., Fano, V., Zuccaro, P. and Forastiere, F. (1996) "Immunological changes among farmers exposed to phenoxy herbicides: preliminary observations", *Occup. Environ. Med.* **53**, 583–585.
[33] Stiller-Winkler, R., Hadnagy, W., Leng, G., Straube, E. and Idel, H. (1999) "Immunological parameters in humans exposed to pesticides in the agricultural environment", *Toxicol. Lett.* **107**, 219–224.
[34] Scherr, P.A. and Mueller, N.E. (1996) "Non-Hodgkin's lymphoma", In: Shottenfeld, D. and Fraumeni, Jr., J.F., eds, Cancer Epidemiology and Prevention (Oxford University Press, New York), pp 920–945.
[35] Kaplan, H.S. (1978) "From experimental animal models to human lymphoid tissue neoplasia: search for viral etiology. Recent Results", *Cancer Res.* **64**, 325–336.
[36] Armenian, H.K. and Hamaden, R.R. (1983) "Epidemiology of non-Hodgkin's lymphoma", In: Lilienfeldt, A.M.,, ed, Reviews In Cancer Epidemiology (Elsevier, New York) **2**, pp 141–169.
[37] Lehtinen, T., Lumio, J., Dillner, J., Hakamma, M., Knekt, P., Lehtinen, M., Teppo, L. and Lenkki, P. (1993) "Increased risk of malignant lymphoma indicated by elevated Epstein–Barr virus antibodies—a prospective study", *Cancer Causes Control* **4**, 187–193.
[38] Manzari, V., Gismondi, A., Barillari, G., Morrone, S., Modesti, G., Albonici, L., De Marchis, L., Fazio, V., Gradilone, A., Zani, M., Frati, L. and Santoni, A. (1987) "HTLV-V: a new human retrovirus isolated in a TAC-negative T-cell lymphoma/leukemia", *Science* **238**, 1581–1583.
[39] Potter, M. (1992) "Pathogenetic mechanisms in B-cell non-Hodgkin's lymphoma in humans", *Cancer Res.* **52**(Suppl), 5522s–5528s.
[40] Newstead, C.G. (1998) "Assessment of risk of cancer after renal transplanatation", *Lancet* **351**, 610–611.
[41] Nordström, M., Näsman, Å., Linde, A., Schloss, L. and Hardell, L. (1999) "Elevated antibody levels to Epstein–Barr virus antigens in patients with hairy cell leukaemia compared to controls in relation to exposure to pesticides, organic solvents, animals and exhausts", *Oncol. Res.* **11**, 539–544.
[42] Nordström, M., Hardell, L., Näsman, Å., Wingfors, H., Hardell, K., Lindström, G. and Linde, A. (2000) "Concentrations of organochlorines related to levels of antibodies to Epstein–Barr virus antigens as risk factors for hairy cell leukemia", *Environ. Health Perspect.* **108**, 441–445.
[43] Lu, Y.C. and Wu, Y.C. (1985) "Clinical findings and immunological abnormalities in Yu-Cheng patients", *Environ. Health Perspect.* **59**, 17–29.
[44] McConnachie, P.R. and Zahalsky, A.C. (1992) "Immune alterations in humans exposed to the termiticide technical chlordane", *Arch. Environ. Health* **47**, 295–301.

UNITED STATES DISTRICT COURT

NORTHERN DISTRICT OF CALIFORNIA

IN RE: ROUNDUP PRODUCTS LIABILITY LITIGATION	MDL No. 2741 Case No. 16-md-02741-VC
This document relates to: ALL ACTIONS	

REBUTTAL EXPERT WITNESS REPORT

OF

BEATE RITZ, M.D., Ph.D.

Introduction

This rebuttal report will address: 1) the draft manuscript[s] of the unpublished Agricultural Health Study (AHS) dated February 6, 2013 (Exhibit 19A to the deposition of Dr. Aaron Earl Blair taken March 20, 2017) and March 15, 2013 (Exhibit 19B to the deposition of Dr. Aaron Earl Blair taken March 20, 2017); 2) epidemiology issues raised by Defendant's experts Dr. Lorelei A. Mucci, Dr. Jennifer S. Rider and Dr. William Fleming; 3) the North American Pooled Project ("NAPP") study.

The Draft Manuscripts of the Unpublished AHS

The draft manuscripts of the unpublished AHS provide analyses of 333 NHL cases within the AHS cohort (DeRoos 2005) that followed individuals from through December 2008 for cancer incidence. The draft manuscripts also purport to give new exposure data collected in the second phase interview of the AHS between 1998 and 2004, together with the original data collected at enrollment of the cohort between 1993 and 1997.

The main problem with these draft AHS manuscripts are the authors' attempts to impute and 'guestimate' exposure for glyphosate or glyphosate-based formulations ("GBFs", including Roundup®). The problems arise because there has been a dramatic increase in the use of and exposure to glyphosate or GBFs in the mid-1990s (Aspelin and Grube 2016; Grube et al 2016; Coupe and Capel 2015; Thelin and Stone 2016; Service. USDoANAS 2016; Benbrook 2015). The authors failed to address this major issue in their draft manuscripts of unpublished AHS data. While under some, limited circumstances it is an acceptable epidemiological approach to impute or 'guestimate' certain unavailable data, one must be extremely careful when imputing/guestimating a critical piece of data, such as exposure or outcome of interest. In the case of the draft AHS manuscripts, the guestimation was conducted to answer the question as to whether or not the cases and controls were even exposed to the products being studied. In the instance of the draft AHS manuscripts, the imputation/guestimation failed, in part, because the draft manuscripts could not accurately account for the major change in the use of GBFs, including Roundup®. The validity of the results of such an imputation/guestimation become extremely questionable because when applied, the study authors need to assume glyphosate/GBF use was based on historical use, and do

not apply the increased use for any person who did not report their pesticide use, i.e. the non-responders. Consequently, such imputation/guestimation is unable to fully contemplate major changes in the professional agricultural environment as seen with the use of glyphosate/GBFs. Further, this change was not captured in the original reporting by AHS participants and generates a unique problem for glyphosate/GBFs compared with all other pesticide exposure assessments performed in this prospective study. After registration in the U.S. in 1974, glyphosate/GBFs were mainly used to kill weeds before planting of crops or spraying for weed control in pastures and non-crop areas, with 6 - 8 million pounds applied by U.S. farmers and ranchers in 1987 [Grube 2016]. The dramatic change in glyphosate/GBF use began in 1996, the first year genetically engineered, glyphosate -tolerant crops were planted commercially in the U.S. Specifically, in 1996, Monsanto first introduced genetically engineered, glyphosate resistant soybeans (Roundup® Ready) to the commercial market, followed by cotton and canola in 1997, corn in 1998, and alfalfa and sugar beets in 2005. Prior to the introduction of genetically modified seeds, glyphosate/GBFs accounted for only 3.8% of the total volume of herbicide active ingredients applied in agriculture, while this changed to 180–185 million pounds by 2007 [EPA reports; Coupe 2015]. This substantial increase established glyphosate/GBFs as 53.5% of total agricultural herbicide use in 2009 according to USGS [Thelin and Stone 2016]; annual farm-sector glyphosate/GBF usage further increased to approximately 240 million pounds in 2014 [based on average annual crop use reported by the NASS; Service. USDoANAS 2016, Benbrook 2015. The original AHS enrollment (Dec 1993-Dec 1997) preceded this tremendous increase in agricultural use of glyphosate/GBFs. Thus, this increase in use was never captured for members of the AHS cohort who did not respond to follow-up interviews in phase 2 (1999-2003) or phase 3 (2005-2010) of the AHS, as set forth below.

Importantly, the second phase of the AHS was plagued by low response: i.e. it generated no more than a 64% response rate among AHS cohort members who were private applicators contacted in 1998-2004 (or a 36% non-response). This is an extremely low response rate when usage increased this much and this fast (furthermore, concerning future glyphosate/GBF analyses in AHS, only 46%, less than half, of all private applicators responded to the third phase 2005-2010 interviews). Thus, one-third

of all cohort subjects never reported their actual exposures or changes in exposures after enrolment interviews were conducted, even though use of glyphosate/GBFs started to change dramatically.

The AHS researchers knew that such a large non-response rate would raise questions about the validity of certain results of their study, so they were forced to come up with a method to address this problem. Otherwise, these studies would be questioned by peer reviewers and unlikely to be published. The AHS researchers attempted to address the loss of active participants with a method called 'imputation' to avoid having large amounts of missing exposure data –for those who did not respond – or generating selection bias (cohort studies may be affected by selection bias due to 'differential' loss to follow-up among the exposed or unexposed cases and controls) (Heltsche, et al. 2012). The method the authors used was a "data driven imputations of exposures"; or, in other words, a 'guestimation' of what exposures would have been in those who did not respond and report. This procedure assumes that it is sufficient to use the data in hand to predict/guestimate all future exposure in AHS participants who did not respond; i.e. that the past and current exposures and characteristics of the participants who responded to multiple interviews over time would accurately predict the use of those who did not respond. For glyphosate/GBFs with a use pattern change as dramatic as described above, it is a flawed approach to predict who would or would not start using Roundup® Ready crops after baseline, and likewise to predict the use of glyphosate/GBFs. This is because this imputation method assumes that those who did not respond had similar pesticide use and exposure pattern as those who did respond whether or not they developed NHL (this is called the 'missing at random assumption'). This assumption - if wrong - may cause enough exposure misclassification (undifferential with regard to disease status) for a large proportion of AHS participants to bias effect estimates towards the null of not finding any associations. An alternative to imputation for non-responders is to restrict the analyses to include only data from those cohort members who actually responded. However, this can cause strong selection bias if the response to the follow-up questionnaires depends on participant characteristics and health status. This is not an issue for assessing effects for exposures measured at enrollment on cancer when outcomes are being obtained through linkage with registries (i.e. cases are almost always found), but it is an issue for assessing effects of time varying

exposures especially when there are considerable changes in exposure that may affect future cancer occurrence. It has been stated in published AHS studies that response to follow-up interviews depended on education and age and on some farming practices including personal pesticide use and a number of health conditions (see for example Rinsky, et al. 2017). Methods have been developed to address selection bias and the most recent paper by Rinsky et al. 2017 for the AHS group addresses the need for bias correction in the AHS and shows how to implement such methods to assess and correct this bias in a quantitative manner. This paper concludes that as long as exposure and disease are not strongly associated with response during follow-up (i.e. to respond to interviews) resulting bias would be small. However, for bias to be assessed and bias correction to work, one needs accurate data for exposure as well as variables identified as predictors of response and disease status. Given that glyphosate/GBF exposure patterns changed dramatically after enrollment and that updated exposure information was only available for responders, this method does not work for glyphosate/GBF exposure in the AHS (in fact the authors state that "farming activities after enrollment may be strongly associated with response to later interviews"). Possibly severe selection bias in estimating these time varying glyphosate/GBF exposures cannot be avoided or corrected in the described way and will continue to affect future glyphosate/GBF exposure and NHL association studies in the AHS.

Another important issue relates to the outcome assessment, i.e. the diagnosis of NHL: how to address the influence of the recent ICD re-classification of NHL subtypes on the AHS results. The issue of disease classifications becomes apparent when we examine the Alavanja 2014 paper supplement that shows major changes by redistributing NHL according to subtypes and newly adding more than 100 cases of NHL cancers from multiple myeloma and chronic lymphocytic leukemia. Most importantly, these changes in outcome classification also affect the pesticide exposure distributions among NHL cases. For example, in the draft manuscript of the unpublished 2013 AHS study, 173 NHL cases were considered unexposed to DDT (in dose-response analyses) while only 152 NHL cases in the published 2014 manuscript are considered unexposed to DDT. But, DDT exposures were assessed with the same method and same data in both manuscripts; the change between the two papers was the disease classification used. Importantly, this resulted in increased risk estimates for

DDT and a statistically significant trend by lifetime years of exposure not seen in the draft manuscript of the unpublished 2013 AHS (according to the supplemental table of the published manuscript, a significant trend would not be seen when using the old ICD classification even though additional years of follow-up added cases (old ICD classification p-trend=0.32; new ICD classification p trend=0.02). This proves that the results presented in the draft manuscript of the unpublished AHS are not a good substitute for glyphosate/GBF exposures related effect estimates with additional follow-up. Furthermore, it contradicts the statement made by Dr. Mucci in her expert report that the draft manuscript of the unpublished AHS results from 2013 are good enough to be included in a meta-analysis; i.e. that: "One minor weakness is that the updated analysis on glyphosate and other herbicides has not been published to date, although the findings on insecticides, fungicides, and fumigants were published" and "concern [about including the results form an unpublished study] is minimized since the methodology is the same as those studies that have undergone peer review." (page 35, Mucci). Thus, the results and conclusions from the draft manuscript of the unpublished 2013 AHS cannot be considered fit for inclusion into a meta-analysis nor are they of the same quality as peer-reviewed and published manuscripts that are included in meta-analysis.

Other reasons for the draft manuscripts of the unpublished 2013 AHS results for NHL overall, or NHL subtypes with glyphosate/GBF exposures may also relate to the very high and almost ubiquitous exposure to glyphosate/GBFs in this cohort. Effects for ubiquitous exposures are difficult or even impossible to estimate since, in order to see effects, we rely on exposure contrasts (i.e. we need both exposed and unexposed subjects; or low and high exposures). In other words, when everyone smokes heavily, we cannot estimate the effect of smoking on lung cancer; or, if the exposure contrast is too small, it is impossible to estimate an incremental increase in risk for the exposure, *i.e.* we need enough of a difference in exposure to see a difference in effect.

Also, the high frequency of co-exposures in those listed as unexposed to glyphosate/GBFs might be yet another problem if these co-exposure chemicals indeed cause NHL. As the 2005 DeRoos paper shows, exposures to potentially carcinogenic pesticides 2,4 D, alachlor and atrazine were very high among both glyphosate/GBF exposed and unexposed AHS participants at baseline. If these chemicals indeed cause NHL, we would expect them to increase the baseline rate of NHL in the glyphosate/GBF

unexposed such that an incremental increase due to glyphosate/GBF exposure would require a much larger sample size to be estimable. This is because we are estimating relative increases in risk of cancer. Now, assume we are interested in estimating the risk of lung cancer from smoking and find in our population among non-smokers 4 lung cancers/100,000 and in smokers 20/100,000; we can use these rates to estimate a (20/4=) 5 fold risk increase for lung cancers due to smoking in this population. Now imagine that we examine smoking in an occupational cohort of miners and that radon exposure adds 10 extra cases of lung cancer per 100,000 miners i.e. no matter whether they smoke. Thus, we would see in non-smoking miners a rate of (10+4 =) 14/100,000 lung cancers (the reference group) to which we compare the rate in smokers of (10+20=) 30/100,000 and estimate a (30/14=) 2.14-fold increase in risk for smoking and lung cancer in miners, i.e. a relative risk much smaller than we estimated in non-miners (5 fold). Statistically, I need less power to be able to estimate a larger relative risk increase than a smaller one i.e. a 5-fold compared with a 2.14 fold risk increase.

Finally, as is the case for most farmer focused studies, the AHS has to address multiple pesticide exposure scenarios and decide whether it is appropriate to adjust for 'proxies' i.e. co-exposures that are not risk factors for the outcome but related to the exposure of interest. This generates the necessity to distinguish between true confounding co-exposures (pesticides that truly cause NHL and are also associated with glyphosate exposures) and co-exposures that solely act as 'proxy measures' for glyphosate/GBFs but do not cause NHL. For the latter, one should not adjust since this would lead to over-adjustment and introduce major bias. There is no analytical or statistical fix for this problem.

Differences Between the Draft Manuscripts of the Unpublished AHS Data and the Peer-Reviewed NAPP Study

There are other problems with the draft manuscripts of the unpublished AHS data which tend to be typical of a non-peer reviewed unpublished study and clearly show why we as both academics and epidemiologists do not normally rely upon such non-peer reviewed unpublished information. As an example, if one looks at page 25 of the February 6, 2013 draft manuscripts of the unpublished AHS, the authors note in

footnote two: "Numbers do not sum to totals (333 cases, 714,770 person-years) due to missing data," with similar comments about "missing data" on page 27. The missing data references continue in the draft manuscript dated March 15, 2013 – see e.g. pages 30 and 45. Furthermore, the comments of certain "unknown" authors are equally telling as to the problems with this draft manuscript of the unpublished AHS. See e.g. page 19 of the March 15, 2013 draft manuscript: "Although this is a large prospective study, there are limitations...need to add a paragraph of exposure assessment. Discuss the information on our exposure scale in relation to the monitoring work. Discuss the likely magnitude of misclassification and its likely impact on the estimates of RR."

For the above-stated reasons, it is not appropriate from an epidemiologically perspective to rely on the data contained in the two draft manuscripts of the unpublished AHS which I have reviewed, or on its conclusions. Furthermore, as I was an external advisor for the AHS for more than a decade, I certainly would have pointed out the above-mentioned significant problems if this data had gotten closer to publication. My reliance on the NAPP report is appropriate because the data contained in the NAPP study has been presented at meetings, both in poster and published abstract form, and thus HAS been peer-reviewed, making reliance on the NAPP appropriate.

Statistical Power and Meta or Pooled Analyses

I would like to briefly comment on the issue of statistical power, since both defense experts Drs. Rider and Mucci misrepresented a major issue when discussing this point or the epidemiology studies in their reports. While the reports are correct in pointing out that statistical power of a study does not only depend on the number of cases and controls but – in addition – on exposure prevalence, they failed to acknowledge or describe a basic fact i.e. that statistical power does not increase linearly with exposure prevalence. Rather the highest power is generally achieved at a 50:50 split of exposed and unexposed – this is why most clinical treatment trials employ this type of treatment allocation. In other words, we cannot estimate effects at the extremes of the exposure distribution i.e. with everyone either exposed or unexposed we cannot study an exposure. As an example: we cannot estimate the effect of smoking on lung cancer in a population in which everyone smokes heavily – in such a population one might have to conclude that lung cancer is a genetic disorder i.e. the only difference

between cases and controls is their genetic/biologic susceptibility to smoke. Thus, the ability to estimate effects in a population with either very low or very high exposure is restricted in terms of statistical power; i.e. it requires more and more subjects to be enrolled in such studies to estimate an effect for the exposure. The latter is the case in the AHS study, rather than becoming the 'statistically most powerful study' nearly universal exposure to glyphosate/GBFs will make it impossible to estimate some of its effects.

In terms of meta-analysis and pooled analysis, Dr. Rider, in her expert report, stated that "Given the potential threats to internal validity in the case-control studies, a meta-analysis that attempts to summarize all of the published data could be misleading. In addition, the published meta-analyses of glyphosate and NHL do not include the unpublished data from the AHS or the findings from the NAPP, which plaintiffs' experts agree should be incorporated. These studies would effectively reduce the summary effect estimate in the meta-analyses and render that point estimate no longer statistically significant [this refers to the Delzell and Chang meta-analysis]." (page 4, Rider). First, the internal validity issues Dr. Rider attributes to population-based case control studies are questionable, because: a) recall bias has not been shown to affect pesticide studies, and is unlikely to affect one specific agent only in studies that assess multiple pesticides; b) similarly, the issue of confounding control as raised by both defense experts is clearly out of step with the current thinking in epidemiology. This methodology, used by both Drs. Rider and Mucci, is not the methodology that is currently accepted by epidemiologists, especially those who study and analyze complex exposures. For example, multiple exposures have to be cautiously addressed in terms of what is or isn't a risk factor for the outcome or should be considered a confounder. We have to consider prior knowledge, and just claiming that something is a confounder is not enough. Rather, the question would be how strong a confounder we would need to change the results we observe and in what direction this change would be [not all confounding changes the estimates away from the null]; and what variables would qualify as confounders (most of the adjustments for a number of moderately strong risk factors including previous cancer history - in McDuffie et al. – did not change the effect estimates for the pesticides by much [for example: for dicamba basic adjustment for age and province resulted in an OR of 1.92 (1.39–2.66) while additional adjustment for all

other risk factor for NHL including history of cancer resulted in an OR of 1.88 (1.32–2.68); for Mecoprop basic adjustment for age and province resulted in an OR of 2.23 (1.38–3.07) while additional adjustment for all risk factor for NHL including history of cancer resulted in an OR of 2.33 (1.58–3.44) – i.e. minimal changes in both directions towards and away from the null); c) selection bias is not a concern in properly conducted population-based studies. Furthermore, this issue has been addressed adequately in the Canadian studies. Even more importantly, the AHS has the potential for severe selection and exposure misclassification biases due to the necessity of active follow-up for exposure assessment and time varying exposures, an issue which has not been addressed in the reports of Dr. Rider or Dr. Mucci. Dr. Rider contradicts herself and Dr. Mucci when stating that the data summary (meta-analysis) should include the unpublished studies (AHS and NAPP) since the AHS is a cohort study with a methodology in design and analysis very different from the case control studies and hence should be considered on its own merits; while the NAPP study summarizes previous data that, if included in the meta-analysis without excluding the primary studies; such an estimate would "double-up" on those studies. Importantly, the statement that "Any limitations of both the study design and statistical analysis of included studies carry forward through the results of the meta-analysis" (page 18, Rider) is only partially correct i.e. this statement assumes that each study has exactly the same bias and moreover that all are biasing the results in the exact same direction - which is highly unlikely in practice.

Fleming Report

As the President Elect of the International Society for Environmental Epidemiology, a sub-discipline of Epidemiology that specifically concentrates among its members those with expertise in examining a wide range of spatial and temporal patterns in exposures and disease, I object strongly to the naïve use of both temporal cancer rates and spatial cancer patterns in Dr. Fleming's report in order to draw conclusions about NHL causes specifically whether or not glyphosate/GBF exposures cause NHL. Our discipline uses maps and graphs extensive because they are very important tools for the purpose of visualizing data i.e. to show general patterns of disease or exposure rates over time and/or space. However, the first thing I teach my

students in environmental epidemiology is that using these tools to claim that a very specific exposure (pesticide) does or does not cause a chronic disease is highly unscientific and unnecessarily invalidates the good use of these tools. For example, the pretty graphs and maps shown by Dr. Fleming cannot tell us anything about the influence of the AIDS epidemic over the years on NHL rates or about other time varying influences. Specifically, if glyphosate/GBFs are not the only agents capable of causing NHL – which defense experts seems to agree to since they are worried about confounding risk factors - and we accept that for example DDT and lindane – pesticides widely used in the 1950 to 70th – may also cause NHL, how could any of these graphs/ maps depict the influence of complex waxing and waning causal exposures over time, some of them increasing and some decreasing and therefore influencing rates in different directions? The spatial map by Fleming includes all races and both sexes, thus, it seems that he assumes that NHL rates in men and women or immigrant Hispanic laborers in central California can be easily compared with all San Francisco inhabitants including white males and that factors such the AIDS epidemic can be ignored; i.e. that we can simply compare age adjusted rates from San Francisco populations to those in central California populations and deduce whether or not glyphosate/GBF alone is the single agent causing NHL. Again, this is not only scientifically untenable but simply wrong.

Conclusion

I hold the above opinions to a reasonable degree of scientific certainty. Furthermore, as previously stated in my earlier expert report, I hold the opinion, to a reasonable degree of scientific certainty that glyphosate and GBFs including Roundup, cause non-Hodgkin's lymphoma. I reserve my right to supplement or amend this report as additional materials become available.

Beate Ritz, M.D., Ph.D.

Date: August 18, 2017

References

Alavanja MC, Hofmann JN, Lynch CF, Hines CJ, Barry KH, Barker J, Buckman DW, Thomas K, Sandler DP, Hoppin JA, Koutros S, Andreotti G, Lubin JH, Blair A, Beane Freeman LE. Non-hodgkin lymphoma risk and insecticide, fungicide and fumigant use in the agricultural health study. PLoS One. 2014 Oct 22;9(10):e109332. doi: 10.1371/journal.pone.0109332. eCollection 2014.

Aspelin A, Grube AH. Pesticide Industry Sales and Usage: 1996 and 1997 Market Estimates, Office of Pesticide Programs, U.S. Environmental Protection Agency, Washington, D.C.; 1999. http://1.usa.gov/20qXcOb. Accessed 03 February 2016.

Benbrook C. Trends in the use of glyphosate herbicide in the U.S. and globally. Environmental Sciences Europe. 2015;28(3). http://dx.doi.org/10. 1186/s12302-016-0070-0. Accessed 03 February 2016

Coupe RH, Capel PD: Trends in pesticide use on soybean, corn and cotton since the introduction of major genetically modified crops in the United States. Pest Manag Sci 2015.

De Roos AJ, Blair A, Rusiecki JA, Hoppin JA, Svec M, Dosemeci M, Sandler DP, Alavanja MC. Cancer incidence among glyphosate-exposed pesticide applicators in the Agricultural Health Study.Environ Health Perspect. 2005 Jan;113(1):49-54.

Grube A DD, Kiely T, Wu L. Pesticides Industry Sales and Usage, 2006 and 2007 Market Estimates, United States Environmental Protection Agency, EPA 733-R-11-001, 34 p. 2011. http://1.usa.gov/1VN2QDo. Accessed 03 February 2016.

Heltshe SL, Lubin JH, Koutros S, Coble JB, Ji BT, Alavanja MC, Blair A, Sandler DP, Hines CJ, Thomas KW, Barker J, Andreotti G, Hoppin JA, Beane Freeman LE. Using multiple imputation to assign pesticide use for non-responders in the follow-up questionnaire in the Agricultural Health Study. J Expo Sci Environ Epidemiol. 2012 Jul;22(4):409-16. doi: 10.1038/jes.2012.31. Epub 2012 May 9.

Myers JP, Antoniou MN, Blumberg B, Carroll L, Colborn T, Everett LG, Hansen M, Landrigan PJ, Lanphear BP, Mesnage R, Vandenberg LN, vom Saal FS, Welshons WY, Benbrook CM. Concerns over use of glyphosate-based herbicides and risks associated with exposures: a consensus statement. Environmental Health (2016) 15:19

Rinsky JL, Richardson DB, Wing S, Beard JD, Alavanja M, Beane Freeman LE, Chen H, Henneberger PK, Kamel F, Sandler DP, Hoppin JA. Assessing the Potential for Bias From Nonresponse to a Study Follow-up Interview: An Example From the Agricultural Health Study.
Am J Epidemiol. 2017 May 9. doi: 10.1093/aje/kwx098. [Epub ahead of print]

Service. USDoANAS: Agricultural Chemical Usage - Field Crops and Potatoes. https://usda.mannlib.cornell.edu/MannUsda/viewDocumentInfo.do?documentID=1001. Accessed 03 February 2016.(multiple years).

Thelin GP, Stone WW. Estimation of annual agricultural pesticide use for counties of the conterminous United States, 1992–2009: U.S. Geological Survey Scientific Investigations Report 2013–5009, 54 p. http://on.doi.gov/ 1TEeEJD. Accessed 03 February 2016.

Defendant's Expert Report of Dr. William Fleming

Defendant's Expert Report Dr. Lorelei A. Mucci,

Defendant's Expert Report of Dr. Jennifer S. Rider

Exhibits 19A and 19B to Deposition of Dr. Aaron Earl Blair, taken March 20, 2017.

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Pesticides and Other Agricultural Risk Factors for Non-Hodgkin's Lympho among Men in Iowa and Minnesota

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ABSTRACT

Data from an in-person interview study of 622 white men with newly diagnosed non-Hodgkin's lymphoma and 1245 population-based controls in Iowa and Minnesota were used to measure the risk associated with farming occupation and specific agricultural exposures. Men who ever farmed were at slightly elevated risk of non-Hodgkin's lymphoma (odds ratio = 1.2, 95% confidence interval = 1.0–1.5) that was not linked to specific crops or particular animals. Elevated risks were found, with odds ratio generally 1.5-fold or greater, for personal handling, mixing, or application of several pesticide groups and for individual insecticides, including carbaryl, chlordane, dichlorodiphenyltrichloroethane, diazinon, dichlorvos, lindane, malathion, nicotine, and toxaphene. Associations were generally stronger for first use prior to 1965 than more recently, and when protective clothing or equipment was not used. Small risks were associated with the use of the phenoxyacetic acid herbicide 2,4-dichlorophenoxyacetic acid, but the risks did not increase with latency or failure to use protective equipment. Exposure to numerous pesticides poses problems of interpreting risk associated with a particular chemical, and multiple comparisons increase the chances of false-positive findings. In contrast, nondifferential exposure misclassification due to inaccurate recall can bias risk estimates toward the null and mask positive associations. In the face of these methodological and statistical issues, the consistency of several findings, both within this study and with observations of others, suggests an important role for several insecticides in the etiology of non-Hodgkin's lymphoma among farmers.

INTRODUCTION

While farmers generally have low rates of morbidity and mortality, they appear to be at excess risk of selected cancers, particularly some of the hematopoietic tumors (1). Some studies suggest that the elevated risk of NHL[2] and leukemia among farmers may be associated with exposure to pesticides and other agricultural chemicals (2). To further evaluate these associations, we conducted parallel population-based case-control interview studies of men newly diagnosed with non-Hodgkin's lymphoma and leukemia in the states of Minnesota and Iowa. Findings for leukemia are reported elsewhere (3).

METHODS

Case Selection. All newly diagnosed cases of non-Hodgkin's lymphoma among men aged 30 or older were ascertained from Iowa State Health Registry records and a special surveillance of Minnesota hospital and pathology laboratory records. In Iowa, the diagnosis period for eligibility was March 1981 to October 1983, and in Minnesota, October 1980 to September 1982. In Iowa, all cases who resided in the state were eligible. In Minnesota, eligibility was restricted to cases who resided in places other than the cities of Minneapolis, St. Paul, Duluth, or Rochester at the time of diagnosis.

Pathology Review. A review panel of 4 experienced regional pathologists confirmed diagnoses and classified NHL cases as to morphological type using the Working Formulation for classification of NHL (4). NHL subtype was designated when at least 3 panelists agreed on a specific diagnosis, either at the initial review or a supplementary review conducted for more difficult cases. The case was considered "unclassifiable" if the pathology panel could not come to consensus on NHL subtype, or if the tissue sample was not adequate to differentiate among subtypes. The NHL subtypes were collapsed into categories as follows: follicular (combining small cleaved cell, mixed cell, and large cell follicular cases); diffuse (combining small cleaved cell, mixed cell, and large cell diffuse cases); small lymphocytic; and "other NHL" (combining large cell immunoblastic, lymphoblastic, small noncleaved, other, and unclassified NHL cases). Additional details regarding histopathology review procedures are presented elsewhere (5, 6).

Control Selection. A population-based control group of white men without a hematopoietic or lymphatic cancer was randomly selected and frequency-matched to NHL and leukemia cases by 5-year age group, vital status at time of interview, and state of residence. The sources of controls were: (*a*) random digit dialing for living subjects under age 65 at diagnosis, using the Waksberg method (7, 8) (data from the 1980 United States Census report that 96 and 97% of Iowa and Minnesota households, respectively, had telephones); (*b*) a 1% random listing from Medicare files provided by the Health Care Financing Administration for living subjects aged 65 and older [United States citizens 65 years of age and older are eligible for Medicare insurance and over 98% have been estimated to be in the roster (9)]; and (*c*) state death certificate files for deceased subjects.

Data Collection. Interviews were conducted during the period of August 1981 to May 1984. A trained interviewer administered an in-person structured interview, taking 45–60 min, to the subject, or the spouse, other close relative, or friend of deceased or incompetent subjects. We asked about sociodemographic characteristics, medical history, smoking habit, occupational history, residential history, familial history of cancer, and other known and suspected risk factors. In addition, we requested a detailed farming and pesticide use history of all subjects who had worked on a farm at least 6 months since age 18. For each farm that the respondent had worked, we recorded the years of farming activity, the total acreage, the number and types of livestock, and the crops grown, with average acreage for each and the number of years they had been grown on that farm. We also asked for a detailed history of pesticide use. Pesticide lists for the questionnaire were developed with the assistance of local agricultural experts. We named 23 specific insecticides used on animals, 34 insecticides applied to crops, 38 herbicides, and 16 fungicides. For each pesticide, we asked if it had ever been used; the first and last year of use; the method of application (aerial, surface application, incorporated into soil, other); whether the respondent had personally applied, mixed, or handled it; and the use of protective equipment.

Response Rates. Seven hundred eighty presumptive NHL cases were ascertained, and 694 (89%) were interviewed. After pathology review of interviewed cases, 622 were confirmed as NHL (438 living cases with direct interviews, 184 deceased or incompetent cases with proxy interviews). Among the 72 cases that could not be confirmed, 26 were

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[2] The abbreviations used are: NHL, non-Hodgkin's lymphoma; DDT, dichlorodiphenyltrichloroethane; CLL, chronic lymphocytic leukemia; OR, odds ratio; CI, 95% confidence interval; 2,4-D, 2,4-dichlorophenoxyacetic acid; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid.

Table 1 *Characteristics of cases and controls from a study of non-Hodgkin's lymphoma in Iowa and Minnesota*[a]

	Cases		Controls	
	No.	(%)	No.	(%)
Type of NHL				
Follicular	195	(31)		
Diffuse	198	(32)		
Small lymphocytic	85	(14)		
Other	144	(23)		
Type of interview				
Direct	438	(70)	820	(66)
Surrogate	184	(30)	425	(34)
State of residence				
Iowa	293	(47)	603	(48)
Minnesota	329	(53)	642	(52)
Age				
<45	73	(12)	134	(11)
45–64	230	(37)	430	(35)
65+	319	(51)	681	(55)
Hair dye use (ever)?				
No	574	(92)	1194	(96)
Yes	48	(8)	51	(4)
Lymphopoietic cancer diagnosed in any first degree relative?				
No	557	(90)	1154	(93)
Yes	54	(9)	66	(5)
High risk occupation (ever)? [b]				
No	524	(84)	1174	(94)
Yes	98	(16)	71	(6)
Used high risk materials at least monthly for a year or more? [c]				
No	369	(59)	840	(67)
Yes	253	(41)	405	(33)
Cigarette smoking habit				
Never smoked	186	(30)	418	(34)
Past smoker	243	(40)	486	(39)
Current smoker	182	(30)	333	(27)

[a] Cases and controls numbered 622 and 1245, respectively. The number of respondents with missing values for selected characteristics is not explicitly listed.
[b] Persons ever employed at an occupation yielding an odds ratio of 1.5 or greater in Mantel-Haenzsel analyses adjusted for age (2 strata) and state of residence.
[c] Persons using one or more materials yielding an odds ratio of 1.5 or greater, from a list of 43 items that included paints, benzene, other organic solvents, resins, and others.

diagnosed as leukemia, and 46 with other conditions. Pathology review was not conducted on material of the persons who were not interviewed. Among random digit dialing controls, the household screening response rate was 87.5%, yielding 474 eligible persons, of whom 415 (87.6%) agreed to participate, for a net response rate of 76.7%. Among the 2 other control groups, 79% of the eligible controls selected from the Health Care Financing Administration rolls participated, and 77% of the eligible proxies for deceased controls provided complete interviews.

Statistical Analysis. The association between a variety of farm-related factors and risk of NHL was measured by the maximum likelihood estimate of the OR. ORs were adjusted for several known or suspected NHL risk factors, using unconditional logistic regression analysis with case-control status as the response variable (10, 11). OR for farmers who raised specific crops or animals, or were exposed to individual pesticides and families of pesticides, were calculated for all NHL and the NHL subtypes, comparing exposed persons to nonfarmers, except as noted. ORs for the histological subtypes of NHL were calculated using software for polychotomous logistic models developed by the Epidemiology and Biostatistics Program of the National Cancer Institute. Logistic models included the following potential confounding variables: vital status (alive, dead); state (Iowa, Minnesota); age (<45, 45–64, 65+); cigarette smoking habit (never, past, current); lymphopoietic cancer in a parent, sibling, or child (yes, no); nonfarming job related to NHL in this study (with OR of 1.5+); exposure to hair dyes (yes, no); and exposure to one or more other substances associated with NHL in this study [with OR of 1.5+, as calculated by standard methods with adjustment for age and state of residence (12)]. Tests for trend in the logistic analysis were obtained by categorizing the exposure variable and treating the scored variable as a continuous variable.

RESULTS

Study Population. Table 1 shows the distribution of the 622 cases and 1245 controls by type of NHL, type of interview, state of residence, age, hair dye use, having had a first degree relative with lymphopoietic cancer, employment in a high risk occupation (*a priori*), exposure to high risk materials (*a posteriori*), and cigarette smoking habit. Among the 622 respondent cases, the distribution of histological types was: 195 follicular (31.4%), 198 diffuse (31.8%), 85 small lymphocytic cell (13.7%), and 144 other and undefined lymphomas (23.2%).

We found elevated relative risks associated with certain occupational exposures and job classifications, hair dye use, as well as a history of familial cancer. These factors were entered as potential confounders in logistic regression models, as were variables for age, state of residence, and vital status of the study subject.

Farming. There was a small, but marginally significant increase in risk for all NHL (OR = 1.2, 95%, CI = 1.0–1.5) associated with ever living or working on a farm as an adult (Table 2). Fifty-seven % of the cases and 56% of controls reported some farm activity. When analyzed by NHL subtype, there was a small excess risk for each, but none was significant. Among subtypes, the highest observed risk for farming was found for small cell lymphocytic lymphoma (OR = 1.4, CI = 0.9–2.3).

No statistically significant trend by first and last year of farming activity, duration, or average yearly number of acres

Table 2 *OR and CI for non-Hodgkin's lymphoma according to ever having been a farmer, timing of farming occupation, and average size of farm (in acres)*[a]

	CO	CA	OR	CI
Nonfarmer	547	266	1.0	
Farmer	698	356	1.2	1.0, 1.5
First year farmed				
<1925	218	105	1.3	0.9, 1.8
1925–1934	200	92	1.1	0.8, 1.5
1935–1944	143	64	0.9	0.7, 1.3
1945+	136	94	1.4	1.0, 1.9
Missing	1	1		
Farmed until				
<1950	190	77	0.9	0.6, 1.3
1950–1969	190	113	1.4	1.1, 1.9
1970+	314	165	1.2	0.9, 1.6
Missing	4	1		
No. of years farmed				
<10	163	89	1.2	0.9, 1.6
10–39	289	153	1.2	0.9, 1.6
40+	239	112	1.2	0.9, 1.6
Missing	7	2		
Average no. of acres				
<120	129	62	1.1	0.8, 1.6
120–199	217	115	1.3	1.0, 1.7
200–319	183	96	1.2	0.9, 1.7
320+	140	72	1.1	0.8, 1.6
Missing	29	11		

[a] All OR relative to risk for subjects who were never farmers (266 cases, 547 controls). All ORs adjusted for vital status, age, state, cigarette smoking, family history of lymphopoietic cancer, high-risk occupations, and high-risk exposures in a logistic analysis.

during farming years was observed for all NHL or any subtype (Table 2). However, we observed slightly higher risks among men who farmed after 1949 than those who stopped before 1950. Men who operated medium-size farms (120–199 acres or 200–319 acres) were at slightly higher risk for all NHL and for most NHL subtypes than men farming smaller or larger establishments.

There was no notable association of risk for all NHL associated with the cultivation of any major crop, nor with the husbandry of the major types of livestock (data not shown). The patterns of OR for the lymphoma histological subtypes, as related to particular crops and livestock, followed the overall pattern for farming in general, with elevated (mostly nonsignificant) OR for small lymphocytic lymphoma associated with corn (OR = 1.4, CI = 0.9–2.4; 52 cases), wheat (OR = 1.5, CI = 0.8–2.9; 21 cases), flax (OR = 2.3, CI = 1.0–5.0; 15 cases), barley (OR = 1.5, CI = 0.7–3.1; 15 cases), and hay (OR = 1.4, CI = 0.8–2.4; 31 cases). Associations of other NHL subtypes with specific crops and livestock were weaker, as were associations of small lymphocytic lymphoma with specific types of livestock.

Among the 356 cases and 698 controls who had lived and worked on one or more farms as an adult, 323 cases (90.7%) and 636 controls (91.4%) reported that they were farm operators on at least one farm. Operators usually plan and execute pest control activities, and are more likely than hired hands to have direct knowledge of the chemicals used.

Pesticide Use (Ever). Among farmers, 300 cases (84%) and 603 controls (86%) reported use of at least one pesticide (for all NHL, OR = 1.2, CI = 0.9–1.4, relative to nonfarmers). The OR for use of one or more insecticides on livestock was 1.1 (CI = 0.9–1.4); for crop insecticide use, 1.2 (CI = 0.9–1.5); for herbicide use, 1.3 (CI = 1.0–1.6); and for fungicide use, 1.3 (CI = 0.8–2.0).

Pesticide Families. Table 3 shows the numbers of cases and controls, OR, and CI for use of one or more members of the listed chemical families of pesticides, by broad grouping of livestock insecticides, crop insecticides, and herbicides. Classification of pesticides into chemical families was done by us. All OR shown are relative to nonfarmers, numbering 266 cases and 547 controls. Significant risk elevations were found for several livestock insecticide families: chlorinated hydrocarbons (OR = 1.3), in particular the cyclodienes (OR = 1.7); natural products (OR = 1.5); and organophosphates (OR = 1.5), in particular the halogenated aromatic organophosphates (OR = 2.0). Among insecticides used on crops, the chlorinated hydrocarbon family showed significant elevation in risk (OR = 1.4). Although based on small numbers, use of nonhalogenated organophosphates on crops was associated with a nonsignificant OR of 3.1. Use of insecticides on livestock or crops resulted in a significant increased risk of NHL associated with chlorinated hydrocarbons (OR = 1.3) and organophosphates (OR = 1.5). No single family of herbicides was significantly associated with overall NHL risk.

The use, handling, or application of pesticides in selected chemical families was associated with elevated risk for several of the NHL morphological subtypes. Significantly elevated OR were found for diffuse NHL and: organophosphates used on crops (OR = 2.3, CI = 1.4–3.8; 26 cases, 101 controls); nonhalogenated aliphatic organophosphates for crops (OR = 2.2, CI = 1.3–3.8; 24 cases, 95 controls); cyclodiene chlorinated hydrocarbons used on livestock (OR = 2.2, CI = 1.1–4.5; 11 cases, 42 controls); and triazine herbicides (OR = 1.6, CI = 1.0–2.6; 25 cases, 133 controls). Small lymphocytic NHL was significantly associated with natural product insecticides used for livestock application (OR = 2.4, CI = 1.1–5.2; 10 cases, 70 controls) and halogenated aromatic organophosphates for livestock (OR = 5.2, CI = 1.9–14.3; 6 cases, 23 controls). Other and unclassified forms of NHL were significantly linked to the chlorinated hydrocarbon insecticide family used for crops (OR = 1.8, CI = 1.1–3.0; 26 cases, 157 controls); the cyclodienes (OR = 2.1, CI = 1.0–4.7; 15 cases, 111 controls) for crops; and halogenated aliphatic organophosphates used on livestock (OR = 2.3, CI = 1.0–5.3; 8 cases, 41 controls). No significant associations with use, handling, or application of pesticide families were found for follicular NHL.

Table 3 *OR[a] and CI for the use of pesticide groups in which at least one pesticide was handled by the respondent[b]*

	Cases	Controls	OR	CI
Insecticides used on livestock				
Carbamates	6	15	0.8	0.3, 2.2
Chlorinated hydrocarbons	112	198	1.3	1.0, 1.7
Cyclodienes	34	42	1.7	1.0, 2.8
Natural products	46	70	1.5	1.0, 2.2
Organophosphates	68	101	1.5	1.0, 2.1
Halogenated aliphatics	20	41	1.2	0.7, 2.0
Nonhalogenated aliphatics	43	67	1.3	0.9, 2.1
Halogenated aromatics	21	23	2.0	1.1, 3.7
Nonhalogenated aromatics	12	16	1.7	0.8, 3.6
Insecticides used on crops				
Carbamates	41	80	1.2	0.8, 1.8
Chlorinated hydrocarbons	96	157	1.4	1.0, 1.9
Cyclodienes	57	111	1.2	0.8, 1.7
Arsenicals	43	75	1.3	0.8, 2.0
Organophosphates	60	101	1.3	0.9, 1.9
Nonhalogenated aliphatics	56	95	1.3	0.9, 1.9
Nonhalogenated aromatics	7	4	3.1	0.9, 11.0
Insecticides used on crops and/or livestock				
Carbamates	43	85	1.1	0.8, 1.7
Chlorinated hydrocarbons	150	262	1.3	1.0, 1.7
Cyclodienes	70	124	1.3	0.9, 1.8
Organophosphates	96	144	1.5	1.1, 2.0
Halogenated aliphatics	21	41	1.2	0.7, 2.1
Nonhalogenated aliphatics	78	119	1.4	1.0, 2.0
Nonhalogenated aromatics	17	20	1.8	0.9, 1.8
Herbicides				
Amides	59	114	1.2	0.8, 1.7
Benzoic acids	53	98	1.3	0.9, 1.9
Carbamates	24	50	1.1	0.7, 1.9
Dinitroaniline	46	88	1.2	0.8, 1.8
Heterocyclics	20	49	0.9	0.5, 1.6
Phenoxyacetic acids	118	231	1.2	0.9, 1.6
Triazines	64	133	1.1	0.8, 1.6
Ureas	5	18	0.6	0.2, 1.6

[a] OR relative to nonfarmers, numbering 266 cases and 547 controls. All ORs adjusted for vital status, age, state, cigarette smoking status, family history of lymphopoietic cancer, high-risk occupations, and high-risk exposures in a logistic analysis.
[b] Individual pesticides were categorized into chemical families by the authors.

Selected Pesticides. Tables 4–6 show the numbers of cases and controls, with OR and CI for all NHL, from analyses of farmers who ever personally handled, mixed, or applied specific pesticides, and for farmers who first handled them prior to 1965 (1965 was chosen because it was 15–18 years prior to diagnosis, a reasonable minimal period for latency). Among livestock insecticides (Table 4), there were significantly elevated risks for *ever* handled, mixed, or applied for chlordane and lindane. Most other livestock insecticides had OR greater than 1.0. In general, first use prior to 1965 was associated with higher risk than ever use, and was significant for early reported use of chlordane, lindane, malathion, and nicotine. Among subjects who *ever* personally handled, mixed, or applied specific

Table 4 *Animal insecticides: ORs and CIs for ever having handled specific animal insecticides, and handled prior to 1965*

Insecticide	Ever handled				Handled prior to 1965			
	No. of cases	No. of controls	OR	CI	No. of cases	No. of controls	OR	CI
Chlordane	31	38	1.7	1.0, 2.9	22	22	2.2	1.2, 4.2
Coumaphos	13	18	1.6	0.8, 3.5	3	5	1.5	0.3, 6.3
DDT	79	149	1.2	0.9, 1.7	68	123	1.3	0.9, 1.8
Dichlorvos	20	38	1.2	0.7, 2.2	12	17	1.8	0.8, 3.9
Famphur	10	14	1.7	0.7, 4.0	1	1	2.4	0.1, 39
Lindane	55	90	1.4	1.0, 2.1	40	55	1.7	1.1, 2.7
Malathion	43	67	1.3	0.9, 2.1	25	30	1.8	1.0, 3.3
Methoxychlor	9	16	1.2	0.5, 2.7				
Nicotine	31	47	1.5	0.9, 2.5	28	36	1.8	1.0, 3.0
Rotenone	12	23	1.0	0.5, 2.2				
Toxaphene	8	19	0.8	0.3, 2.0				
Flyspray (NOS)	185	394	1.1	0.9, 1.4	173	368	1.1	0.9, 1.4

[a] OR relative to nonfarmers, numbering 266 cases and 547 controls. All ORs adjusted for vital status, age, state, cigarette smoking status, family history of lymphopoietic cancer, high-risk occupations, and high-risk exposures in a logistic analysis.

Table 5 *Crop insecticides: ORs and CIs for ever having handled specific insecticides, and handled prior to 1965*[a]

Insecticide	Ever handled				Handled prior to 1965			
	No. of cases	No. of controls	OR	CI	No. of cases	No. of controls	OR	CI
Aldrin	47	97	1.1	0.7, 1.7	34	59	1.3	0.8, 2.1
Carbofuran	29	65	1.0	0.6, 1.7	28	63	1.0	0.6, 1.7
Carbaryl	21	26	1.7	0.9, 3.1	7	4	3.8	1.1, 13.6
Chlordane	21	26	1.7	0.9, 3.2	12	16	1.6	0.7, 3.6
Copper acetoarsenate	36	63	1.3	0.8, 2.0	30	54	1.2	0.7, 2.0
DDT	57	75	1.7	1.2, 2.6	45	57	1.8	1.1, 2.7
Diazinon	27	39	1.5	0.9, 2.5	14	12	2.6	1.2, 5.9
Dieldrin	17	26	1.4	0.7, 2.8	10	13	1.9	0.8, 4.4
Fonofos[b]	15	30	1.1	0.6, 2.1				
Heptachlor	25	43	1.3	0.7, 2.2	14	25	1.3	0.6, 2.6
Lindane	21	23	2.0	1.0, 3.7	14	15	2.2	1.0, 4.7
Malathion	21	30	1.5	0.8, 2.7	11	9	2.9	1.1, 7.4
Phorate	21	48	1.0	0.6, 1.7	9	12	1.8	0.7, 4.5
Turbufos[b]	15	36	0.9	0.5, 1.7				
Toxaphene	10	13	1.5	0.6, 3.5	6	5	2.4	0.7, 8.2

[a] OR relative to nonfarmers, numbering 266 cases and 547 controls. All ORs adjusted for vital status, age, state, cigarette smoking status, family history of lymphopoietic cancer, high-risk occupations, and high-risk exposures in a logistic analysis.
[b] No reported use of fonofos or turbufos prior to 1965.

Table 6 *Herbicides: OR and CI for ever having handled specific herbicides, and handled prior to 1965*[a]

Herbicide	Ever handled				Handled prior to 1965			
	No. of cases	No. of controls	OR	CI	No. of cases	No. of controls	OR	CI
Alachlor	57	109	1.2	0.8, 1.7				
Atrazine	59	108	1.2	0.9, 1.8	19	32	1.3	0.7, 2.5
Bentazon	18	45	0.9	0.5, 1.6				
Butylate	22	44	1.2	0.7, 2.1	1	6	0.5	0.1, 4.3
Chloramben	39	70	1.3	0.8, 2.0	16	19	2.0	1.0, 4.0
Cyanazine	27	64	0.9	0.6, 1.5				
2,4-D	115	227	1.2	0.9, 1.6	86	153	1.3	0.9, 1.8
Dicamba	28	57	1.2	0.7, 2.0	7	7	2.8	0.96, 8.1
Glyphosate	26	49	1.1	0.7, 1.9				
Metribuzen	12	38	0.7	0.4, 1.4				
Popachlor	13	25	1.2	0.6, 2.5				
2,4,5-T	25	48	1.2	0.7, 1.9	13	18	1.7	0.8, 3.6
Trifluralin	45	87	1.2	0.8, 1.8	14	23	1.5	0.8, 3.1

[a] OR relative to nonfarmers, numbering 266 cases and 547 controls. All ORs adjusted for vital status, age, state, cigarette smoking status, family history of lymphopoietic cancer, high-risk occupations, and high-risk exposures in a logistic analysis.

insecticides for application on crops (Table 5), significant risk elevations were observed for DDT and lindane; and for use prior to 1965, carbaryl, DDT, diazinon, lindane, and malathion. We also calculated the OR for pre-1965 personal handling, mixing, or application of specific insecticides that could have been used on either animals or crops. Elevated risk was found for carbaryl (OR = 2.8, CI = 1.0–7.7; 9 cases), chlordane (OR = 1.8, CI = 1.1–3.1; 30 cases); DDT (OR = 1.4, CI = 1.0–1.8; 93 cases), dieldrin (OR = 2.2, CI = 1.0–4.9; 13 cases), lindane (OR = 1.7, CI = 1.1–2.7; 47 cases), and malathion (OR = 1.8, CI = 1.1–3.1; 31 cases). No significant risk elevations were observed for ever handling, mixing, or applying specific herbicides (Table 6). Among the herbicides marketed prior to 1965, use before 1965 of chloramben and dicamba was significantly associated with total NHL. The risk for *ever* having handled, mixed, or applied phenoxy acids was 1.2 for 2,4-D and for 2,4,5-T. For use and handling of these 2 chemicals prior to 1965, risks were 1.3 and 1.7, respectively. Analyses restricting the "exposed" group to farmers who reported that they had not used protective equipment in the handling of specific pesticides were conducted for pesticides showing associations with NHL in previous analyses, either for *ever* handling the pesticide, or

Table 7 *Pesticides ever handled with and without protective clothing or equipment: OR and CI for selected pesticides*[a]

Pesticide	Ever handled[b]				Handled without protective equipment			
	No. of cases	No. of controls	OR	CI	No. of cases	No. of controls	OR	CI
Animal insecticides								
Chlordane	31	38	1.7	1.0, 2.9	24	30	2.2	1.2, 4.2
DDT	79	149	1.2	0.9, 1.7	72	127	1.3	0.9, 1.8
Lindane	55	90	1.4	1.0, 2.1	45	67	1.6	1.0, 2.4
Malathion	43	67	1.3	0.9, 2.1	33	52	1.4	0.8, 2.2
Nicotine	31	47	1.5	0.9, 2.5	24	41	1.4	0.8, 2.3
Crop insecticides								
Carbaryl	21	26	1.7	0.9, 3.1	22	22	2.2	1.2, 4.2
Chlordane	21	26	1.7	0.9, 3.2	17	18	2.1	1.1, 4.3
DDT	57	75	1.7	1.2, 2.6	48	54	2.0	1.3, 3.1
Diazinon	27	39	1.5	0.9, 2.5	17	22	1.7	0.9, 3.2
Lindane	21	23	2.0	1.0, 3.7	16	14	2.6	1.2, 5.5
Malathion	21	30	1.5	0.8, 2.7	14	16	1.9	0.9, 4.1
Herbicides								
Chloramben	39	70	1.3	0.8, 2.0	31	44	1.7	1.1, 2.8
2,4-D	115	227	1.2	0.9, 1.6	89	175	1.2	0.9, 1.7
Dicamba	28	57	1.2	0.7, 2.0	19	32	1.4	0.8, 2.5
2,4,5-T	25	48	1.2	0.7, 1.9	18	30	1.4	0.7, 2.5

[a] OR relative to nonfarmers, numbering 266 cases and 547 controls. All ORs adjusted for vital status, age, state, cigarette smoking status, family history of lymphopoietic cancer, high-risk occupations, and high-risk exposures in a logistic analysis.
[b] Results for ever having used or handled these pesticides (with or without protective clothing or equipment) are from Tables 4, 5, and 6.

Table 8 *Selected pesticides first used prior to 1965: OR and CI for residents of Iowa and Minnesota, respectively*[a]

Pesticide	Iowa				Minnesota			
	No. of cases	No. of controls	OR	CI	No. of cases	No. of controls	OR	CI
Animal insecticides								
Chlordane	15	15	2.2	1.0, 4.8	7	7	2.2	0.8, 6.6
DDT	27	67	0.9	0.5, 1.5	41	56	1.7	1.1, 2.7
Lindane	33	47	1.5	0.9, 2.5	7	8	1.9	0.6, 5.5
Malathion	16	21	1.5	0.7, 3.1	9	9	2.0	0.7, 5.3
Nicotine	15	16	2.1	1.0, 4.6	13	20	1.4	0.7, 2.9
Crop insecticides								
Carbaryl	5	3	3.5	0.8, 15.5	2	1	4.9	0.4, 56
Chlordane	8	13	1.3	0.5, 3.3	4	3	3.1	0.7, 14.7
DDT	28	40	1.5	0.9, 2.6	17	17	2.3	1.1, 4.8
Diazinon	10	10	2.4	0.9, 6.2	4	2	3.8	0.7, 22
Lindane	9	13	1.4	0.6, 3.5	5	2	6.5	1.2, 35
Malathion	6	6	2.1	0.6, 7.0	5	3	4.1	0.9, 18.6
Herbicides								
Chloramben	7	10	1.6	0.6, 4.4	9	9	2.6	1.0, 6.8
2,4-D	51	96	1.2	0.8, 1.9	35	57	1.4	0.9, 2.3
Dicamba	4	5	2.1	0.6, 8.1	3	2	3.9	0.6, 24
2,4,5-T	9	16	1.2	0.5, 2.9	4	2	4.7	0.8, 26.4

[a] OR relative to nonfarmers, numbering 120 cases and 255 controls in Iowa, and 146 cases and 292 controls in Minnesota. All ORs adjusted for vital status, age, cigarette smoking status, family history of lymphopoietic cancer, high-risk occupations, and high-risk exposures in logistic analyses.

handling it prior to 1965, as well as for the 2 most commonly used phenoxyacetic acid herbicides (Table 7). Among insecticides used on livestock, all except one (nicotine) showed a stronger association among those who did not use protective equipment than for the entire exposed group. All of the crop insecticides showed stronger risk among farmers who did not use protective gear, as did 3 of 4 herbicides (the OR for 2,4-D remained the same).

We also calculated odds ratios for pre-1965 use and handling of selected pesticides separately for respondents from Iowa and Minnesota (Table 8). The pesticides with OR greater than 1.5 in both states were: the insecticides chlordane, lindane, and malathion applied to livestock; the insecticides carbaryl, DDT, diazinon, and malathion applied to crops; and the herbicides chloramben and dicamba. Findings from analyses of pre-1965 use of specific pesticides that included only direct respondents resembled results of OR calculations that included both direct and proxy respondents.

There was minimal evidence for confounding of results for any single pesticide by exposure to pesticides belonging to other chemical families. This was indicated by little change in OR when a variable for exposure to any of several pesticide families was added to logistic regression models for individual pesticides (for use, handling, or applying prior to 1965) that had shown statistically significant results.

DISCUSSION

We conducted this population based case-control study of NHL in 2 states with intensive agricultural activity to investigate risk factors for NHL among farmers. As compared with nonfarmers, farmers were at slightly elevated risk of NHL (OR = 1.2), in agreement with some population surveys (13, 14) and other case-control studies of NHL or CLL (3, 15–25), based on mortality records or incident cases. Other population surveys have found no risk elevation for farmers (26–31); some case-

control studies have observed elevated, though nonsignificant, risk elevations (32–36); and others, null or slightly lower risk for NHL (37–41). Among the studies that have found statistically significant positive associations for NHL or CLL among farmers, the risk ratios have generally been in the range of 1.2 to 1.9. In this study, the cell type with the strongest association with farming was small lymphocytic lymphoma (OR = 1.4), a NHL subtype morphologically similar to CLL. Farming occupation has been linked to CLL risk in several case-control studies, including the study parallel to this one (3) and others (21–23), with OR in the range of 1.4 to 1.8.

We found no striking differences or trends in NHL risk by several measures of the time or intensity of farming, including first year farmed, total duration of farming, or average number of acres farmed. However, the association among men who were farming after 1949 was slightly stronger than for those who stopped earlier. In addition, the NHL risk among farmers of midsized farms (average farm size of 120–199, or 200–319 acres) was slightly higher (OR of 1.3 and 1.2) than for men who farmed more acreage (OR of 1.1). This is consistent with findings from Saskatchewan, where NHL risk was higher among farmers of <300 acres than larger establishments (27). The findings that relate temporal period of farming and average farm size with NHL risk are consistent with associations with chemical pesticide use. There were increases in the use of agricultural chemicals after World War II (42, 43), and major usage occurred after 1950, increasing the opportunity for exposure among individuals who farmed more recently.

We observed no meaningful elevation or consistent trends in risk with average acreage of a number of major crops (including corn, wheat, and soybeans) or the average or maximum number of several types of livestock (including dairy cows, beef cattle, hogs, and chickens).

There were small elevations in risk for NHL among farmers who ever used pesticides, or who used pesticides belonging to very broad groups according to usage, including livestock insecticides, crop insecticides, herbicides, and fungicides. However, larger risks were observed when more specific definitions of pesticide exposure were used (*i.e.*, chemical classes or specific chemicals); when risk was measured by whether a farmer had personally handled, mixed, or applied the pesticides; and among farmers who did not use protective clothing or equipment. Among chemical classes of insecticides used on livestock, we found statistically elevated risk for the grouped chlorinated hydrocarbons, natural products, and organophosphates. Among the chlorinated hydrocarbons, larger OR occurred for the grouped cyclodienes (chlordane and dieldrin) and among the organophosphates, greater risks occurred for halogenated aromatics (chlorphyrifos, coumaphos, crufomate, ronnel, and tetrachlorvinphos). Among crop insecticide families that we evaluated, only the chlorinated hydrocarbons showed statistically elevated OR. No single family of herbicides was associated with NHL risk.

We found significantly elevated risks, with OR of 1.5 or more, for personal handling, mixing, or application of several individual insecticides, including carbaryl, chlordane, DDT, diazinon, lindane, malathion, and nicotine. Dieldrin, dichlorvos, famphur, and toxaphene also showed notable, though nonsignificant risk elevations. Patterns of risk from 3 other analyses were consistent with the hypothesis of an etiological role for these insecticides. Risk of NHL was greater for most chemicals among farmers who first used these chemicals before 1965 (15–18 years before diagnosis) and among those who did not use protective equipment, and there was notable consistency in the risk estimates from the 2 states. Associations with specific chemicals were not confounded by exposure to families of other pesticides. Other investigations of lymphopoietic cancer and pesticide exposure have also noted a rise in risk with increasing time since first exposure, suggesting the need for longer latency (3, 33, 39).

Three of the 4 chemicals that showed excesses, and are used both on crops and livestock, had larger OR associated with crops (DDT, lindane, and malathion), while for chlordane the OR was greater for use on animals. This contrasts with the parallel study of leukemia in Iowa and Minnesota, in which we generally found higher risks for chemicals used as animal insecticides (3).

Several insecticides associated with NHL in this study (chlordane, dieldrin, DDT, lindane, and toxaphene) are classified as having sufficient or limited evidence for carcinogenicity in animals by the International Agency for Research on Cancer (42). For some other insecticides associated here with NHL (carbaryl and malathion), information for evaluation is insufficient. With the exception of phenoxyacetic acid herbicides, the epidemiological literature regarding cancer risks from specific pesticide exposures is quite limited. Cancer risks have been assessed in cohort studies of insecticide manufacturing workers and applicators (44–55), but these are generally not useful in evaluating the risk of NHL associated with specific pesticides. In most cohort studies, the specific pesticide exposures experienced by individuals were not well documented, or the effects of multiple exposures could not be disentangled. In addition, most cohorts were too small or the follow-up period too brief to adequately assess risk of NHL. Hematopoietic and lymphopoietic cancers, however, have been elevated in some of these studies. In Northern Italy, incident lymphatic tissue cancers were in excess among agriculture and forestry workers licensed to use pesticides (Standardized Incidence Ratio = 1.4, CI = 1.0–1.9; 45 cases), especially among persons applying pesticides to only arable land (Standardized Incidence Ratio = 1.8, CI = 1.2–2.5; 31 cases) (47). Excess NHL risk was found in a cohort of United States grain industry workers (Standardized Mortality Ratio = 149), and within the cohort, a nested case-control study showed flour millers to be at especially high risk (OR = 4.2, CI = 1.2–14.2) (44). A variety of insecticides has been used in the grain industry, including DDT, hydrogen cyanide, ethylene dibromide, phosphine, and carbon tetrachloride. Among pesticide manufacturing workers exposed primarily to DDT (740 persons, 17,186.9 person-years of follow-up), no excess of all lymphopoietic and hematopoietic cancer was found (3 observed, 2.40 expected) (51).

Six case-control studies, 4 of NHL (19, 38, 39, 56) and 2 of CLL (3, 17), provide limited information on risk associated with exposure to specific insecticides or insecticide families. A third case-control study of CLL found a nonsignificant risk elevation among persons exposed to "pesticides," not further defined (57). Exposure to DDT was linked with CLL in 2 case-control studies (3, 17), and associated with NHL in 2 others (19, 56), with OR between 1.5 and 6.1. In the 2 other case-control studies, either DDT was not reported separately (39) or no association was found (0 exposed cases, 3 exposed controls) (38). In the current study, we found an association with ever handling, mixing, or applying DDT that was stronger for its use on crops than on livestock, and that was more pronounced for first exposure prior to 1965 than later. We found elevated

risk for pre-1965 application of DDT to crops in both Iowa and Minnesota.

The grouped chlorinated hydrocarbon insecticides were associated with small (nonsignificant) risk elevations for NHL in a Nebraska study (58). Other than DDT, the only chlorinated hydrocarbons reported specifically in other case-control studies are chlordane and lindane. Chlordane was significantly associated with NHL risk in Nebraska (OR = 2.1), and nonsignificantly in Washington State (OR = 1.61) (19). Lindane, another organochlorine, was significantly associated here with NHL when used either on crops or animals, and risks were elevated in both Iowa and Minnesota. Lindane has also been associated with NHL in a study from Kansas (2).

Risks associated with organophosphate exposure, either collectively, or as individual chemicals, were reported for CLL in the parallel study of leukemia in Iowa and Minnesota (3) and for NHL in a study with similar methods from Eastern Nebraska (39, 58). In the Nebraska study, the OR for organophosphate exposure study was 1.9 (OR = 1.1–3.1), and risk increased with days/year of use to OR = 3.1 for 21+ days. In Nebraska, 2 organophosphates, diazinon and malathion, showed significant positive associations with NHL, similar to our findings. In the parallel leukemia study in Iowa and Minnesota (3), elevated risk was found for CLL among farmers exposed to dichlorvos as an animal insecticide (OR = 2.2, CI = 1.0–4.6). We found significant associations for the grouped organophosphate insecticides used on livestock (OR = 1.5), especially halogenated aromatic organophosphates (OR = 2.0, CI = 1.1–3.7). The ORs for grouped nonhalogenated aromatic organophosphates used on livestock and crops were also elevated, but not statistically significant. Regarding specific organophosphate insecticides, we observed significant associations of NHL with use of malathion prior to 1965 on both crops and animals, and OR were above 1.5 for both types of application in Iowa and in Minnesota. In addition, we found significant OR for pre-1965 use of diazinon on crops, with comparable risk elevations in the 2 study states. Use of other organophosphates before 1965, including coumaphos and dichlorvos on livestock, and phorate on crops, also were associated with increased risk of NHL, although the 95% confidence interval for each included 1.0.

In the study from Nebraska (58), the carbamate insecticide family was significantly associated with NHL (OR = 1.8). We did not find significant associations with carbamates as a group. However, use of carbaryl prior to 1965 was associated with NHL (OR = 3.8, CI = 1.1–13.6), and risk was elevated in both study areas. However, the number of exposed subjects was small (7 cases, 4 controls).

Phenoxyacetic acid herbicides have been linked to NHL risk in several (19, 33, 39, 56), but not all (38, 59), case-control studies. Excesses have also been noted in 2 phenoxyacetic acid manufacturing cohorts, although few deaths occurred (60, 61). In our data, the risk of NHL associated with *ever* handling, mixing, or applying members of the phenoxy acid herbicide family, or the specific herbicides 2,4-D or 2,4,5-T, was small and about the same as for farmers overall. However, when latency was considered, the association with 2,4,5-T was somewhat stronger. Although our findings are not entirely negative, the risk of NHL with 2,4-D use is considerably weaker than observed in studies of similar design from Kansas and Nebraska (33, 39). Risks here were considerably lower and did not increase with latency or failure to use protective equipment. The reasons for the inconsistencies are not obvious. Use patterns of 2,4-D in Iowa and Minnesota may differ from Kansas or Nebraska. In the latter states, the bulk of 2,4-D is for postemergent application on small grains, whereas in Iowa it may be more frequently used on corn. It is unclear whether this difference affects exposures to farmers. It is also possible that the inconsistencies between this and other studies of 2,4-D are simply due to chance, since random variation in risk estimates among studies is to be expected.

Additional comments on the limitations of this study are warranted. Some associations found here may have arisen due to chance or bias. Numerous comparisons were made, and results must be evaluated in this context and judged against epidemiological rules of causality. Bias in selecting cases or controls was absent since eligibility for the study was unrelated to current or previous status as a farmer or the exercise of particular agricultural practices. However, willingness to participate could have been related to farm residence or occupation as a farmer. The fairly high and similar response rates in cases and controls, however, diminishes the possibility of such bias.

Bias due to differential response or recollection of cases and controls regarding specific pesticide exposure is possible. Such bias is unlikely because at the time interviews were held, respondents and interviewers were not aware of hypotheses regarding specific pesticides. Moreover, we found no excess risk for many pesticides but rather some internal consistency for elevated risk with others, such as some of the chlorinated hydrocarbons and organophosphates.

Nondifferential misclassification of specific pesticide exposures is a more likely source of distortion of risk estimates. For dichotomous measures of exposure, however, this distortion would tend to bias risk estimates toward the null (62) and is unlikely to yield false-positive findings. The effect of nondifferential misclassification on polychotomous measures can be more complex (63). There are many ways in which exposure misclassification may occur in studies of this design (64). Most, however, would yield false-negative findings. More than 90% of the farmers in this study operated one or more farms, in contrast to working as hired help. Most farm operators plan their own pest control operations, personally purchase pesticides, and mix and apply the chemicals themselves. They are thus more likely to remember names of specific chemicals that they used than most other pesticide users. However, when many different chemicals were involved, when their use was several decades in the past, and when the use of particular chemicals was brief or episodic, accuracy in reporting chemical names and the timing of application undoubtedly suffers. Proxy respondents not directly involved in farming operations may have been more prone to inaccurate responses than directly interviewed subjects. Among farmers, proxies responded for 28.9% of cases and 34.2% of controls. Among controls who had farmed, 18.4% of proxies did not know whether crop insecticides had been used, and 17.2% did not know about herbicide use. In contrast, 3.3% of directly interviewed farmers didn't know about crop insecticide use, and 3.1% didn't know about herbicide use. Among the controls who reported insecticide use on crops, DDT use was reported as unknown by 11 of 86 proxies (13%) but only 8 of 233 alive subjects (3.4%), and crop application of malathion was unknown by 16 of 86 proxies (19%) and 7 of 233 living subjects (3.0%). Among controls who ever used herbicides, 2,4-D use was reported as unknown by 9 of 88 proxies (10.2%) and 5 of 256 direct respondents (2.0%). Differential effects on risk estimates due to proxy responses among cases and controls should not occur because we adjusted for

type of respondent in the analysis.

This investigation supports findings from earlier studies that point to an elevated risk of non-Hodgkin's lymphoma among farmers, and our data strongly suggest a relationship with certain pesticide exposures. Interpretation of results regarding individual pesticides is fraught with difficulties, including the problems of interpreting risk of individual factors in the multiple exposure setting of modern agriculture as well as the chance occurrence of finding positive associations with multiple comparisons. Of equal concern is the possibility of missing important associations due to nondifferential exposure misclassification because of difficulties in accurate recall of past pesticide exposures. This would bias risk estimates toward the null. Despite these qualifications, the many internal consistencies of this study and concordance with observations of others support the notion that elevated NHL risk among farmers is associated with exposure to several insecticides, and support the use of protective equipment. The chemicals most strongly associated with risk of NHL were carbaryl, chlordane, DDT, diazinon, dichlorvos, lindane, malathion, nicotine, and toxaphene. Many of these insecticides are still in widespread use today, in the United States or elsewhere, and deserve further epidemiological evaluation.

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REFERENCES

1. Blair, A., Malker, H., Cantor, K. P., Burmeister, L., and Wiklund, K. Cancer among farmers: a review. Scand. J. Work Environ. Health, *11:* 397–407, 1985.
2. Blair, A., Axelson, O., Franklin, C., Paynter, O. E., Pearce, N., Stevenson, D., Trosko, J. E., Vainio, H., Williams, G., Woods, J., and Zahm, S. H. Carcinogenic effects of pesticides. *In:* S. R. Baker and C. F. Wilkinson (eds.), The Effects of Pesticides on Human Health, pp. 201–260. Princeton, NJ: Princeton Scientific Publishing Co., 1990.
3. Brown, L. M., Blair, A., Gibson, R., Everett, G. D., Cantor, K. P., Schuman, L. M., Burmeister, L. F., VanLier, S. F., and Dick, F. Pesticide exposures and other agricultural risk factors for leukemia among men in Iowa and Minnesota. Cancer Res., *50:* 6585–6591, 1990.
4. Non-Hodgkin's Lymphoma Pathologic Classification Project. National Cancer Institute sponsored study of classifications of non-Hodgkin's lymphomas. Cancer (Phila.), *49:* 2112–2135, 1982.
5. Dick, F., Van Lier, S., Banks, P., Frizzera, G., Witrak, G., Gibson, R., Everett, G., Schuman, L., Isacson, P., O'Conor, G., Cantor, K., Blattner, W., and Blair, A. Use of the working formulation for Non-Hodgkin's lymphoma in epidemiologic studies: agreement between reported diagnoses and a panel of experienced pathologists. J. Natl. Cancer Inst., *78:* 1137–1144, 1987.
6. Dick, F. R., Van Lier, S. F., McKeen, K., Everett, G. D., and Blair, A. Nonconcurrence in abstracted diagnoses of Non-Hodgkin's lymphoma. J. Natl. Cancer Inst., *78:* 675–678, 1987.
7. Hartge, P., Brinton, L. A., Rosenthal, J. F., Cahill, J. I., Hoover, R. N., and Waksberg, J. Random digit dialing in selecting a population-based control group. Am. J. Epidemiol., *120:* 825–833, 1984.
8. Waksberg, J. Sampling methods for random digit dialing. J. Am. Stat. Assoc., *73:* 40–46, 1978.
9. Hartge, P., Cahill, J. I., West, D., Hauck, M., Austin, D., Silverman, D., and Hoover, R. Design and methods in a multi-center case-control interview study. Am. J. Public Health, *74:* 52–56, 1984.
10. Cox, D. R. The Analysis of Binary Data, p. 14. London: Methuen, 1970.
11. Dixon, W. J. (ed.) BMDP Statistical Software. p. 330. Berkeley, CA: University of California Press, 1983.
12. Gart, J. J. Point and interval estimation of the common odds ratio in the combination of 2X2 tables with fixed marginals. Biometrika, *57:* 471–475, 1970.
13. Burmeister, L. F. Cancer mortality in Iowa farmers, 1971–78. J. Natl. Cancer Inst., *66:* 461–464, 1981.
14. Buesching, D. P., and Wollstadt, L. Cancer mortality among farmers (letter). J. Natl. Cancer Inst., *72:* 503–504, 1984.
15. Balajaran, R. Malignant lymphomas in agricultural and forestry workers in England and Wales. Public Health, *102:* 585–592, 1988.
16. Cantor, K. P. Farming and mortality from non-Hodgkin's lymphoma: a case-control study. Int. J. Cancer, *29:* 239–247, 1982.
17. Flodin, U., Fredriksson, M., Persson, B., and Axelson, O. Chronic lymphatic leukaemia and engine exhausts, fresh wood, and DDT: a case-referent study. Br. J. Ind. Med., *45:* 33–38, 1988.
18. Pearce, N. E., Smith, A. H., and Fisher, D. O. Malignant lymphoma and multiple myeloma linked with agricultural occupations in a New Zealand cancer registry-based study. Am. J. Epidemiol., *121:* 225–237, 1985.
19. Woods, J. S., Polissar, L., Severson, R. K., Heuser, L. S., and Kulander, B. G. Soft tissue sarcoma and non-Hodgkin's lymphoma in relation to phenoxyherbicide and chlorinated phenol exposure in western Washington. J. Natl. Cancer Inst., *78:* 899–910, 1987.
20. LaVecchia, C., Negri, E., D'Avanzo, B., and Franceschi, S. Occupation and lymphoid neoplasms. Br. J. Cancer, *60:* 385–388, 1989.
21. Burmeister, L. F., Van Lier, S. F., and Isacson, P. Leukemia and farm practices in Iowa. Am. J. Epidemiol., *115:* 720–728, 1982.
22. Blair, A., and White, D. W. Leukemia cell types and agricultural practices in Nebraska. Arch. Environ. Health, *40:* 211–214, 1985.
23. Pearce, N. E., Sheppard, R. A., Howard, J. K., Fraser, J., and Lilley, B. M. Leukemia among New Zealand agricultural workers. Am. J. Epidemiol., *124:* 402–409, 1986.
24. Reif, J., Pearce, N., and Fraser, J. Cancer risks in New Zealand farmers. Int. J. Epidemiol., *18:* 768–774, 1989.
25. Brownson, R. C., Reif, J. S., Chang, J. C., and Davis, J. R. Cancer risks among Missouri farmers. Cancer (Phila.), *64:* 2381–2386, 1989.
26. Wiklund, K., Lindefors, B-M., and Holm, L-E. Risk of malignant lymphoma in Swedish agricultural and forestry workers. Br. J. Ind. Med., *45:* 19–24, 1988.
27. Wigle, D. T., Semenciw, R. M., Wilkins, K., Riedel, D., Ritter, L., Morrison, H. I., and Mao, Y. Mortality study of Canadian male farm operators: non-Hodgkin's lymphoma mortality and agricultural practices in Saskatchewan. J. Natl. Cancer Inst., *82:* 575–582, 1990.
28. Stark, A. D., Chang, H-G., Fitzgerald, E. F., Riccardi, K., and Stone, R. R. A retrospective cohort study of cancer incidence among New York State Farm Bureau members. Arch. Environ. Health, *45:* 155–162, 1990.
29. Stark, A. D., Chang, H. G., Fitzgerald, E. F., Riccardi, K., and Stone, R. R. A retrospective cohort study of mortality among New York State farm bureau members. Arch. Environ. Health, *42:* 204–212, 1987.
30. Fasal, E., Jackson, E. W., and Klauber, M. R. Leukemia and lymphoma mortality and farm residence. Am. J. Epidemiol., *87:* 267–274, 1968.
31. Delzell, E., and Grufferman, S. Mortality among white and nonwhite farmers in North Carolina, 1976–1978. Am. J. Epidemiol., *121:* 391–402, 1985.
32. Brownson, R. C., and Reif, J. S. A cancer registry-based study of occupational risk for lymphoma, multiple myeloma and leukemia. Int. J. Epidemiol., *17:* 27–32, 1988.
33. Hoar, S. K., Blair, A., Holmes, F. F., Boysen, C. D., Robel, R. J., Hoover, R., and Fraumeni, J. F. Agricultural herbicide use and risk of lymphoma and soft-tissue sarcoma. J. Am. Med. Assoc., *256:* 1141–1147, 1986.
34. Cartwright, R. A., McKinney, P. A., O'Brien, C., Richards, I. D. G., Roberts, B., Lauder, I., Darwin, C. M., Bernard, S. M., and Bird, C. C. Non-Hodgkin's lymphoma: case control epidemiologic study in Yorkshire. Leuk. Res., *12:* 81–88, 1988.
35. Dubrow, R., Paulson, J. O., and Indian, R. W. Farming and malignant lymphoma in Hancock County, Ohio. Br. J. Ind. Med., *45:* 25–28, 1988.
36. Milham, S., Jr. Leukemia and multiple myeloma in farmers. Am. J. Epidemiol., *94:* 307–310, 1971.
37. Pearce, N. E., Sheppard, R. A., Smith, A. H., and Teague, C. A. Non-Hodgkin's lymphoma and farming: an expanded case-control study. Int. J. Cancer, *39:* 155–161, 1987.
38. Persson, B., Dahlander, A-M., Fredriksson, M., Brage, H. N., Ohlson, C-G., and Axelson, O. Malignant lymphomas and occupational exposures. Br. J. Ind. Med., *46:* 516–520, 1989.
39. Zahm, S. H., Weisenburger, D. D., Babbitt, P. A., Saal, R. C., Vaught, J. B., Cantor, K. P., and Blair, A. A case-control study of non-Hodgkin's lymphoma and the herbicide 2,4-dichlorophenoxyacetic acid (2,4-D) in Eastern Nebraska. Epidemiology, *1:* 349–356, 1990.
40. Franceschi, S., Serraino, D., Bidoli, E., Talamini, R., Tirelli, U., Carbone, A., and LaVecchia, C. The epidemiology of non-Hodgkin's lymphoma in the north-east of Italy: a hospital-based case-control study. Leuk. Res., *13:* 465–472, 1989.
41. Schumacher, M. C., and Delzell, E. A death-certificate case-control study of non-Hodgkin's lymphoma and occupation in men in North Carolina. Am. J. Ind. Med., *13:* 317–330, 1988.
42. International Agency for Research on Cancer. Overall Evaluations of Carcinogenicity: An Updating of IARC Monographs Volumes 1 to 42. Lyon, France: International Agency for Research on Cancer, 1987.
43. International Agency for Research on Cancer. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans: Volume 30, Miscellaneous Pesticides. Lyon: International Agency for Research on Cancer, 1983.
44. Alavanja, M. C. R., Blair, A., and Masters, M. N. Cancer mortality in the U. S. flour industry. J. Natl. Cancer Inst., *82:* 840–848, 1990.
45. Blair, A., Grauman, D. J., Lubin, J. H., and Fraumeni, J. F. Lung cancer and other causes of death among licensed pesticide applicators. J. Natl. Cancer Inst., *71:* 31–37, 1983.

46. Barthel, E. Increased risk of lung cancer in pesticide-exposed male agricultural workers. J. Toxicol. Environ. Health, *8:* 1027–1040, 1981.
47. Corrao, G., Calleri, M., Carle, F., Russo, R., Bosia, S., and Piccioni, P. Cancer risk in a cohort of licensed pesticide users. Scand. J. Work Environ. Health, *15:* 203–209, 1989.
48. Cantor, K. P., and Booze, C. F. Mortality among aerial pesticide applicators and flight instructors. Arch. Environ. Health, *45:* 295–302, 1990.
49. MacMahon, B., Monson, R. R., Wang, H. H., and Zheng, T. A second follow-up of mortality in a cohort of pesticide applicators. J. Occup. Med., *30:* 429–432, 1988.
50. Wiklund, K., Dich, J., and Holm, L-E. Risk of malignant lymphoma in Swedish pesticide appliers. Br. J. Cancer, *56:* 505–508, 1987.
51. Wong, O., Brocker, W., Davis, H. V., and Nagle, G. S. Mortality of workers potentially exposed to organic and inorganic brominated chemicals, DBCP, TRIS, PBB, and DDT. Br. J. Ind. Med., *41:* 15–24, 1984.
52. Mabuchi, K., Lilienfeld, A. M., and Snell, L. M. Lung cancer among pesticide workers exposed to inorganic arsenicals. Arch. Environ. Health, *34:* 312–320, 1979.
53. Ditraglia, D., Brown, D. P., Namekata, T., and Iverson, N. Mortality study of workers employed at organochlorine pesticide manufacturing plants. Scand. J. Work Environ. Health, *7*(Suppl. 4): 140–146, 1981.
54. Ribbens, P. H. Mortality study of industrial workers exposed to aldrin, dieldrin and endrin. Int. Arch. Occup. Environ. Health, *56:* 75–79, 1985.
55. Wang, H. H., and MacMahon, B. Mortality of workers employed in the manufacture of chlordane and heptachlor. J. Occup. Med., *21:* 745–748, 1979.
56. Hardell, L., Eriksson, M., and Lenner, P. Malignant lymphoma and exposure to chemicals, especially organic solvents, chlorophenols and phenoxy acids: a case-control study. Br. J. Cancer, *43:* 169–176, 1981.
57. Malone, K. E., Koepsell, T. D., Daling, J. R., Weiss, N. S., Morris, P. D., Taylor, J. W., Swanson, G. M., and Lyon, J. L. Chronic lymphocytic leukemia in relation to chemical exposures. Am. J. Epidemiol., *130:* 1152–1158, 1989.
58. Zahm, S. H., Weisenburger, D. D., Babbitt, R. C., Saal, R. C., Cantor, K. P., and Blair, A. A case-control study of non-Hodgkin's lymphoma and agricultural factors in Eastern Nebraska (abstract). Am. J. Epidemiol., *128:* 901, 1988.
59. Pearce, N. Phenoxy herbicides and non-Hodgkin's lymphoma in New Zealand: frequency and duration of herbicide use (letter). Br. J. Ind. Med., *46:* 143–144, 1989.
60. Bond, G. G., Wetterstroem, N. H., Roush, G. J., McLaren, E. A., Lipps, T. E., and Cook, R. R. Cause specific mortality among employees engaged in the manufacture, formulation, or packaging of 2,4-dichlorophenoxyacetic acid and related salts. Br. J. Ind. Med., *45:* 98–105, 1988.
61. Coggon, D., Pannett, B., and Winter, P. Mortality and incidence of cancer at four factories making phenoxy herbicides. Br. J. Ind. Med., *48:* 173–178, 1991.
62. Checkoway, H., Pearce, N. E., and Crawford-Brown, D. J. Research Methods in Occupational Epidemiology. New York: Oxford University Press, 1989.
63. Dosemeci, M., Wacholder, S., and Lubin, J. H. Does nondifferential misclassification of exposure always bias a true effect toward the null value? Am. J. Epidemiol., *132:* 746–748, 1990.
64. Blair, A., and Zahm, S. H. Methodologic issues in exposure assessment for case-control studies of cancer and herbicides. Am. J. Ind. Med., *18:* 285–293, 1990.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

23 DEC 1975

Monsanto Company
Attention: Mr. Hannah
800 N. Lindbergh Boulevard
St. Louis, Missouri 63166

Gentlemen:

Subject : ROUNDUP
EPA Reg. No. 524-308
Your application of
December 22, 1975

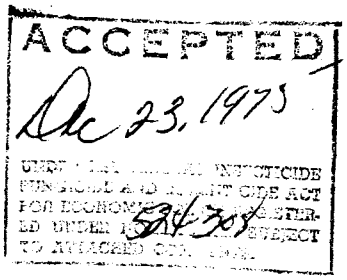
The labeling referred to above, submitted in connection with registration under the Federal Insecticide, Fungicide, and Rodenticide Act, as amended, is acceptable, and a stamped copy is enclosed for your records.

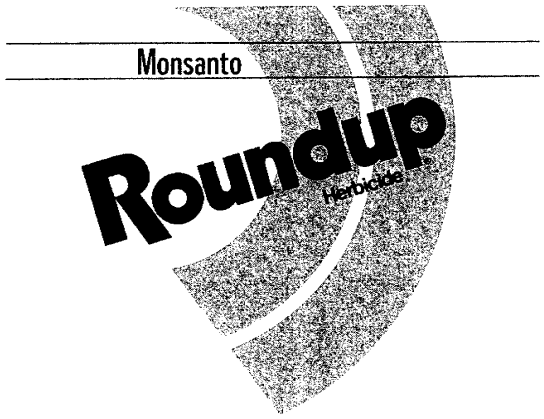
Note that this submission was processed and accepted under the 1947 Federal Insecticide, Fungicide, and Rodenticide Act. At such time as re-registration is required or amendments are proposed, the Registration, Re-registration and Classification Procedures, as published in the Federal Register on July 3, 1975, will be applied. Refer to Section 162.23 of that document. Refer also to PR Notice 75-1 and 75-4.

Sincerely,

Robert J. Taylor
Product Manager (25)
Fungicide-Herbicide Branch
Registration Division (WH-567)

Enclosure


ACCEPTED
Dec 23, 1975
FOR ECONOMIC
34-305



DIRECTIONS FOR USE
It is a violation of Federal Law to use this product in any manner inconsistant with its labeling.

Carefully read and follow directions for use in attached labeling.

Read the entire label.

Use only according to label instructions.

LIMIT OF WARRANTY AND LIABILITY

This company warrants that this material conforms to the chemical description on the label and is reasonably fit for the purposes referred to in the directions for use. This product is sold subject to the understanding that the buyer assumes all risks of use or handling which may result in loss or damage which are beyond the control of the seller, such as for example, incompatibility with other products, the manner of its use or application, or the presence of other products or materials in or on the soil or crop. NO OTHER EXPRESS OR IMPLIED WARRANTY OF FITNESS OR MERCHANTABILITY IS MADE. The exclusive remedy of the user or buyer and the limit of the liability of this company or any other seller for any and all losses, injuries or damages resulting from the use or handling of this product shall be the purchase price paid by the user or buyer for the quantity of this product involved. The buyer and all users are deemed to have accepted the terms of this notice which may not be varied by any verbal or written agreement.

MONSANTO COMPANY
AGRICULTURAL PRODUCTS
ST. LOUIS, MISSOURI 63166 U.S.A.

PRECAUTIONARY STATEMENTS
Hazard to Humans

WARNING! Keep out of reach of children.

CAUSES EYE IRRITATION.
HARMFUL IF SWALLOWED
Do not get in eyes, on skin or on clothing.

FIRST AID: In case of contact, immediately flush eyes with plenty of water for at least 15 minutes. Call a physician. Flush skin with water. Wash clothing before reuse

Storage and Disposal

STORE ABOVE 10°F. TO KEEP FROM FREEZING. Freezing will result in crystals which settle to the bottom of the can. If allowed to freeze, place in a warm room (72°F.) and roll and shake the can frequently for several days to redissolve.

Avoid contamination of seed, feed and food stuffs.

Do not reuse container, destroy when empty.

In case of an emergency involving this product, Call Collect, day or night, (314) 694-1000.

EPA Est. 524-MO-1
897.10-003.09

MINIATURE FACSIMILE
Smallest Type size on package 12 point.

Water soluble herbicide for non-selective control of many annual and perennial weeds:
in industrial and non-crop areas;
in non-bearing apple and cherry trees;
and
in cropping r... ems before emergence of barley, corn (all), oats, sorghum (milo), soybeans and wheat only.

Read the entire label. Use only according to label instructions

Water soluble herbicide for non-selective control of many annual and perennial weeds.
Carefully follow detailed instructions in attached labeling.
Avoid contact with foliage, green stems, or fruit of crops, desirable plants and trees, since severe injury or destruction may result.

Read "LIMIT OF WARRANTY AND LIABILITY" before buying or using. If terms are not acceptable, return at once unopened.

Read precautions on back panel.

WARNING! Keep out of reach of children.

Active Ingredient:
*Isopropylamine salt of glyphosate ... 41.0%
Inert Ingredients ... 59.0%
... 100.0%

NET 5 U.S. GAL.

*Contains 480 grams per liter or 4 pounds of the active ingredient isopropylamine salt of N-(phosphonomethyl) glycine per U.S. gallon. Equivalent to 356 grams per liter or 3 pounds per U.S. gallon of the acid, glyphosate.

EPA Reg. No. 524-308-AA

Monsanto

Roundup® Herbicide

PRECAUTIONARY STATEMENTS

Hazard to Humans

WARNING! Keep out of reach of children.

CAUSES EYE IRRITATION.

HARMFUL IF SWALLOWED.

Do not get in eyes, on skin or on clothing.

FIRST AID: In case of contact, immediately flush eyes with plenty of water for at least 15 minutes. Call a physician. Flush skin with water. Wash clothing before reuse.

Storage and Disposal

STORE ABOVE 10°F. TO KEEP FROM FREEZING. Freezing will result in crystals which settle to the bottom of the can. If allowed to freeze, place in a warm room (72°F.) and roll and shake the can frequently for several days to redissolve.

Avoid contamination of seed, feed and food stuffs.

Do not reuse container, destroy when empty.

In case of an emergency involving this product, Call Collect, day or night, (314) 694-1000.

897.10-000.12

Monsanto

Roundup® Herbicide

Water soluble herbicide for non-selective control of many annual and perennial weeds.
Carefully follow detailed instructions in attached labeling.
Avoid contact with foliage, green stems, or fruit of crops, desirable plants and trees, since severe injury or destruction may result.

Read "LIMIT OF WARRANTY AND LIABILITY" before buying or using. If terms are not acceptable, return at once unopened.

WARNING! Read precautions on back panel.
Keep out of reach of children.

Active Ingredient:	
*Isopropylamine salt of Glyphosate	41.0%
Inert Ingredients:	59.0%
	100.0%

*Contains 480 grams per liter or 4 pounds of the active ingredient isopropylamine salt of N-(phosphonomethyl) glycine per U.S. gallon. Equivalent to 359 grams per liter or 3 pounds per U.S. gallon of the acid, glyphosate.

NET 1 GAL

EPA Reg. No. 524-308-AA

Monsanto

Roundup® Herbicide

DIRECTIONS FOR USE
It is a violation of Federal Law to use this product in any manner inconsistant with its labeling.

Carefully read and follow directions for use in attached labeling.

Read the entire label.

Use only according to label instructions.

LIMIT OF WARRANTY AND LIABILITY

This company warrants that this material conforms to the chemical description on the label and is reasonably fit for the purposes referred to in the directions for use. This product is sold subject to the understanding that the buyer assumes all risks of use or handling which may result in loss or damage which are beyond the control of the seller, such as for example, incompatibility with other products, the manner of its use or application, or the presence of other products or materials in or on the soil or crop. NO OTHER EXPRESS OR IMPLIED WARRANTY OF FITNESS OR MERCHANTABILITY IS MADE. The exclusive remedy of the user or buyer and the limit of the liability of this company or any other seller for any and all losses, injuries or damages resulting from the use or handling of this product shall be the purchase price paid by the user or buyer for the quantity of this product involved. The buyer and all users are deemed to have accepted the terms of this notice which may not be varied by any verbal or written agreement.

ROUNDUP® Herbicide Complete Directions for Use. EPA Reg. No. 524-308-AA

Water soluble herbicide for non-selective control of many annual and perennial weeds:
in industrial and non-crop areas;
in non-bearing apple and cherry trees;
and
in cropping systems before emergence of barley, corn (all), oats, sorghum (milo), soybeans and wheat only.

Read the entire label. Use only according to label instructions.

AVOID CONTACT WITH FOLIAGE, GREEN STEMS, OR FRUIT OF CROPS, DESIRABLE PLANTS AND TREES, SINCE SEVERE INJURY OR DESTRUCTION MAY RESULT.

MONSANTO COMPANY
AGRICULTURAL PRODUCTS
ST. LOUIS, MISSOURI 63166 U.S.A.

EPA Est. 524-MO-1

In case of an emergency involving this product, Call Collect, day or night, (314) 694-1000.

ELECTRONIC PAPER

Integrative assessment of multiple pesticides as risk factors for non-Hodgkin's lymphoma among men

A J De Roos, S H Zahm, K P Cantor, D D Weisenburger, F F Holmes, L F Burmeister, A Blair

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See end of article for authors' affiliations

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Background: An increased rate of non-Hodgkin's lymphoma (NHL) has been repeatedly observed among farmers, but identification of specific exposures that explain this observation has proven difficult.

Methods: During the 1980s, the National Cancer Institute conducted three case-control studies of NHL in the midwestern United States. These pooled data were used to examine pesticide exposures in farming as risk factors for NHL in men. The large sample size (n = 3417) allowed analysis of 47 pesticides simultaneously, controlling for potential confounding by other pesticides in the model, and adjusting the estimates based on a prespecified variance to make them more stable.

Results: Reported use of several individual pesticides was associated with increased NHL incidence, including organophosphate insecticides coumaphos, diazinon, and fonofos, insecticides chlordane, dieldrin, and copper acetoarsenite, and herbicides atrazine, glyphosate, and sodium chlorate. A subanalysis of these "potentially carcinogenic" pesticides suggested a positive trend of risk with exposure to increasing numbers.

Conclusion: Consideration of multiple exposures is important in accurately estimating specific effects and in evaluating realistic exposure scenarios.

Farming occupation has been associated with an increased risk of non-Hodgkin's lymphoma (NHL) in the United States and other countries.[1-4] Specific farming exposures contributing to the excess risk have not been clearly discerned, but pesticides have received considerable attention. Associations have been observed between NHL risk and exposure to phenoxyacetic acids, most notably 2,4-dichlorophenoxyacetic acid (2,4-D).[5-10] Organochlorine, organophosphate, carbamate, and triazine pesticides have also been implicated.[8 9 11-14]

There are several analytical challenges in studying health effects of pesticide exposures among farmers. Farmers are typically exposed to multiple pesticides during a lifetime, and pesticides are frequently used together or during the same growing season, posing a challenge for identifying specific risk factors. Although multiple and simultaneous exposures are common in epidemiology and the situation regarding pesticides is not unique, they do require large numbers to successfully identify risks from specific exposures. Many of the past studies of NHL and pesticides had limited power to adjust for potential confounding by associated pesticide exposures. Limited study power has also hindered investigation of the risk associated with common pesticide combinations.

In principle, multiple pesticide exposures should be modelled simultaneously to account for their probable correlation; however, modelling multiple pesticides can lead to imprecise estimates, particularly where exposures are infrequent. In addition, some estimates are expected to be very inaccurate, either due to chance or systematic error (such as recall bias). Hierarchical regression models, also known as multilevel or multistage models, allow the researcher to specify prior distributions for multiple effect parameters of interest (for example, pesticide effects), and to adjust the observed likelihood estimates towards these prior distributions with the objective of obtaining increased precision and accuracy for the ensemble of estimates.[15-17] Although the true prior distributions are rarely known, factors hypothesised to determine or explain the magnitude of the true effects of interest can be used to specify the form of the prior distributions, whose magnitudes are then estimated.[15]

During the 1980s, the National Cancer Institute conducted three population based case-control studies of NHL in Nebraska,[5] Iowa and Minnesota,[11] and Kansas.[7] Each of these studies focused on farming exposure to pesticides, and data from the three studies have been pooled. In the pooled data, certain organophosphate[12] and carbamate[13] insecticides were positively associated with the risk of NHL. Lindane use was associated with slightly increased incidence of NHL,[18] whereas DDT use was not.[19] There was also a slightly increased incidence associated with atrazine exposure.[20]

We used these pooled data to conduct an analysis of exposure to multiple pesticides in farming as risk factors for NHL among men. The larger sample size provided adequate numbers of exposed persons to analyse a set of pesticide exposures simultaneously, using hierarchical regression to adjust estimates based on prior distributions for the pesticide effects. In addition, effects of the number of pesticides used and of common pesticide combinations were explored to assess the risk associated with realistic scenarios of farmers' exposures to multiple pesticides.

METHODS

Study population

The three case-control studies had slightly different methods of subject recruitment. In Nebraska,[5] all cases of NHL diagnosed between July 1983 and June 1986 among white subjects 21 years of age and older, and living in one of the 66 counties of eastern Nebraska were identified through the Nebraska Lymphoma Study Group and area hospitals. In Iowa and Minnesota,[11] all newly diagnosed cases of NHL among

Abbreviations: 2,4-D, 2,4-dichlorophenoxyacetic acid; NHL, non-Hodgkin's lymphoma; OP, organophosphorus

white men aged 30 years or older were ascertained from records of the Iowa State Health Registry from 1981 to 1983, and a special surveillance system of Minnesota hospitals and pathology laboratories from 1980 to 1982. In Kansas,[7] a random sample of cases diagnosed between 1979 and 1981 among white men age 21 years or older was selected from the statewide cancer registry run by the University of Kansas Cancer Data Service. Population based controls were randomly selected from the same geographical areas as the cases, frequency matched to cases by race, sex, age, and vital status at the time of interview. Potential controls were identified by random digit dialing and from Medicare records, and for deceased cases, from state mortality files.

Only one study included women; in this pooled analysis we excluded female cases and controls. Those who lived or worked on a farm when younger than 18 years of age, but not after age 18, were not asked about their pesticide use in the Nebraska study; persons with this history from any of the three studies were therefore excluded from analyses of the pooled data. Following exclusions, the study population included 870 cases and 2569 controls.

Interviews

Interviews were conducted with the subjects or their next of kin if the subjects were dead or incapacitated. In each study, detailed questions were asked about the use of agricultural pesticides as well as other known or suspected risk factors for NHL. In Nebraska, information was obtained through questioning about the use of any pesticide, followed by prompting for selected specific pesticides, with details on the total number of years of use and average number of days per year. In Iowa and Minnesota, use was assessed by a direct question about a selected list of specific pesticides. Pesticide users were also asked the first and last year each pesticide was used. In Kansas, use of pesticides was assessed by an open ended question without prompting for specific pesticides, and duration of use and days per year were obtained for groups of pesticides (herbicides, insecticides, and fungicides), but not for each pesticide individually.

Statistical analyses

Each pesticide for which there were data from all three studies, and to which 20 or more persons were exposed, was included in the pooled analysis. The set of pesticides examined included 47 insecticides and herbicides. Exposure to each pesticide was coded as an indicator variable for exposed (1) or not exposed (0). Because these analyses of multiple pesticides modelled the pesticides simultaneously, any subject with a missing or "don't know" response for any one of the 47 pesticides of interest was excluded from all analyses. Following exclusion of subjects with missing data, analyses of multiple pesticides included 650 cases (74.7%) and 1933 controls (75.2%). We employed two approaches to our analyses: standard logistic regression (maximum likelihood estimation) and hierarchical regression, calculating odds ratios to estimate the relative risk associated with each pesticide. All models included variables for age (coded as a quadratic spline variable with one knot at 50 years)[21] and indicator variables for study site. Other factors known or suspected to be associated with NHL, including first degree relative with haematopoietic cancer, education, and smoking, were evaluated and found not to be important confounders of the associations between NHL and pesticides. The standard logistic regression models did not assume any prior distribution of pesticide effects, in contrast to the hierarchical regression modelling.

Hierarchical regression of multiple pesticide exposures

In the first-level model of the hierarchical regression analysis, NHL disease status was regressed simultaneously on the 47 pesticide exposures, age, and study site. The maximum likelihood estimates for the 47 pesticides from the first-level model were regressed in a second-level linear regression model as a function of prespecified prior covariates for each of the pesticides. The second-level model should incorporate what is known about each true effect parameter prior to seeing the study data.[15 22] Information derived from the second-level model was used to adjust the beta coefficient for each pesticide exposure according to its "prior distribution"; the beta for each pesticide was adjusted in the direction of its prior mean, or expected value (from the second-level model), with the magnitude of shrinkage dependent on the precision of its likelihood estimate (from the first-level model) and a prespecified variance of the assumed normal distribution for that parameter. SAS Proc GLIMMIX was used to run the hierarchical models. This program can be adapted for the purpose of hierarchical modelling of multiple exposures, and uses a penalised likelihood function to fit the first- and second-level models by an iterative procedure.[23]

Information on pesticides that would give a priori reason to believe that the true effect parameters for certain specific pesticides would be more or less similar to each other was constructed into a matrix for use in the second level of the hierarchical regression analysis (table 1). The second-level, or prior covariates, were factors hypothesised to determine the magnitude of, or explain some of the variability between, the individual true effects. The covariates were indicators of pesticide class, structure, and toxicity, used to define categories of pesticide effects which would be regarded as "exchangeable", or as draws from a common prior distribution.[15 22] These "categories of exchangeability" included the groupings: insecticides (versus herbicides), organochlorines, organophosphates, carbamates, phenoxyacetic acids, triazines, amides, and benzoic acids (see table 1). In addition to categories of exchangeability, we defined a prior covariate incorporating prior evidence for carcinogenicity of the pesticide. Based on data from the United States Environmental Protection Agency's (US EPA) Integrated Risk Information System (http://www.epa.gov/iris/) and the International Agency for Research on Cancer's Program on the Evaluation of Cancer Risks to Humans (http://monographs.iarc.fr/), carcinogenic probability for any cancer (not limited to NHL), was defined as a continuous variable ranging between 0 and 1 (algorithm for variable definition is included as footnote to table 1).

Another component of each pesticide effect's prior distribution was a value for the residual variance, which captures effects above and beyond those accounted for by the "group" effects of the second-level covariates, and determines the degree of shrinkage of a likelihood estimate toward its prior mean.[15 22] This residual variance was defined as a value relating to a range of probable values for the true effect parameter. We assumed, with 95% certainty, that the rate ratio for each pesticide, after adjusting for the second-level covariates, would fall within a 10-fold range around its prior mean (for example, between 0.5 and 5.0), by defining the prior residual variance as 0.35 (note: for a 10-fold range, residual variance = $((\ln(10))/3.92)^2 \cong 0.35$), assuming normality).

Because our prior covariates were crudely defined, and because there is little information on factors that would be expected to affect the magnitude of the effect of pesticides on NHL incidence, we also performed a hierarchical regression analysis of multiple pesticides using an intercept-only model, in which all pesticide effects were assumed to arise from a common prior distribution, with a prior residual variance of 0.35. In other words, this modelling strategy assumed that there was no a priori reason to believe that any specific pesticide was more likely to be associated with NHL incidence than any other pesticide in the model.

Number of pesticides used

We conducted analyses to estimate NHL incidence associated with the number of pesticides used, out of the total number of

Table 1 Second-level matrix for hierarchical regression analysis, showing values of "prior covariates" for each pesticide of interest*†

Pesticides	Insecticides	Organo-chlorines	Organo-phospates	Carbamates	Phenoxy-acetic acids	Triazines	Amides	Benzoic acids	Carcinogenic probability
Insecticides									
Aldrin	1	1	0	0	0	0	0	0	0.6
Bufencarb	1	0	0	1	0	0	0	0	0.3
Carbaryl	1	0	0	1	0	0	0	0	0.3
Carbofuran	1	0	0	1	0	0	0	0	0.3
Chlordane	1	1	0	0	0	0	0	0	0.8
Copper acetoarsenite*	1	0	0	0	0	0	0	0	1.0
Coumaphos	1	0	1	0	0	0	0	0	0.3
DDT	1	1	0	0	0	0	0	0	0.8
Diazinon	1	0	1	0	0	0	0	0	0.3
Dichlorvos	1	0	1	0	0	0	0	0	0.8
Dieldrin	1	1	0	0	0	0	0	0	0.6
Dimethoate	1	0	1	0	0	0	0	0	0.3
Ethoprop	1	0	1	0	0	0	0	0	0.3
Famphur	1	0	1	0	0	0	0	0	0.3
Fly, lice, tick spray	1	0	0	0	0	0	0	0	0.3
Fonofos	1	0	1	0	0	0	0	0	0.3
Heptachlor	1	1	0	0	0	0	0	0	0.8
Lead arsenate*	1	0	0	0	0	0	0	0	1.0
Lindane	1	1	0	0	0	0	0	0	0.3
Malathion	1	0	1	0	0	0	0	0	0.3
Methoxychlor	1	1	0	0	0	0	0	0	0.3
Nicotine	1	0	0	0	0	0	0	0	0.3
Phorate	1	0	1	0	0	0	0	0	0.3
Pyrethrins	1	0	0	0	0	0	0	0	0.3
Rotenone	1	0	0	0	0	0	0	0	0.3
Tetrachlorvinphos	1	0	1	0	0	0	0	0	0.3
Toxaphene	1	1	0	0	0	0	0	0	0.8
Terbufos	1	0	1	0	0	0	0	0	0.3
Herbicides									
Alachlor	0	0	0	0	0	0	1	0	0.3
Atrazine	0	0	0	0	0	1	0	0	0.3
Bentazon	0	0	0	0	0	0	0	0	0.1
Butylate	0	0	0	1	0	0	0	0	0.3
Chloramben	0	0	0	0	0	0	0	1	0.3
Cyanazine	0	0	0	0	0	1	0	0	0.3
2,4-D	0	0	0	0	1	0	0	0	0.5
Dicamba	0	0	0	0	0	0	0	1	0.3
EPTC	0	0	0	1	0	0	0	0	0.3
Glyphosate	0	0	0	0	0	0	0	0	0.3
Linuron	0	0	0	0	0	0	0	0	0.5
MCPA	0	0	0	0	1	0	0	0	0.3
Metolachlor	0	0	0	0	0	0	1	0	0.5
Metribuzin	0	0	0	0	0	0	0	0	0.3
Paraquat	0	0	0	0	0	0	0	0	0.5
Propachlor	0	0	0	0	0	0	1	0	0.3
Sodium chlorate	0	0	0	0	0	0	0	0	0.3
2,4,5-T	0	0	0	0	1	0	0	0	0.5
Trifluralin	0	0	0	0	0	0	0	0	0.5

*Carcinogenic probability value is created by combining the classifications from the IARC Monographs Programme on the Evaluation of Carcinogenic Risks to Humans and the US EPA Integrated Risk Information System. Assignment of carcinogenic probability by order of priority: 1.0 = classified as a human carcinogen on either assessment; 0.9 = probable human carcinogen in both assessments; 0.8 = probable human carcinogen in one assessment and possible human carcinogen in other assessment; 0.6 = probable human carcinogen in one assessment and unclassifiable in the other; 0.5 = possible human carcinogen in both assessments, or possible human carcinogen in one assessment and not assessed by the other group; 0.3 = not assessed by IARC or US EPA IRIS, or deemed unclassifiable in one or both assessments; 0.1 = evidence for non-carcinogenicity in either assessment.
†Used the IARC assessment for arsenic and arsenic compounds.

86 pesticides reported in all three of the pooled studies (many of these 86 pesticides were not included in the multivariable analysis of the set of 47 specific pesticides because of their infrequent use). The number of pesticides was coded using indicator variables (1 pesticide, 2–4 pesticides, 5 or more pesticides). Similar analyses were conducted for the number of insecticides and herbicides used. For those pesticides showing positive associations with NHL in the hierarchical regression analysis of 47 specific pesticides (nine pesticides total, see table 3), we conducted a similar analysis of the number of pesticides used, restricted to these "potentially carcinogenic" pesticides. In addition to logistic regression analyses, we evaluated the effect of the number of pesticides used by hierarchical regression with an intercept-only model, in which all pesticide effects (those indicating number of pesticides, as well as the 47 specific pesticides) were assumed to have been sampled from a common prior distribution with an unknown mean and a residual variance of 0.35.

Combined pesticide exposures

We explored the risk associated with combined pesticide exposures, defined as two pesticides used by the same person, but not necessarily at the same time. For any two pesticides for which more than 75 persons reported use of both (representing the 5% most common of all possible combinations of the 47 pesticides), and at least 20 persons reported use of each of the two individual pesticides not in combination, we evaluated potential superadditivity of pesticide effects on NHL (the appendix contains a list of the pesticide combinations evaluated). Individual and joint effects were first estimated

Table 2 Characteristics of subjects in the study population* and those subjects included in analyses of multiple pesticides†

Characteristics	Pooled study			Included in analyses of multiple pesticides		
	Cases (n=870)	Controls (n=2569)	OR (95% CL)‡	Cases (n=650)	Controls (n=1933)	OR (95% CL)
Study site						
Iowa/Minnesota	520 (60.9%)	1039 (40.4%)	1.0	436 (67.1%)	895 (46.3%)	1.0
Kansas	153 (17.6%)	862 (33.6%)	0.3 (0.3 to 0.4)§	101 (15.5%)	596 (30.8%)	0.3 (0.3 to 0.4)
Nebraska	187 (21.5%)	668 (26.0%)	0.5 (0.4 to 0.7)§	113 (17.4%)	442 (22.9%)	0.5 (0.4 to 0.7)
Respondent status						
Self respondent	545 (62.6%)	1413 (55.0%)	1.0	449 (69.1%)	1166 (60.3%)	1.0
Proxy respondent	325 (37.4%)	1156 (45.0%)	0.7 (0.6 to 0.9)§	201 (30.9%)	767 (39.7%)	0.7 (0.6 to 0.8)
Age (years)						
<40	53 (6.1%)	280 (11.0%)	0.7 (0.5 to 1.0)§	40 (6.2%)	211 (10.9%)	0.7 (0.5 to 1.1)
40–59	196 (22.6%)	493 (19.3%)	1.5 (1.1 to 1.9)§	160 (24.6%)	388 (20.1%)	1.6 (1.2 to 2.1)
60–79	478 (55.1%)	1261 (49.4%)	1.4 (1.1 to 1.7)§	355 (54.6%)	969 (50.1%)	1.4 (1.1 to 1.8)
≥80	141 (16.2%)	521 (20.4%)	1.0	95 (14.6%)	365 (18.9%)	1.0
Educational level						
Less than high school graduation	387 (45.2%)	1126 (44.7%)	1.0	276 (43.0%)	806 (42.4%)	1.0
High school graduation or GED¶	226 (26.4%)	629 (25.0%)	1.0 (0.9 to 1.3)	171 (26.6%)	467 (24.6%)	1.1 (0.9 to 1.3)
Some college or vocational school	151 (17.6%)	457 (18.1%)	1.0 (0.8 to 1.2)	122 (19.0%)	368 (19.4%)	1.0 (0.8 to 1.2)
College graduate or more	93 (10.9%)	308 (12.2%)	1.0 (0.7 to 1.1)	73 (11.4%)	261 (13.7%)	0.8 (0.6 to 1.1)
Ever lived or worked on a farm as an adult						
No	243 (28.1%)	780 (30.4%)	1.0	243 (37.5%)	775 (40.1%)	1.0
Yes	621 (71.9%)	1780 (69.5%)	1.1 (0.9 to 1.3)	405 (62.5%)	1157 (59.9%)	1.1 (0.9 to 1.3)
First degree relative with haematopoietic cancer						
No	792 (92.5%)	2452 (96.8%)	1.0	594 (92.8%)	1863 (96.7%)	1.0
Yes	64 (7.5%)	80 (3.2%)	2.5 (1.8 to 3.5)	46 (7.2%)	63 (3.3%)	2.3 (1.5 to 3.4)
Histological subtype						
Follicular	243 (28.0%)			196 (30.1%)		
Diffuse	334 (38.5%)			233 (35.9%)		
Small lymphocytic	99 (11.4%)			77 (11.9%)		
Other	192 (22.1%)			144 (22.2%)		

*Pooled study population limited to males and following exclusions.
†Any observation with a missing value for any of the 47 multiple pesticides was not included in analyses.
‡Odds ratios (OR) and 95% confidence limits (CL).
§Odds ratios for the matching factors are not interpretable for their relation with NHL, but are presented for comparison to odds ratios for the subgroup included in analyses of multiple pesticides.
¶GED, General Equivalency Diploma.

using logistic regression in models including variables for the joint exposure and two individual exposures, the 45 other specific pesticides, age, and study site. Where the OR for the joint effect was 1.3 or higher, positive interaction on the additive scale was evaluated using the interaction contrast ratio ($ICR = OR_{\text{joint exposure}} - OR_{\text{individual exposure \#1}} - OR_{\text{individual exposure \#2}} + 1$).[24] ICR values above 0.5 were considered indicative of superadditivity, and these pesticide combinations were further analysed using hierarchical regression with an intercept-only model, in which all pesticide effects (those indicating joint and individual exposures to the two pesticides, as well as the other 45 specific pesticides) were assumed to have been sampled from a common prior distribution with an unknown mean and a residual variance of 0.35.

RESULTS

Table 2 shows characteristics of men in the pooled studies. In the control population, which was representative of this part of the midwestern United States, approximately 70% of the men had lived or worked on a farm as an adult. There was a 10% increased NHL incidence associated with living or working on a farm as an adult; this increase is similar in magnitude to meta-analyses of farming and NHL mortality and morbidity.[4 25] Cases were slightly more likely than controls to have been directly interviewed, to be between the ages of 40 and 79, and they were more than twice as likely to have a first degree relative with haematopoietic cancer. The subset of subjects included in analyses of multiple pesticides was less likely than those in the overall study population to be from the Kansas or Nebraska studies, to have lived or worked on a farm as an adult, or to have had a proxy respondent, and they were slightly more likely to be more highly educated; however, the relation of these factors with case status did not differ between the overall study and the subset included in the analyses of multiple pesticides.

Use of most specific pesticides was more frequent among cases than controls; however, most of the odds ratios were not increased in the multivariable models (table 3), primarily due to adjustment for study site, since both the frequency of pesticide use and case-to-control ratios differed by study site. The results of the hierarchical regression analysis of 47 pesticides were generally similar to, but had somewhat more narrow confidence intervals than results from the logistic regression model. Only a few pesticides were associated with a possible increased NHL incidence (judged by OR ≥1.3 and lower confidence limit ≥0.8), including the organophosphate (OP) insecticides coumaphos, fonofos, and diazinon, the organochlorine insecticides chlordane and dieldrin, the insecticide copper acetoarsenite, and the herbicides atrazine, glyphosate, and sodium chlorate. There was also a significantly decreased risk associated with aldrin exposure. These suggested effects occurred in both the logistic and hierarchical regression analyses. For pesticides that had wider confidence intervals in the logistic regression model, odds ratios from the hierarchical model were generally closer to the null value, based on a priori assumptions about the probable magnitudes of effect. For example, we assumed that the effect of sodium chlorate would be similar to that of other herbicides and other pesticides for which there was a low carcinogenic probability, and that after accounting for these prior covariates, the rate ratio would likely fall within a 10-fold range around its expected value. Based on these assumptions, a fourfold risk associated with the use of sodium chlorate in the logistic regression analysis was adjusted to a 1.8-fold risk using hierarchical regression. Although unstable estimates were adjusted, results of the

Table 3 Effect estimates for use of specific pesticides and NHL incidence, adjusting for use of other pesticides*

Pesticides	Exposed [n (%)] Cases (n=650)	Controls (n=1933)	Logistic regression OR (95% CL)†	Hierarchical regression OR (95% CL)
Insecticides				
Aldrin	47 (7.2%)	115 (5.9%)	0.5 (0.3 to 0.9)	0.6 (0.4 to 1.0)
Bufencarb‡	6 (0.9%)	12 (0.6%)	1.1 (0.3 to 3.7)	1.0 (0.4 to 2.3)
Carbaryl	30 (4.6%)	57 (2.9%)	1.0 (0.5 to 1.9)	1.1 (0.6 to 1.9)
Carbofuran	41 (6.3%)	96 (5.0%)	0.9 (0.5 to 1.6)	1.0 (0.6 to 1.7)
Chlordane	39 (6.0%)	65 (3.4%)	1.5 (0.8 to 2.6)	1.3 (0.8 to 2.1)
Copper acetoarsenite	41 (6.3%)	68 (3.5%)	1.4 (0.9 to 2.3)	1.4 (0.9 to 2.1)
Coumaphos	15 (2.3%)	22 (1.1%)	2.4 (1.0 to 5.8)	1.7 (0.9 to 3.3)
DDT	98 (15.1%)	226 (11.7%)	1.0 (0.7 to 1.3)	1.0 (0.7 to 1.3)
Diazinon	40 (6.1%)	62 (3.2%)	1.9 (1.1 to 3.6)	1.7 (1.0 to 2.8)
Dichlorvos	16 (2.5%)	37 (1.9%)	0.9 (0.4 to 2.0)	0.9 (0.5 to 1.7)
Dieldrin	21 (3.2%)	39 (2.0%)	1.8 (0.8 to 3.9)	1.4 (0.8 to 2.6)
Dimethoate‡	5 (0.8%)	11 (0.6%)	1.2 (0.3 to 5.3)	1.2 (0.5 to 2.8)
Ethoprop‡	4 (0.6%)	14 (0.7%)	0.7 (0.2 to 2.9)	0.9 (0.4 to 2.1)
Famphur	12 (1.8%)	34 (1.8%)	0.7 (0.3 to 1.7)	0.8 (0.4 to 1.5)
Fly, lice, or tick spray	162 (24.9%)	408 (21.1%)	0.9 (0.7 to 1.1)	0.9 (0.7 to 1.1)
Fonofos	28 (4.3%)	44 (2.3%)	1.8 (0.9 to 3.5)	1.5 (0.9 to 2.7)
Heptachlor	28 (4.3%)	53 (2.7%)	1.1 (0.6 to 2.4)	1.1 (0.6 to 2.0)
Lead arsenate	9 (1.4%)	25 (1.3%)	0.5 (0.2 to 1.2)	0.6 (0.3 to 1.3)
Lindane	59 (9.1%)	109 (5.6%)	1.2 (0.7 to 2.0)	1.2 (0.8 to 1.9)
Malathion	53 (8.1%)	100 (5.2%)	1.1 (0.6 to 1.8)	1.1 (0.7 to 1.7)
Methoxychlor	9 (1.4%)	20 (1.0%)	0.8 (0.3 to 2.1)	0.9 (0.4 to 1.9)
Nicotine	24 (3.7%)	50 (2.6%)	0.9 (0.5 to 1.6)	1.0 (0.6 to 1.6)
Phorate	28 (4.3%)	67 (3.5%)	0.8 (0.4 to 1.6)	0.9 (0.5 to 1.5)
Pyrethrins‡	6 (0.9%)	12 (0.6%)	1.0 (0.3 to 3.2)	1.0 (0.4 to 2.3)
Rotenone	10 (1.5%)	26 (1.4%)	0.7 (0.3 to 1.7)	0.8 (0.4 to 1.5)
Tetrachlorvinphos‡	3 (0.5%)	11 (0.6%)	0.4 (0.1 to 1.8)	0.8 (0.3 to 1.9)
Toxaphene	17 (2.6%)	34 (1.8%)	1.1 (0.5 to 2.4)	1.1 (0.6 to 2.0)
Terbufos	21 (3.2%)	50 (2.6%)	0.8 (0.4 to 1.8)	0.8 (0.5 to 1.6)
Herbicides				
Alachlor	68 (10.5%)	152 (7.9%)	1.1 (0.7 to 1.8)	1.0 (0.6 to 1.6)
Atrazine	90 (13.8%)	185 (9.6%)	1.6 (1.1 to 2.5)	1.5 (1.0 to 2.2)
Bentazon	22 (3.4%)	58 (3.0%)	0.7 (0.3 to 1.5)	0.8 (0.4 to 1.4)
Butylate	28 (4.3%)	56 (2.9%)	1.2 (0.6 to 2.3)	1.2 (0.7 to 2.0)
Chloramben	34 (5.2%)	81 (4.2%)	0.9 (0.5 to 1.6)	0.9 (0.5 to 1.5)
Cyanazine	37 (5.7%)	96 (5.0%)	0.6 (0.3 to 1.0)	0.6 (0.4 to 1.1)
2,4-D	123 (18.9%)	314 (16.2%)	0.8 (0.6 to 1.1)	0.9 (0.6 to 1.2)
Dicamba	39 (6.0%)	79 (4.1%)	1.2 (0.6 to 2.3)	1.2 (0.7 to 2.1)
EPTC + protectant	13 (2.0%)	29 (1.5%)	1.2 (0.5 to 3.1)	1.1 (0.5 to 2.3)
Glyphosate	36 (5.5%)	61 (3.2%)	2.1 (1.1 to 4.0)	1.6 (0.9 to 2.8)
Linuron	5 (0.8%)	22 (1.1%)	0.3 (0.1 to 1.2)	0.5 (0.2 to 1.2)
MCPA	8 (1.2%)	16 (0.8%)	1.0 (0.4 to 2.6)	0.9 (0.4 to 2.0)
Metolachlor	13 (2.0%)	37 (1.9%)	0.7 (0.3 to 1.6)	0.7 (0.4 to 1.5)
Metribuzen	20 (3.1%)	53 (2.7%)	0.8 (0.4 to 1.7)	0.8 (0.4 to 1.5)
Paraquat‡	2 (0.3%)	15 (0.8%)	0.1 (0.02 to 0.7)	0.5 (0.2 to 1.2)
Propachlor	20 (3.1%)	50 (2.6%)	1.0 (0.5 to 2.0)	1.0 (0.6 to 1.9)
Sodium chlorate‡	8 (1.2%)	7 (0.4%)	4.1 (1.3 to 13.6)	1.8 (0.8 to 4.1)
2,4,5-T	25 (3.9%)	63 (3.3%)	1.0 (0.5 to 1.9)	0.9 (0.5 to 1.6)
Trifluralin	52 (8.0%)	120 (6.2%)	0.9 (0.5 to 1.6)	0.9 (0.5 to 1.4)

*Each estimate is adjusted for use of all other pesticides listed in table 3, age, and study site.
†Odds ratios (OR) and 95% confidence limits (CL).
‡Criteria for inclusion in the models was a pesticide use frequency of ≥20; however, some pesticide use frequencies are <20 in the multivariable models since observations with missing values were dropped.

hierarchical model including prior covariates and those from the hierarchical intercept-only model were virtually identical (results for intercept-only model not shown), indicating that the prior covariates representing pesticide category and carcinogenic probability were not important determinants of the variability between the observed effects, and that adjustment of estimates primarily occurred because of the a priori restriction on their variance. Indeed, a linear regression analysis of the 47 logistic regression beta coefficients for the pesticides regressed on the prior covariates found no statistically significant associations (at a significance level of $p < 0.05$; results not shown).

Among the farmers who used pesticides, the number of total pesticides ever used ranged between 1 and 32, but approximately 50% of farmers reported using only one or two pesticides. There was no association between NHL incidence and either the total number of pesticides or herbicides used (see table 4). There was a 40% increased incidence associated with the use of five or more insecticides; however, there was no apparent exposure-response trend. In an analysis of the number of "potentially carcinogenic" pesticides, NHL incidence increased by the number of pesticides used by the subject. Subjects who reported using any five or more "potentially carcinogenic" pesticides were twice as likely to be NHL cases than controls, compared to those using no pesticides. The results for "potentially carcinogenic" pesticides were highly sensitive to removal of certain pesticides from the count, including dieldrin, atrazine, or glyphosate. For example, removal of glyphosate from the count resulted in a lack of trend for increasing number of "potentially carcinogenic" pesticides (1 pesticide: OR = 1.2; 2–4 pesticides: OR = 1.2; ≥5 pesticides: OR = 1.1).

Table 4 Effect of number of pesticides used on NHL incidence*

Number of pesticides used	Exposed [n (%)] Cases (n=650)	Controls (n=1933)	Logistic regression OR (95% CL)†	Hierarchical regression OR (95% CL)
Any pesticide				
0	370	1252	1.0	1.0
1	89 (13.7%)	230 (11.9%)	1.2 (0.8 to 1.8)	1.1 (0.9 to 1.7)
2–4	87 (13.4%)	221 (11.4%)	1.0 (0.6 to 1.6)	1.0 (0.7 to 1.5)
≥5	104 (16.0%)	230 (11.9%)	0.8 (0.4 to 1.9)	1.0 (0.5 to 1.8)
Any insecticide				
0	382	1292	1.0	1.0
1	114 (17.5%)	281 (14.5%)	1.3 (0.9 to 1.9)	1.2 (0.9 to 1.7)
2–4	86 (13.2%)	237 (12.3%)	1.0 (0.5 to 1.8)	0.9 (0.6 to 1.4)
≥5	68 (10.5%)	123 (6.4%)	1.9 (0.6 to 5.7)	1.4 (0.7 to 2.9)
Any herbicide				
0	489	1544	1.0	1.0
1	50 (7.7%)	132 (6.8%)	1.0 (0.6 to 1.9)	1.1 (0.7 to 1.7)
2–4	52 (8.0%)	132 (6.8%)	0.8 (0.4 to 1.9)	1.0 (0.6 to 1.6)
≥5	59 (9.1%)	125 (6.5%)	0.8 (0.2 to 3.3)	1.0 (0.5 to 2.2)
"Potentially carcinogenic" pesticides				
0	496	1632	1.0	1.0
1	74 (11.4%)	168 (8.7%)	1.6 (0.8 to 3.1)	1.1 (0.8 to 1.7)
2–4	68 (10.5%)	123 (6.4%)	2.7 (0.7 to 10.8)	1.3 (0.7 to 2.3)
≥5	12 (1.8%)	10 (0.5%)	25.9 (1.5 to 450.2)	2.0 (0.8 to 5.2)

*Each estimate is adjusted for use of all pesticides listed in table 3, age, and study site.
†Odds ratios (OR) and 95% confidence limits (CL).

The analysis of 48 pesticide combinations in relation to NHL incidence revealed few joint effects of 1.3 or higher that were indicative of superadditivity (table 5). Combined exposures to carbofuran and atrazine, diazinon and atrazine, and alachlor and atrazine had estimated joint effects that were more than additive (ICR ≥0.5), even following shrinkage in hierarchical regression analyses. Other joint pesticide effects which seemed indicative of superadditivity in results from logistic regression analyses, such as that for atrazine and dicamba, were probably misleading due to imprecision of estimates; these results did not hold up following shrinkage in hierarchical regression analyses, according to our prior distribution of complete exchangeability.

DISCUSSION

Incidence and mortality rates for NHL have been generally increasing in the United States and in most industrialised countries for several decades, with an 85–100% increase in

Table 5 Estimated individual and joint effects of pesticide combinations on NHL incidence*†

Individual and joint pesticide exposures	Exposed [n (%)] Cases (n=650)	Controls (n=1933)	Logistic regression OR (95% CL)‡	Hierarchical regression OR (95% CL)
Chlordane and DDT				
Neither	543	1687	1.0	1.0
Chlordane only	9 (1.4%)	20 (1.0%)	1.1 (0.4 to 2.7)	1.0 (0.5 to 1.9)
DDT only	68 (10.5%)	181 (9.4%)	0.9 (0.6 to 1.3)	0.9 (0.6 to 1.2)
Both	30 (4.6%)	45 (2.3%)	1.7 (0.7 to 3.2)	1.3 (0.8 to 2.3)
Carbofuran and atrazine				
Neither	557	1728	1.0	1.0
Carbofuran only	3 (0.5%)	20 (1.0%)	0.2 (0.1 to 1.1)	0.6 (0.3 to 1.3)
Atrazine only	52 (8.0%)	109 (5.6%)	1.4 (0.9 to 2.2)	1.3 (0.9 to 1.9)
Both	38 (5.9%)	76 (3.9%)	1.6 (0.8 to 3.3)	1.5 (0.9 to 2.7)
Diazinon and atrazine				
Neither	551	1730	1.0	1.0
Diazinon only	9 (1.4%)	18 (0.9%)	1.2 (0.5 to 3.1)	1.1 (0.5 to 2.3)
Atrazine only	59 (9.1%)	141 (7.3%)	1.5 (1.0 to 2.3)	1.3 (0.9 to 1.9)
Both	31 (4.8%)	44 (2.3%)	3.9 (1.7 to 8.8)	2.3 (1.2 to 4.2)
Alachlor and atrazine				
Neither	545	1695	1.0	1.0
Alachlor only	15 (2.3%)	53 (2.7%)	0.7 (0.3 to 1.3)	0.7 (0.4 to 1.3)
Atrazine only	37 (5.7%)	86 (4.5%)	1.3 (0.8 to 2.1)	1.2 (0.8 to 1.8)
Both	53 (8.2%)	99 (5.1%)	2.1 (1.1 to 3.9)	1.6 (1.0 to 2.7)
Atrazine and dicamba				
Neither	552	1729	1.0	1.0
Atrazine only	59 (9.1%)	125 (6.5%)	1.5 (1.0 to 2.4)	1.4 (0.9 to 2.0)
Dicamba only	8 (1.2%)	19 (1.0%)	0.9 (0.3 to 2.6)	1.0 (0.5 to 2.0)
Both	31 (4.8%)	60 (3.1%)	2.1 (1.0 to 4.7)	1.6 (0.9 to 2.9)

*Effects of combined pesticide exposures were estimated in models including terms for the joint exposure, two individual exposures, the use of each other pesticide listed in table 2, age, and study site.
†Pesticide combinations considered are listed in the appendix.
‡Odds ratios (OR) and 95% confidence limits (CL).

mortality among whites and non-whites from the late 1940s to the late 1980s,[26] a time period relevant for this study. This increase may be partially attributed to improved diagnosis and in later years to AIDS related lymphomas, but cannot be completely explained by these factors.[27] Environmental factors such as pesticides could play a role in this persistent increase, since their use became more widespread during this time period.[28–30] Several aetiological mechanisms of pesticides in relation to NHL have been proposed, including genotoxicity and immunotoxicity,[31 32] increased cell proliferation,[33] and chromosomal aberrations.[34] In our analysis of multiple pesticides in farming, we found only a small number of the pesticides to be risk factors for NHL, with the highest increased risks among subjects exposed to five or more of these "potentially carcinogenic" pesticides, or those with certain combined pesticide exposures.

The large number of exposed subjects in this pooled analysis allowed adjustment for the use of other pesticides, and hierarchical regression modelling resulted in estimates that were in some instances more stable than those from logistic regression models. However, the effect estimates from the logistic and hierarchical analyses were quite similar overall, with a few standout exceptions. The hierarchical results are more conservative than those from the logistic regressions, given the uninformed nature of the prior distributions we specified, particularly in analyses of the number of pesticides used and combined pesticide exposures. For example, in the hierarchical regression analysis of the number of pesticides used, we assumed that the use of any five or more pesticides was no more likely to be associated with NHL than use of any one pesticide. A less conservative prior distribution could have been specified in which a higher probability would be placed on a positive association for the greater number of pesticides used. However, the uninformed nature of these priors seemed appropriate in a largely exploratory analysis of multiple exposures for which there is little prior knowledge about how pesticide exposures interact in relation to the risk of NHL. Both analyses showed increasing odds ratios with the number of "potentially carcinogenic" pesticides used, but the relative risks in the upper category were substantially different—25.9 for the logistic regression and 2.0 for the hierarchical analysis—probably indicating inappropriate use of logistic regression for these sparse data.

Adjustment for multiple pesticides suggested that there were few instances of substantial confounding of pesticide effects by other pesticides. Nevertheless, some previous findings in our data appear to be due to confounding by correlated pesticide exposures. In particular, a previously reported positive association for carbaryl[13] was not replicated in the adjusted analyses. Further analysis here revealed that carbaryl and diazinon use were highly associated ($p < 0.001$), and previously reported associations of different carbaryl measures with NHL were eliminated by adjustment for diazinon, including carbaryl use, personal handling of carbaryl, and use longer than 10 years. In the previous analysis, estimates were adjusted for groups of pesticides, including a group for organophosphate insecticides,[13] but adjustment for specific pesticides here gave different results. Similarly, previous observations of increased NHL risk associated with use of the OP insecticides dimethoate and tetrachlorvinphos[12] were negligible on inclusion of other OP insecticides in the model. These findings underscore the importance of considering correlated pesticide exposures.

Our observation of increased risk associated with the use of certain OP insecticides, including coumaphos, diazinon, and fonofos, is consistent with previous analyses of the pooled data,[12 20] and also corroborates findings of other studies.[8 34] OP insecticides are known to cause cytogenetic damage, and could thereby contribute to NHL aetiology.[35] There are data from in vitro, animal, and human studies that show effects of several OP insecticides on the immune system,[36–40] indicating another potential mechanism. OP compounds may impair immune function through pathways involving cholinergic stimulation,[41] or inhibition of serine esterases found in monocytes, natural killer cells, and cytotoxic T lymphocytes,[42] but it is unknown whether such immune effects might be chemical specific or related to general OP toxicity. Our data do not indicate an aetiological mechanism for NHL common to all OP insecticides, since increased NHL incidence was associated only with certain OPs evaluated.

We observed a possible effect of the organochlorine insecticides chlordane and dieldrin. There is some evidence that chlordane is immunotoxic, causing decreased lymphocyte function in vitro.[43] The concentration of chlordane in adipose tissue was higher among NHL cases than controls in a small case-control study in Sweden,[44] but a larger study in the United States found no such association.[45] Although these chemicals have been banned in the United States, their continued use in some developing countries, and bioaccumulation of their chemical residues in the food chain,[46] justify further research on health effects.

Use of the herbicide atrazine was associated with increased risk of NHL. Increased risk was observed in each of the three pooled studies separately, but a previous analysis of the Nebraska study data found that the risk was diminished on adjustment for use of OP insecticides and 2,4-D.[20] There have been few other epidemiological studies of atrazine in relation to NHL. In a cohort of triazine herbicide manufacturing workers, there was an excess number of deaths from NHL ($n = 3$) among a group of men with definite or probable exposure; however, some of the cases worked in triazine related jobs for short time periods, thus clouding interpretation.[47] A recent NHL study where cases were further distinguished by presence or absence of the t(14;18) chromosomal translocation found that the risk of NHL associated with atrazine use was solely observed among t(14;18) positive cases, suggesting a cytogenetic mechanism.[14] However, there is only very limited evidence for genotoxicity of atrazine, although there are no studies in humans.[48] A small number of studies of atrazine on immune function in rodents and in vitro suggest a decreased lymphocyte count and cytokine production following exposure; however, these effects were not always dose dependent or statistically significant.[37 48 49] In our data, there was an indication of superadditive effects of atrazine in combination with carbofuran, diazinon, or alachlor. This is a factor to consider in future studies of this widely used pesticide.

Glyphosate, commercially sold as Roundup, is a commonly used herbicide in the United States, both on crops and on non-cropland areas.[50] An association of glyphosate with NHL was observed in another case-control study, but the estimate was based on only four exposed cases.[51] A recent study across a large region of Canada found an increased risk of NHL associated with glyphosate use that increased by the number of days used per year.[8] These few suggestive findings provide some impetus for further investigation into the potential health effects of glyphosate, even though one review concluded that the active ingredient is non-carcinogenic and non-genotoxic.[50]

Much attention in NHL research has focused on the herbicide 2,4-D as a potential risk factor, and several studies have observed positive associations with 2,4-D exposure.[6 8 9] Whereas an indicated effect of 2,4-D exposure on NHL was reported in NCI's Nebraska and Kansas studies,[5 7] this analysis of the pooled data found no association with having ever used 2,4-D. The null association does not result from adjustment for other pesticides, missing data, or from the hierarchical regression modelling approach, but is rather due to pooling data from the Iowa and Minnesota study, in which no association of 2,4-D with NHL incidence was observed, with data from the Nebraska and Kansas studies. The literature on the relation between 2,4-D and NHL is not consistent.[32 52] Some recent studies have reported excess risk among

manufacturers[53] and farmers,[8] while others have not.[51] The study in Nebraska,[5] however, observed that NHL risk increased by number of days per year of 2,4-D use, which we were unable to duplicate in the pooled analysis because of lack of such data from the other two studies. It is possible that a more refined metric incorporating frequency of use better captures relevant exposure. Some recent studies may shed light on potential mechanisms of 2,4-D in relation to NHL. A study of 10 farmers who applied 2,4-D and MCPA observed a significant reduction of several immune parameters, including CD4, CD8, natural killer cells, and activated CD8 cells (expressing the surface antigen HLA-DR), and a reduction in lymphoproliferative response.[54] Furthermore, a study of professional 2,4-D applicators in Kansas observed an increase in the lymphocyte replication index following application.[33]

This pooled study of multiple agricultural pesticides provided an opportunity to estimate the effect of each specific pesticide and certain pesticide combinations on NHL incidence, adjusted for the use of other pesticides. Overall, few pesticides and pesticide combinations were associated with increased NHL risk; this has several implications. First, it is consistent with results from bioassays where only a few of the pesticides tested have caused cancer in laboratory animals.[55] Although epidemiological data on cancer risks from exposure to specific pesticides are scant, it also suggests that while some pesticides may present a cancer risk to humans, many, maybe even most, pesticides do not. Second, the fact that there were few associations suggests that the positive results we observed are not likely to be due to a systematic recall bias for pesticide exposures, or selection bias for the subgroup included in the analyses of multiple pesticides. Third, although some of the positive results could be due to chance, the hierarchical regression analysis placed some restriction on the variance of estimates, theoretically decreasing the chances of obtaining false positive results. On the other hand, it is possible that the assumptions for the hierarchical regression are too restrictive and that this has increased the number of false negatives.

Certain limitations of our data hinder the inferences we can make regarding specific pesticides in their association with NHL. Our exposure metric of having ever used a pesticide is rather crude, offering no distinctions based on use by the number of years or the number of days per year. Further exploration of observed associations by more refined exposure metrics is warranted. In addition, this analysis provides no information on the timing of pesticide use in relation to disease onset or in conjunction with the timing of other pesticides used. This has particular relevance in our analysis of "combined pesticide exposures", in which two pesticides may or may not have been used at the same time or even during the same year. Lastly, if a study subject had a missing value for any one of the 47 pesticides evaluated, that person was excluded from analyses, resulting in analyses on a limited subset (about 75%) of the pooled study population. Although we have no way to evaluate potential bias due to missing data, some assurances are provided by the fact that cases and controls were equally likely to be included in analyses, and that there were similarities between the entire group of study subjects and subjects included our analyses, in terms of NHL status in relation to demographic factors (table 2). If simultaneous analysis of multiple exposures is to become standard, statistical techniques to impute values for subjects with "don't know" or missing responses should be further developed in order to prevent biased results.

Despite limitations of our study, certain inferences are possible. Our results indicate increased NHL incidence by number of pesticides used, only for the subgroup of "potentially carcinogenic" pesticides, suggesting that specific chemicals, not pesticides, insecticides, or herbicides, as groups, should be examined as potential risk factors for NHL. In addition, argument against an analysis approach focused on classes or groups of pesticides is provided by the fact that our prior covariates of pesticide classes and groups in the hierarchical regression model were not important predictors of the magnitude of observed pesticide effects. A chemical specific approach to evaluating pesticides as risk factors for NHL should facilitate interpretation of epidemiological studies for regulatory purposes. However, the importance of additionally considering multiple correlated exposures is clear.

APPENDIX

Table A1 shows the pesticide combinations considered in analyses of joint and individual exposures.

Table A1 Pesticide combinations considered in analyses of joint and individual exposures

Insecticides	Insecticide and herbicide	Herbicides
DDT and chlordane	Aldrin and alachlor	Alachlor and atrazine
DDT and lindane	Aldrin and atrazine	Alachlor and chloramben
DDT and malathion	Aldrin and 2,4-D	Alachlor and cyanazine
DDT and fly, lice, or tick spray	Aldrin and trifluralin	Alachlor and 2,4-D
DDT and aldrin	Carbofuran and alachlor	Alachlor and dicamba
Lindane and malathion	Carbofuran and atrazine	Alachlor and glyphosate
Lindane and aldrin	Carbofuran and 2,4-D	Alachlor and trifluralin
Malathion and aldrin	Chlordane and 2,4-D	Atrazine and cyanazine
	DDT and alachlor	Atrazine and 2,4-D
	DDT and atrazine	Atrazine and dicamba
	DDT and 2,4-D	Atrazine and glyphosate
	DDT and trifluralin	Atrazine and trifluralin
	Diazinon and atrazine	Chloramben and trifluralin
	Fly, lice, or tick spray and alachlor	Cyanazine and 2,4-D
	Fly, lice, or tick spray and atrazine	Cyanazine and trifluralin
	Fly, lice, or tick spray and 2,4-D	2,4-D and trifluralin
	Fly, lice, or tick spray and trifluralin	
	Lindane and alachlor	
	Lindane and atrazine	
	Lindane and 2,4-D	
	Lindane and trifluralin	
	Malathion and alachlor	
	Malathion and atrazine	
	Malathion and 2,4-D	

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REFERENCES

1 **Blair A**, Dosemeci M, Heineman EF. Cancer and other causes of death among male and female farmers from twenty-three states. *Am J Ind Med* 1993;**23**:729–42.
2 **Blair A**, Zahm SH. Agricultural exposures and cancer. *Environ Health Perspect* 1995;**103**(suppl 8):205–8.
3 **Keller-Byrne JE**, Khuder SA, Schaub EA, *et al*. A meta-analysis of non-Hodgkin's lymphoma among farmers in the central United States. *Am J Ind Med* 1997;**31**:442–4.
4 **Khuder SA**, Schaub EA, Keller-Byrne JE. Meta-analyses of non-Hodgkin's lymphoma and farming. *Scand J Work Environ Health* 1998;**24**:255–61.
5 **Zahm SH**, Weisenburger DD, Babbitt PA, *et al*. A case-control study of non-Hodgkin's lymphoma and the herbicide 2,4-dichlorophenoxyacetic acid (2,4-D) in eastern Nebraska. *Epidemiology* 1990;1:349–56.
6 **Hardell L**, Eriksson M, Lenner P, *et al*. Malignant lymphoma and exposure to chemicals, especially organic solvents, chlorophenols and phenoxy acids: a case-control study. *Br J Cancer* 1981;**43**:169–76.
7 **Hoar SK**, Blair A, Holmes FF, *et al*. Agricultural herbicide use and risk of lymphoma and soft-tissue sarcoma. *JAMA*,1986;**256**:1141–7.
8 **McDuffie HH**, Pahwa P, McLaughlin JR, *et al*. Non-Hodgkin's lymphoma and specific pesticide exposures in men: cross-Canada study of pesticides and health. *Cancer Epidemiol Biomarkers Prev* 2001;**10**:1155–63.
9 **Woods JS**, Polissar L, Severson RK, *et al*. Soft tissue sarcoma and non-Hodgkin's lymphoma in relation to phenoxyherbicide and chlorinated phenol exposure in western Washington. *J Natl Cancer Inst* 1987;**78**:899–910.
10 **Wigle DT**, Semenciw RM, Wilkins K, *et al*. Mortality study of Canadian male farm operators: non-Hodgkin's lymphoma mortality and agricultural practices in Saskatchewan. *J Natl Cancer Inst* 1990;**82**:575–82.
11 **Cantor KP**, Blair A, Everett G, *et al*. Pesticides and other agricultural risk factors for non-Hodgkin's lymphoma among men in Iowa and Minnesota. *Cancer Res* 1992;**52**:2447–55.
12 **Waddell BL**, Zahm SH, Baris D, *et al*. Agricultural use of organophosphate pesticides and the risk of non-Hodgkin's lymphoma among male farmers (United States). *Cancer Causes Control* 2001;**12**:509–17.
13 **Zheng T**, Zahm SH, Cantor KP, *et al*. Agricultural exposure to carbamate pesticides and risk of non-Hodgkin lymphoma. *J Occup Environ Med* 2001;**43**:641–9.
14 **Schroeder JC**, Olshan AF, Baric R, *et al*. Agricultural risk factors for t(14;18) subtypes of non-Hodgkin's lymphoma. *Epidemiology* 2001;**12**:701–9.
15 **Greenland S**. Hierarchical regression for epidemiologic analyses of multiple exposures. *Environ Health Perspect* 1994;**102**(suppl 8):33–9.
16 **Witte JS**, Greenland S, Haile RW, *et al*. Hierarchical regression analysis applied to a study of multiple dietary exposures and breast cancer. *Epidemiology* 1994;**5**:612–21.
17 **Steenland K**, Bray I, Greenland S, *et al*. Empirical Bayes adjustments for multiple results in hypothesis-generating or surveillance studies. *Cancer Epidemiol Biomarkers Prev* 2000;**9**:895–903.
18 **Baris D**, Zahm SH, Cantor KP, et al. Agricultural use of DDT and risk of non-Hodgkin's lymphoma: pooled analysis of three case-control studies in the United States. *Occup Environ Med* 1998;**55**:522–7.
19 **Blair A**, Cantor KP, Zahm SH. Non-Hodgkin's lymphoma and agricultural use of the insecticide lindane. *Am J Ind Med* 1998;**33**:82–7.
20 **Hoar Zahm SK**, Weisenburger DD, Cantor KP, *et al*. Role of the herbicide atrazine in the development of non-Hodgkin's lymphoma. *Scand J Work Environ Health* 1993;**19**:108–14.
21 **Greenland S**. Introduction to regression models. In: Rothman K, Greenland S, eds. *Modern epidemiology*. Philadelphia: Lippincott-Raven Publishers, 1998:359–99.
22 **Greenland S**. Principles of multilevel modelling. *Int J Epidemiol* 2000;**29**:158–67.
23 **Witte JS**, Greenland S, Kim LL, *et al*. Multilevel modeling in epidemiology with GLIMMIX. *Epidemiology* 2000;**11**:684–8.
24 **Greenland S**, Rothman KJ. Concepts of interaction. In: Rothman K, Greenland S, eds. *Modern epidemiology*. Philadelphia: Lippincott-Raven Publishers, 1998:329–42.
25 **Blair A**, Zahm SH, Pearce NE, *et al*. Clues to cancer etiology from studies of farmers. *Scand J Work Environ Health* 1992;**18**:209–15.
26 **Devesa SS**, Fears T. Non-Hodgkin's lymphoma time trends: United States and international data. *Cancer Res* 1992;**52**:5432s–40s.
27 **Hartge P**, Devesa SS. Quantification of the impact of known risk factors on time trends in non-Hodgkin's lymphoma incidence. *Cancer Res* 1992;**52**:5566s–9s.
28 **Palackdharry CS**. The epidemiology of non-Hodgkin's lymphoma: why the increased incidence? *Oncology (Huntingt)* 1994;**8**:67–73.
29 **Rabkin CS**, Devesa SS, Zahm SH, *et al*. Increasing incidence of non-Hodgkin's lymphoma. *Semin Hematol* 1993;**30**:286–96.
30 **Wilkinson CF**. Introduction and overview. In: Baker SR, Wilkinson CF, eds. *The effect of pesticides on human health*. Princeton, NJ: Princeton Scientific Publishing Co. Inc., 1990:5–33.
31 **Zahm SH**, Blair A. Pesticides and non-Hodgkin's lymphoma. *Cancer Res* 1992;**52**:5485s–8s.
32 **Zahm SH**, Ward MH, Blair A. Pesticides and cancer. *Occup Med* 1997;**12**:269–89.
33 **Figgs LW**, Holland NT, Rothmann N, *et al*. Increased lymphocyte replicative index following 2,4-dichlorophenoxyacetic acid herbicide exposure. *Cancer Causes Control* 2000;**11**:373–80.
34 **Nanni O**, Amadori D, Lugaresi C, *et al*. Chronic lymphocytic leukaemias and non-Hodgkin's lymphomas by histological type in farming-animal breeding workers: a population case- control study based on a priori exposure matrices. *Occup Environ Med* 1996;**53**:652–7.
35 **Lieberman AD**, Craven MR, Lewis HA, *et al*. Genotoxicity from domestic use of organophosphate pesticides. *J Occup Environ Med* 1998;**40**:954–7.
36 **Vial T**, Nicolas B, Descotes J. Clinical immunotoxicity of pesticides. *J Toxicol Environ Health* 1996;**48**:215–29.
37 **Vos JG**, Krajnc EI. Immunotoxicity of pesticides. *Dev Toxicol Environ Sci* 1983;**11**:229–40.
38 **Esa AH**, Warr GA, Newcombe DS. Immunotoxicity of organophosphorus compounds. Modulation of cell-mediated immune responses by inhibition of monocyte accessory functions. *Clin Immunol Immunopathol* 1988;**49**:41–52.
39 **Lee TP**, Moscati R, Park BH. Effects of pesticides on human leukocyte functions. *Res Commun Chem Pathol Pharmacol* 1979;**23**:597–609.
40 **Hermanowicz A**, Kossmon S. Neutrophil function and infectious disease in workers occupationally exposed to phosphoorganic pesticides: role of mononuclear-derived chemotactic factor for neutrophils. *Clin Immunol Immunopathol* 1984;**33**:13–22.
41 **Casale GP**, Cohen SD, DiCapua RA. The effects of organophosphate-induced cholinergic stimulation on the antibody response to sheep erythrocytes in inbred mice. *Toxicol Appl Pharmacol* 1983;**68**:198–205.
42 **Newcombe DS**. Immune surveillance, organophosphorus exposure, and lymphomagenesis. *Lancet* 1992;**339**:539–41.
43 **McConnachie PR**, Zaholsky AC. Immune alterations in humans exposed to the termiticide technical chlordane. *Arch Environ Health* 1992;**47**:295–301.
44 **Hardell L**, Liljegren G, Lindstrom G, *et al*. Polychlorinated biphenyls, chlordanes, and the etiology of non-Hodgkin's lymphoma. *Epidemiology* 1997;**8**:689.
45 **Cantor KP**, Strickland PT, Brock JW, *et al*. Risk of Non-Hodgkin's lymphoma and prediagnostic serum organochlorines: ss-hexachlorocyclohexane, chlordane/heptachlor-related compounds, dieldrin and hexochlorobenzene. *Environ Health Perspect* 2003;**111**:179–84.
46 **Nigg HNWCF**, Beier RC, Carter O, *et al*. Exposure to pesticides. In: Baker SR, Wilkinson CF, eds. *The effect of pesticides on human health*. Princeton, NJ: Princeton Scientific Publishing Co. Inc., 1990:35–130.
47 **Sathiakumar N**, Delzell E, Cole P. Mortality among workers at two triazine herbicide manufacturing plants. *Am J Ind Med* 1996;**29**:143–51.
48 **IARC**. Atrazine . *IARC Monogr Eval Carcinog Risks Hum* 1999;**73**:59–113.
49 **Hooghe RJ**, Devos S, Hooghe-Peters EL. Effects of selected herbicides on cytokine production in vitro. *Life Sci* 2000;**66**:2519–25.
50 **Williams GM**, Kroes R, Munro IC. Safety evaluation and risk assessment of the herbicide Roundup and its active ingredient, glyphosate, for humans. *Regul Toxicol Pharmacol* 2000;**31**:117–65.
51 **Hardell L**, Eriksson M. A case-control study of non-Hodgkin lymphoma and exposure to pesticides. *Cancer* 1999;**85**:1353–60.
52 **Dich J**, Zahm SH, Hanberg A, *et al*. Pesticides and cancer. *Cancer Causes Control* 1997;**8**:420–43.
53 **Burns CJ**, Beard KK, Cartmill JB. Mortality in chemical workers potentially exposed to 2,4- dichlorophenoxyacetic acid (2,4-D) 1945–94: an update. *Occup Environ Med* 2001;**58**:24–30.
54 **Faustini A**, Settimi L, Pacifici R, *et al*. Immunological changes among farmers exposed to phenoxy herbicides: preliminary observations. *Occup Environ Med* 1996;**53**:583–5.
55 **Blair A**, Axelson O, Franklin C, *et al*. Carcinogenic effects of pesticides. In: Baker SR, Wilkinson CF, eds. *The effect of pesticides on human health*. Princeton, NJ: Princeton Scientific Publishing Co. Inc., 1990:201–60.

A Case-Control Study of Non-Hodgkin's Lymphoma and the Herbicide 2,4-Dichlorophenoxyacetic Acid (2,4-D) in Eastern Nebraska

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To evaluate the role of the herbicide 2,4-dichlorophenoxyacetic acid (2,4-D) in the development of non-Hodgkin's lymphoma (NHL), we conducted a population-based, case-control study in 66 counties in eastern Nebraska. Telephone interviews were conducted with 201 white men diagnosed with NHL between July 1, 1983, and June 30, 1986, and with 725 controls. There was a 50% excess of NHL among men who mixed or applied 2,4-D (odds ratio [OR] = 1.5; 95% confidence interval = 0.9, 2.5). The risk of NHL increased with the average frequency of use to over threefold for those exposed 20 or more days per year (p for trend = 0.051). Adjusting for use of organophosphate insecticides lowered the risk estimate for frequent users (OR = 1.8), but adjustment for fungicide use increased the risk estimate (OR = 4.5). Simultaneous adjustment for organophosphates and fungicides yielded an OR of 3.1 for farmers who mixed or applied 2,4-D more than 20 days per year. Risk also increased with degree of exposure, as indicated by application method and time spent in contaminated clothing, but not with the number of years of 2,4-D use or failure to use protective equipment. Although other pesticides, especially organophosphate insecticides, may be related to NHL, the risk associated with 2,4-D does not appear to be explained completely by these other exposures. (Epidemiology 1990;1:349–356)

Keywords: agriculture, cancer, 2,4-dichlorophenoxyacetic acid, herbicides, insecticides, non-Hodgkin's lymphoma, occupation, pesticides.

In 1986, a case-control study conducted in Kansas showed an association between the development of non-Hodgkin's lymphoma (NHL) and agricultural use of herbicides (1). Risk for NHL increased with the average number of annual days of exposure to herbicides. Farmers exposed for more than 20 days per year had a sixfold increased risk for NHL. This increased risk seemed to be related specifically to 2,4-dichlorophenoxyacetic acid (2,4-D) use and could not be explained by differential recall, exposure to other pesticides, or other factors. Because of the magnitude of these risks and the widespread potential for exposure to 2,4-D in agriculture, forestry, lawn care, and other uses, we undertook a similar population-based case-control study in Nebraska, another midwestern agricultural state.

Subjects and Methods

Cases of NHL, Hodgkin's disease, multiple myeloma, and chronic lymphocytic leukemia among white men and women, aged 21 years or older, residing in 66 counties in eastern Nebraska, and diagnosed between July 1, 1983, and June 30, 1986, were identified through the Nebraska Lymphoma Study Group and area hospitals. Although not an ongoing population-based cancer registry, special procedures were instituted by the Nebraska Lymphoma Study Group to ascertain all cases in eastern Nebraska. The observed incidence rate for NHL among white males, aged 21 years or older, in eastern Nebraska (18.0/100,000 person-years) was 77% of the rate reported for white men, aged 20 years or older, 1983–1986, by the nearby Iowa component of the National Cancer Institute-sponsored Surveillance, Epidemiology, and End Results program (23.5/100,000 person-years) (L. Ries, personal communication). This report will present data on the white male NHL cases (N = 227).

All cases underwent pathology review and were clas-

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TABLE 1. Distribution of Non-Hodgkin's Lymphomas by Histologic and Immunologic Type in Interviewed White Men

Histology	Number	Percent
Low grade		
A. Small lymphocytic	14	(7)
B. Follicular, predominantly small cleaved cell	20	(10)
C. Follicular, mixed small cleaved and large cell	22	(11)
Intermediate grade		
D. Follicular, predominantly large cell	15	(8)
E. Diffuse, small cleaved cell	23	(11)
F. Diffuse, mixed small and large cell	16	(8)
G. Diffuse, large cell	51	(25)
High grade		
H. Large cell, immunoblastic	30	(15)
I. Lymphoblastic	1	(<1)
J. Small noncleaved cell	4	(2)
Miscellaneous*	5	(3)
	201	
Immunologic type		
T	20	(10)
B	160	(80)
Indeterminant	11	(5)
Not available	10	(5)
	201	

* Composite lymphomas were assigned to the follicular component if the follicular and diffuse components had the same cell type and to the most indolent cell type if the follicular and diffuse components differed.

sified according to the Working Formulation (2) (Table 1). Only histologically confirmed cases (N = 220) were included. The review also included immunologic phenotyping of the NHL. All follicular lymphomas were considered to be B-cell lymphomas. The diffuse lymphomas were phenotyped using the monoclonal antibodies L26 and UCHL1 (DAKO Corporation, Santa Barbara, CA) that mark B cells and T cells, respectively, in paraffin-embedded tissues (3,4).

Control subjects were selected from residents of the same 66-county area by 3:1 frequency matching by race, sex, vital status, and age (±2 years) to the combined age distribution of the four cancer case series (NHL, Hodgkin's disease, multiple myeloma, and chronic lymphocytic leukemia). For living cases under age 65 (N = 73), controls were selected by two-stage random digit dialing (5). For living cases aged 65 or older (N = 67), controls were selected from the Health Care Financing Administration (Medicare) records. For deceased cases (N = 80), controls were selected from the Nebraska state mortality files using the additional matching factor of year of death. Persons with an underlying cause of death of NHL, Hodgkin's disease, multiple myeloma, leukemia, malignancy of unknown site, aplastic anemia, suicide, homicide, or legal intervention were excluded as controls. A total of 831 white male controls were selected.

Telephone interviews were conducted with 201 NHL cases and 725 controls, or with their next-of-kin, between May, 1986, and October, 1987. The interviewers were not aware of the subjects' case-control status. The response rates for the cases and controls were 91% (living: 93%; deceased: 89%) and 87% (living: 89%; deceased: 85%), respectively. The overall control response rate was 85% and consisted of a weighted average accounting for the refusals in the household census phase of the random digit dialing procedure and the refusals of the randomly selected eligible controls to provide interviews.

This investigation covers the findings related to the association between NHL and agricultural exposure to 2,4-D. The interview questions on agricultural practices included those regarding the herbicides and insecticides used, the application method used most often, use of protective equipment, duration of time wearing work clothes after handling pesticides, cattle raising, and use of fungicides, rodenticides, fumigants, wood preservatives, and fertilizers. For each herbicide and insecticide, the years of use, the average annual number of days of use on the farm, and the average annual number of days the pesticides were personally handled were obtained. The interviewer noted whether the response about each pesticide was volunteered in answer to an open-ended question or reported only after a probe naming the specific pesticide.

All odds ratio (OR) estimates were adjusted for age by stratification (21–59, 60–69, 70–79, and greater than 80 years). Maximum likelihood estimates of a uniform odds ratio and 95% confidence intervals (CI) were computed by Gart's method (6). We assessed duration- and dose-response relationships by means of Mantel's one-tailed linear trend test (7). Logistic regression was also used for the data from farmers to evaluate the effects of several pesticide factors simultaneously (8).

Results

There was no overall excess of NHL among persons who had ever lived or worked on a farm; however, a 50% excess risk of NHL was found among men who mixed or applied 2,4-D (Table 2). Men who lived or worked on farms where 2,4-D was used, but who did not personally handle 2,4-D, had an OR of 1.2 (CI = 0.3, 4.2).

Among men who personally handled 2,4-D, risk in-

TABLE 2. Number of White Men with Non-Hodgkin's Lymphoma, Number of Controls, and Odds Ratios by Farming History

Farming History	Cases	Controls*	OR (95% CI)†
Never lived or worked on farm	54	184	1.0
Ever lived or worked on farm	147	539	0.9 (0.6,1.4)
Insecticides used on farm	104	321	1.1 (0.7,1.6)
Herbicides used on farm	75	203	1.3 (0.8,2.0)
Mixed or applied 2,4-D	43	98	1.5 (0.9,2.5)

* Two controls had unknown values for ever having lived or worked on a farm.
† OR (95% CI) = Age-adjusted odds ratio (95% confidence interval).

creased according to the average annual number of days spent mixing or applying 2,4-D in comparison with men who never lived or worked on a farm (Table 3). Risk increased to more than threefold for those with 21 or more days of exposure per year ($p = 0.051$). There was no consistent increase in risk with the number of years of 2,4-D use while the subjects lived or worked on a farm or with the first year of 2,4-D use.

Several characteristics of pesticide use that indicate potential for exposure were evaluated. Among men who personally handled 2,4-D, risk varied by the method used most often to apply herbicides. Tractor-mounted spraying was associated with an OR of 1.4 (CI = 0.8, 2.6; 27 cases, 62 controls) and handheld spraying with an OR of 1.7 (CI = 0.4, 6.7; 4 cases, 9 controls). Risk increased substantially the longer farmers usually waited to change into clean work clothes after handling pesticides (Table 4). Farmers who changed immediately, at the end of the work day, or the following day or later (presumably, these farmers wore the clothes for more than one work day but did not sleep in them) had ORs of 1.1, 1.5, and 4.7, respectively (p for trend = 0.015). Risk did not increase if the farmers reported that they usually failed to use any protective equipment (eg, rubber gloves, rubber boots, mask, spray suit) when handling pesticides. Among farmers who mixed or applied 2,4-D, those who typically used protective equipment while handling any pesticide had an OR of 1.7 (CI = 0.9, 3.1; 25 cases, 48 controls), whereas farmers who did not had an OR of 1.2 (CI = 0.6, 2.4; 16 cases, 49 controls).

Possible confounding of the results for 2,4-D by use of other pesticides was evaluated. The risks associated with

TABLE 3. Number of White Men with Non-Hodgkin's Lymphoma, Number of Controls, and Odds Ratios by Characteristics of Exposure to 2,4-Dichlorophenoxyacetic Acid (2,4-D)

Use of 2,4-D	Cases	Controls	OR (95% CI)*
Never lived or worked on farm	54	184	1.0
Days/year mixing or applying 2,4-D:			
1–5	16	44	1.2 (0.6,2.4)
6–20	12	25	1.6 (0.7,3.6)
21+	3	4	3.3 (0.5,22.1)
Unknown days/year	12	25	—
Chi for trend = 1.639, $p = 0.051$			
Years 2,4-D used on farm:			
1–5	3	12	0.9 (0.2,3.6)
6–15	11	15	2.8 (1.1,7.1)
16–20	3	18	0.6 (0.1,2.1)
21+	13	33	1.3 (0.6,2.7)
Unknown years	15	29	—
Chi for trend = 0.601, $p = 0.274$			
First year of 2,4-D use:			
Prior to 1945	8	21	1.4 (0.5,3.5)
1946–1955	13	39	1.1 (0.5,2.3)
1956–1965	5	8	2.1 (0.6,7.7)
1965–1986	4	12	1.3 (0.3,4.9)
Unknown year	13	18	—
Chi for trend = 0.955, $p = 0.170$			

* OR (95% CI) = age-adjusted odds ratio (95% confidence interval).

use of any phenoxyacetic acid herbicide (ever and average annual number of days) were identical to the risks for 2,4-D alone. All 13 cases and 27 controls who handled 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) (ever handled 2,4,5-T: OR = 1.6, CI = 0.7, 3.6; average days per year of exposure 1–5: OR = 1.1; 6–20: OR = 6.4, 4 cases, 2 controls) were also 2,4-D users. None of the subjects who handled 2,4-D more than 20 days per year was a 2,4,5-T user. Excluding the 2,4,5-T users did not change the risks for handling 2,4-D (ever handled 2,4-D: OR = 1.5, CI = 0.8, 2.6; days per year 1–5: OR = 1.1; 6–20: OR = 1.3; 21+: OR = 3.3). Restricting the analysis to farmers and adjusting for the use of other herbicides by class (triazines, amides, benzoics, carbamates, trifluralins, and other) resulted in no meaningful changes in the ORs for those who ever handled 2,4-D or in the positive trend associated with average annual days of exposure to 2,4-D. Adjustments for the use of insecticides by class (chlorinated hydrocarbons, carbamates, organophosphates, metals, and other) also resulted in no meaningful changes in the risk estimates for 2,4-D, except for the use of organophosphates. Adjusting for or-

TABLE 4. Number of White Men with Non-Hodgkin's Lymphoma and Controls Who Mixed and Applied 2,4-Dichlorophenoxyacetic Acid (2,4-D) by Timing of Change to Clean Work Clothes after Handling Pesticides

When Subject Usually Changed to Clean Work Clothes	Cases	Controls*	OR (95% CI)†
Never lived or worked on farm	54	184	1.0
Immediately after handling pesticides	6	19	1.1 (0.4,3.1)
At end of work day	31	73	1.5 (0.8,2.6)
Following day or later	6	4	4.7 (1.1,21.5)
Chi for trend = 2.166, p = 0.015			

* Two controls who personally handled 2,4-D had unknown values.
† OR (95% CI) = age-adjusted odds ratio (95% confidence interval).

ganophosphate use on the farm yielded an OR of 1.1 for men who ever handled 2,4-D and ORs of 0.9, 1.3, and 1.8 for men exposed to 2,4-D for 1–5, 6–20, and more than 20 days per year (p for trend = 0.246) relative to farmers with no 2,4-D exposure. Adjustments using more detailed measures of organophosphate exposure (eg, duration and average annual days spent mixing or applying) also resulted in approximately twofold increased risks of NHL among the most frequent handlers of 2,4-D. Analysis of organophosphate use, adjusted for use of 2,4-D, showed an independent association with NHL (ever: OR = 2.4; days per year 1–5: OR = 1.7; 6–20: OR = 1.8; 21+: OR = 3.1) and will be described more thoroughly in a future report. The risk among 2,4-D users compared with nonusers, excluding all organophosphate users, was similar to the adjusted 2,4-D risk for ever use (OR = 1.1) and for the two lower use categories (days per year 1–5: OR = 0.7; 6–20: OR = 1.5). There were no cases exposed to 2,4-D for 21 or more days who were unexposed to organophosphates. Adjustments for the use of fungicides led to increases in the risk estimates associated with 2,4-D exposure (OR = 1.8, CI = 1.1, 3.0) and with average annual days of exposure to 2,4-D (1–5 days: OR = 1.6; 6–20 days: OR = 2.2; 21+ days: OR = 4.5; p for trend = 0.003). Simultaneous adjustment for use of organophosphates, fungicides, and age resulted in ORs of 0.8, 1.3, and 3.1 for farmers who mixed or applied 2,4-D 1–5, 6–20, and more than 20 days per year, respectively. The results of logistic regression analyses, restricted to farmers and including the variables age and use of 2,4-D, organophosphates, and fungicides, were consistent with the stratified analyses. Use of organophosphate insecticides (ever used on farm: OR = 2.4) and 2,4-D (handled 21+ days per year: OR = 2.1) were independent risk factors for NHL.

Approximately two-thirds of both the exposed cases (63%) and controls (64%) volunteered the history of 2,4-D use on the farms where they lived or worked, whereas about one-third of the exposed cases (37%) and controls (36%) reported 2,4-D use only after a specific probe. Risk estimates were similar among the two groups for the use of 2,4-D on the farm (volunteers: OR = 1.5; probes: OR = 1.5), personal handling of 2,4-D (volunteers: OR = 1.5; probes: OR = 1.5), and more than 20 days per year exposure to 2,4-D (volunteers: OR = 2.5, 1 case, 2 controls; probes: OR = 3.8, two cases, 2 controls).

The risk of NHL associated with personal handling of 2,4-D was higher among persons with proxy interviews (1–5 days per year: OR = 2.2; 6–20 days: OR = 2.2; 21+ days: OR = 2.4) than among self-respondents (1–5 days per year: OR = 1.0; 6–20 days: OR = 1.6; 21+ days: OR = 1.4).

Histology, tumor grade, degree of maturation, and immunologic type of the NHLs were evaluated. The association with 2,4-D did not appear to be specific to any subgroup of NHL, although small numbers limited the reliability of the risk estimates. There was a slight suggestion that risk may be higher in intermediate grade NHL (Working Formulation groups D–G, Table 1) (ever: OR = 1.7; 21+ days per year: OR = 5.0, 2 cases, 4 controls), follicular center cell NHL (Working Formulation groups B–D, F–G, Table 1) (ever: OR = 1.7; 21+ days per year: OR = 6.4, 2 cases, 4 controls), large cell NHL (Working Formulation groups G–H) (ever: OR = 1.5; 21+ days per year: OR = 6.2, 1 case, 4 controls), and blastic NHL (Working Formulation groups D, G, and J) (ever: OR = 2.3; 21+ days per year: OR = 9.3, 1 case, 4 controls). Personally handling 2,4-D was associated with both T-cell (OR = 2.0; CI = 0.5, 7.3) and B-cell (OR = 1.5; CI = 0.9, 2.6) lymphomas; however, the trend with days per year was significant (p = 0.045) for B-cell lymphomas only. The ORs for B-cell lymphomas were 1.1, 1.6, and 4.3 for persons exposed to 2,4-D for 1–5, 6–20, and 21 or more days per year, respectively. There were no T-cell lymphoma cases who were exposed to 2,4-D more than 20 days per year.

None of the other factors covered in the interviews, including family history of cancer, prior radiation treatment, other aspects of the medical history, tobacco consumption, or use of hair coloring products, was responsible for the observed 2,4-D associations.

Discussion

This population-based case-control study conducted in eastern Nebraska found a 50% excess of NHL associated with mixing or applying 2,4-D. The risk for NHL increased with the average frequency of use to more than threefold among those exposed more than 20 days per year. These findings are consistent with those of a previous case-control study conducted in Kansas (1), although the risk estimates are lower in the present study. The difference in risks in the two states may be explained by statistical variation, since the confidence intervals for risk estimates obtained in Nebraska (CI = 0.5, 22.1) and Kansas (CI = 1.8, 32.3) show considerable overlap.

Some, but not all, variables that indicated the degree of exposure to 2,4-D were related to an increased risk of NHL. In addition to the average annual number of days mixing or applying 2,4-D, the potential for dermal exposure of the usual method of herbicide application (9,10) and the time of change to clean work clothes after handling pesticides were both related to increased risk. However, the number of years of 2,4-D use while the subject lived or worked on the farm was not consistently related to an increased risk for NHL. Interestingly, a similar lack of association with years of use was observed in the Kansas study (1). Computing years of use as a measure of exposure assumes that the level of exposure is similar throughout the year and from year to year. Pesticide use, however, is sporadic, not continuous, throughout the work year, and the amount used may vary considerably from year to year depending on the need and on the use of other farm workers to mix and apply the pesticides. Annual frequency of exposure is more strongly correlated with risk than years of use and may be a better surrogate for delivered dose.

In contrast to the findings of the Kansas study (1), failure to use protective equipment regularly was inversely associated with an increased risk of NHL among 2,4-D users. The elevated risks for users and nonusers of protective equipment were not substantially different from one another. Certainly, one should not discourage the use of protective equipment based on the present study's results.

Exposure to other pesticides affecred risk estimates from exposure to 2,4-D. Adjustment for the use of organophosphate insecticides reduced the observed risk associated with 2,4-D exposure, while adjustment for fungicide use increased the risk. Simultaneous adjustment for both resulted in risk estimates for average annual days of exposure similar to the values adjusted for age alone. Logistic regression analyses also indicated independent effects of 2,4-D and organophosphates. Because of the small number of subjects and the high proportion of subjects with multiple exposures, it is not possible in this study to entirely disentangle these relationships. There may be some residual confounding. Case-control studies of larger populations with detailed data on more variable patterns of exposures are needed.

This study relied upon study subjects or their next-of-kin to recall complicated lifetime exposure histories. While there is a great need to improve methods for estimating exposure to pesticides in epidemiologic studies (11), exposure misclassification is not likely to have created spurious risks in this study or in the Kansas study (12). The similarity of the proportions of cases and controls who volunteered histories of 2,4-D use in response to an open-ended question as compared with those who responded to a specific probe for 2,4-D use and the increased risks among frequent users in both the subjects and proxy respondents suggest that recall bias did not occur in this study. Corroboration of a sample of the exposure histories in the Kansas study (1) and methodologic studies of industrial workers (13) observed little difference in accuracy of reports from cases and controls and suggest that the exposure misclassification in this study is likely to be independent of case-control status. Such misclassification tends to decrease risk estimates and reduce exposure-response gradients (14). Thus, misclassification in the Nebraska study is likely to result in an underestimate of the true risk associated with 2,4-D exposure. In addition, increasingly detailed measures of exposure to organophosphates did not further reduce the adjusted OR for 2,4-D exposure, suggesting that misclassification of organophosphate exposure did not lead to an artificial inflation of the risk estimate for 2,4-D.

The large proportion of farmers with no known history of pesticide use in this study (37% of the controls) suggests inaccurate recall by the study subjects. The study definition of farmers, however, included anyone who had ever lived or worked on a farm. This definition includes dependents of farmers and persons who farmed for only brief periods of time. Their opportunity to use pesticides would have been considerably less than for career farmers. Also, some of the older study subjects farmed several decades ago when pesticide use was much less common than in recent years. In addition, some subjects who reported no use of pesticides probably used them. Such misclassification would result in some exposed farmers being classified as nonexposed. In the presence of a positive association, these improperly classified "nonexposed" farmers would reduce the true risk estimates for farmers as a group and lower risk estimates for frequent users of 2,4-D. In fact, the farmers who reported no exposure to 2,4-D had an odds ratio of 0.8

(CI = 0.5, 1.2). This deviation from 1.0 could result from random variation or uncontrolled negative confounding. If confounding were the explanation, the odds ratios reported for the exposed farmers are likely to be underestimates of the true risks.

Other Epidemiologic Studies

There have been many epidemiologic studies evaluating the relation of pesticides to cancer which, at first glance, appear to report inconsistent results. The studies generally have not evaluated the same chemicals with the same measures of exposure, however. Only the Kansas study (1) appears comparable with the Nebraska study, ie, based on days per year of agricultural exposure to 2,4-D. Other case-control studies of NHL and herbicides have either treated the phenoxyacetic acid herbicides as a group, with no specific information on 2,4-D and/or lacked information on the number of days per year of exposure (15–21). Case-control studies in Sweden, however, have also noted excess risks for NHL among persons having contact with phenoxyacetic acid herbicides (15,16,21), with an indication in one study (15) that excess risks were present among persons exposed to 2,4,5-T and those exposed only to phenoxys considered unlikely to be contaminated by polychlorinated dibenzodioxins and dibenzofurans, such as 2,4-D and 4-chloro-2-methyl phenoxyaceric acid (MCPA). A study in western Washington state (22) observed a small, but significant, excess risk of NHL among farmers, but the risk did not increase with duration in farming occupations nor with estimated level of exposure in other occupations to 2,4-D; however, no data on the annual number of days of exposure were available. Pearce (19), who found no association between duration or frequency of herbicide use and lymphoma among New Zealand applicarors, was studying workers exposed almost entirely to 2,4,5-T. Exposure to 2,4,5-T was not associated with an elevated risk of NHL in the Kansas study, but was associated with a nonsignificant increased risk in the Nebraska study. The results of the Kansas and the Nebraska studies indicate that evaluating risk by job title or duration of exposure only may be inadequate, missing important information. It is apparent that considerable variation of exposure occurs among farmers and that personal exposure histories must be obtained in such studies.

Cohort studies of manufacturers and applicators have also been subject to the problems of mixed exposures. Most of the cohorts exposed to 2,4-D have also been exposed to either 2,4,5-T (23–25) or MCPA (26–29). These investigations have generally not observed excesses of NHL, but the small number of subjects in these studies has limited their usefulness in examining NHL, a rare cause of death (23,24). A recent cohort study of farmers in Canada reported that the risk of NHL increased with the number of acres sprayed with herbicides, particularly in smaller farming operations of less than 1,000 acres (30). Bond et al (31) studied a group of 878 chemical workers who were potentially exposed to several agricultural chemicals, including 2,4-D, and observed a nonsignificant excess of lymphatic and hematopoietic cancers. This excess occurred exclusively among workers who were employed in the 2,4-D plant (5 deaths observed, relative risk = 3.1, $p \leq 0.05$). Two of the five lymphatic and hematopoietic cancers were non-Hodgkin's lymphomas.

Experimental Studies

There is little evidence that 2,4-D is mutagenic or genotoxic (32,33). A 2-year animal feeding study of 2,4-D resulted in a statistically significant excess of astrocytomas in male rats at the highest dose level (Industry Task Force on 2,4-D research data, as cited in Bond et al [31]). The International Agency for Research on Cancer (34) recently concluded that there is inadequate evidence of animal carcinogenicity for 2,4-D. 2,4-D has been associated with increased rates of sister chromatid exchanges and other chromosomal aberrations in vitro (35–37) and in vivo (37,38). The possibility that 2,4-D may be carcinogenic, not by mutagenic activity, but by excessive production of hydrogen peroxide and the proliferation of peroxisomes has been suggested (39).

Immunosuppression, a well-established strong risk factor for NHL (40), could be a possible mechanism by which 2,4-D might increase the risk of NHL. Acute exposure of female mice to high levels of 2,4-D resulted in suppression of antibody production against sheep red blood cells; however, subacute exposure, more comparable with human occupational exposures, did not affect antibody production but, rather, enhanced B- and T-lymphocyte proliferative responses (41). 2,4-D has rarely been reported to be contaminated with 2,3,7,8-tetrachlorodibenzo-p-dioxin (42), the dioxin congener that is a frequent contaminant of some other phenoxy herbicides and that has been reported to be both immunosuppressive and carcinogenic (43–49).

The fact that the mechanism for 2,4-D's putative action is unknown should not detract from the strength and consistency of the results in Kansas and Nebraska concerning risk by days per year of herbicide use. Based on the positive results in these two studies and the likelihood that any exposure misclassification has probably decreased the risk estimates and diluted exposure-response gradients, we believe that the weight of evi-

dence indicates that the use of 2,4-D in an agricultural setting increases the risk of NHL among persons handling the chemical frequently.

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References

1. Hoar SK, Blair A, Holmes FF, Boysen CD, Robel RJ, Hoover R, Fraumeni JF Jr. Agricultural herbicide use and risk of lymphoma and soft-tissue sarcoma. JAMA 1986;256:1141–7.
2. The Non-Hodgkin's Lymphoma Pathologic Classification Project. National Cancer Institute sponsored study of classifications of non-Hodgkin's lymphomas: Summary and description of a Working Formulation for Clinical Usage. Cancer 1982;49:2112–35.
3. Linder J, Ye Y, Harrington DS, Armitage JO, Weisenburger DD. Monoclonal antibodies marking T lymphocytes in paraffin-embedded tissue. Am J Pathol 1987;127:1–8.
4. Linder J, Ye Y, Armitage JO, Weisenburger DD. Monoclonal antibodies marking B-cell non-Hodgkin's lymphoma in paraffin-embedded tissue. Modern Pathol 1988;1:29–34.
5. Waksberg J. Sampling methods for random digit dialing. J Am Stat Assoc 1978;73:40–6.
6. Gart JJ. Point and interval estimation of the common odds ratio in the combination of 2 × 2 tables with fixed marginals. Biometrika 1970;57:471–5.
7. Mantel N. Chi square test with 1 degree of freedom, extension of the Mantel-Haenszel procedure. Am Stat Assoc J 1963;58:690–700.
8. Engelman L. Stepwise logistic regression. In: Dixon WJ, ed. BMDP statistical software. Berkeley, CA: University of California Press, 1983.330–44.
9. Lavy TL, Shepard JS, Mattice JD. Exposure measurements of applicators spraying (2,4,5-trichlorophenoxy) acetic acid in the forest. J Agric Food Chem 1980;28:626–30.
10. Lavy TL, Norris LA, Mattice JD, Marx DB. Exposure of forestry ground workers to 2,4-D, picloram, and dichlorprop. Environ Toxicol Chem 1987;6:209–24.
11. Blair A, Zahm SH, Cantor KP, Stewart PA. Estimating exposure to pesticides in epidemiologic studies of cancer. In: Wang RGM, Franklin CA, Honeycutt RC, et al, eds. Biological monitoring for pesticide exposure—measurement, estimation, and risk reduction. Washington, DC: American Chemical Society, ACS Symposium Series 382, 1989:38–46.
12. Blair A, Zahm SH. Herbicides and cancer: A review and discussion of methodologic issues. In: Band P, ed. Recent results in cancer research: Occupational cancer epidemiology. Vancouver, Canada: 1989;120:132–45.
13. Bond GG, Bodner KM, Sobel W, Shellenberger RJ, Flores GH. Validation of work histories obtained from interviews. Am J Epidemiol 1988;128:343–51.
14. Marshall JR, Priore R, Graham S, Brasure J. On the distortion of risk estimates in multiple exposure level case-control studies. Am J Epidemiol 1981;113:464–80.
15. Hardell L, Eriksson M, Lenner P, Lundgren E. Malignant lymphoma and exposure to chemicals, especially organic solvents, chlorophenols and phenoxy acids: A case-control study. Br J Cancer 1981;43:169–76.
16. Hardell L. Relation of soft-tissue sarcoma, malignant lymphoma and colon cancer to phenoxy acids, chlorophenols and other agents. Scand J Work Environ Health 1981;7:119–30.
17. Pearce NE, Smith AH, Howard JF, Sheppard RA, Giles HJ, Teague CA. Non-Hodgkin's lymphoma and exposure to phenoxyherbicides, chlorophenols, fencing work, and meat works employment: A case-control study. Br J Ind Med 1986;43:75–83.
18. Pearce NE, Sheppard RA, Smith AH, Teague CA. Non-Hodgkin's lymphoma and farming: An expanded case-control study. Int J Cancer 1987;39:155–61.
19. Pearce N. Phenoxy herbicides and non-Hodgkin's lymphoma in New Zealand: Frequency and duration of herbicide use. Br J Ind Med 1989;46:143–44.
20. Woods JS, Polissar L, Severson RK, Heuser LS, Kulander BG. Soft tissue sarcoma and non-Hodgkin's lymphoma in relation to phenyoxyherbicide and chlorinated phenol exposure in Western Washington State. J Natl Cancer Inst 1987;78:899–910.
21. Persson B, Dahlander A-M, Fredriksson M, Brage HN, Ohlson CG, Axelson O. Malignant lymphoma and occupational exposures. Br J Ind Med 1989;46:516–20.
22. Woods JS, Polissar L. Non-Hodgkin's lymphoma among phenoxy herbicide-exposed farm workers in Western Washington State. Chemosphere 1989;18:401–6.
23. Riihimaki V, Asp S, Hernberg S. Mortality of 2,4-dichlorophenoxyacetic acid and 2,4,5-trichlorophenoxyacetic acid herbicide applicators in Finland: First report of an ongoing prospective cohort study. Scand J Work Environ Health 1982;8:37–42.
24. Riihimaki V, Asp S, Pukkala E, Hernberg S. Mortality and cancer morbidity among chlorinated phenoxyacid applicators in Finland. Chemosphere 1983;12:779–84.
25. Bond AG, Bodner KM, Cook RR. Phenoxy herbicides and cancer: Insufficient epidemiologic evidence for a causal relationship. Fund Appl Toxicol 1989;12:172–88.
26. Lynge E. Background and design of a Danish cohort study of workers in phenoxy herbicide manufacture. Am J Indus Med 1987;11:427–37.
27. Lynge E. A follow-up study of cancer incidence among workers in manufacture of phenoxy herbicides in Denmark. Br J Cancer 1985;52:259–70.
28. Wiklund K, Dich J, Holm L-E. Risk of malignant lymphoma in Swedish pesticide appliers. Br J Cancer 1987;56:505–8.
29. Wiklund K, Lindefors B-M, Holm L-E. Risk of malignant lymphoma in Swedish agricultural and forestry workers. Br J Ind Med 1988;45:19–24.
30. Wigle DT, Semenciw RM, Wilkins K, et al. Mortality study of Canadian male farm operators: Non-Hodgkin's lymphoma mortality and agricultural practices in Saskatchewan. J Natl Cancer Inst 1990;82:575–82.
31. Bond GG, Wetterstroem NH, Rousch GJ, McLaren EA, Lipps TE, Cook RR. Cause-specific mortality among employees engaged in the manufacture, formulation, or packaging of 2,4-dichlorophenoxyacetic acid and related salts. Br J Ind Med 1988;45:98–105.
32. Canadian Centre for Toxicology. Expert panel report on carcinogenicity of 2,4-D. Guelph, Ontario: 1987.
33. Seiler JP. The genetic toxicology of phenoxy acids other than 2,4,5-T. Mutat Res 1978;55:197–226.
34. International Agency for Research on Cancer. IARC monographs on the evaluation of carcinogenic risks to humans. Overall evaluation of carcinogenicity: An update of IARC monographs volumes 1 to 42. Lyon, France: IARC, 1987:156–60.
35. Korte C, Jalal SM. 2,4-D induced clastogenicity and elevated rates of sister chromatid exchanges in cultured human lymphocytes. J Heredity 1982;73:224–6.
36. Turkula TE, Jalal SM. Increased rates of sister chromatid exchanges induced by the herbicide 2,4-D. J Heredity 1985;76:213–4.
37. Musronen R, Kangas J, Vuojolahti P, Linnainmaa K. Effects of phenoxyacetic acids on the induction of chromosome aberrations in vitro and in vivo. Mutagenesis 1986;1:241–5.
38. Yoder J, Watson M, Benson WW. Lymphocyte chromosome analysis of agricultural workers during extensive occupational exposure to pesticides. Mutation Res 1973;21:335–40.

39. Vainio H, Nickels J, Linnainmaa K. Phenoxy acid herbicides cause peroxisome proliferation in Chinese hamsters. Scand J Work Environ Health 1982;8:70–73.
40. Greene MH. Non-Hodgkin's lymphoma and mycosis fungoides. In: Schottenfeld D, Fraumeni JF, Jr., eds. Cancer epidemiology and prevention. Philadelphia: WB Saunders Company, 1982:754–78.
41. Blakely BR, Schiefer BH. The effect of topically applied n-butylester of 2,4-dichlorophenoxyacetic acid on the immune response in mice. J Appl Toxicol 1986;6:291–5.
42. Hagenmaier H. Determination of 2,3,7,8-tetrachlorodibenzo-p-dioxin in commercial chlorophenols and related products. Fresenius Z Anal Chem 1986;325:603–6.
43. Vos JG, Moore JA, Zinkl JG. Effect of 2,3,7,8-tetrachlorodibenzo-p-dioxin on the immune system of laboratory animals. Environ Health Perspect 1973;5:149–62.
44. Harris MW, Moore JA, Vos JG, Gupta BN. General biological effects of TCDD in laboratory animals. Environ Health Perspect 1973;5:101–9.
45. Kociba RJ, Keyes DG, Beyer JE, Carreon RM, Wade CE, Dittenber DA, Kalnins RP, Frauson LE, Park CN, Barnard SD, Hummel RA, Humiston CG. Results of a two-year chronic toxicity and oncogenicity study of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) in rats. Toxicol Appl Pharmacol 1978;46:279–303.
46. Kociba RJ, Keyes DG, Beyer JE, Carreon RM, Gehring PJ. Long-term toxicologic studies of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) in laboratory animals. Ann NY Acad Sci 1979;320:397–404.
47. Van Miller JP, Lalich JJ, Allen JR. Increased incidence of neoplasms in rats exposed to low levels of 2,3,7,8-tetrachlorodibenzo-p-dioxin. Chemosphere 1977;10:625–32.
48. National Toxicology Program. (Report 80-31) Carcinogenesis bioassay of 2,3,7,8-tetrachlorodibenzo-p-dioxin (CAS N. 1746-01-6) in Osborne-Mendel rats and B6C3F1 mice (Gavage study), technical report series 209, National Institutes of Health publication 82-1765. Research Triangle Park, NC, Dept of Health and Human Services, 1982.
49. National Toxicology Program. (Report 80-32) Carcinogenesis bioassay of 2,3,7,8-tetrachlorodibenzo-p-dioxin (CAS No. 1746-01-6) in Swiss-Webster mice (Dermal study), technical report series 209, National Institutes of Health publication 82-1757. Research Triangle Park, NC, Dept of Health and Human Services, 1982.

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NON-HODGKIN'S LYMPHOMA AMONG ASTHMATICS EXPOSED TO PESTICIDES

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We conducted a pooled analysis of population-based case-control studies in Iowa, Minnesota and Nebraska to investigate whether asthma modifies risk of non-Hodgkin's lymphoma (NHL) associated with pesticide exposures. Cases (n = 872) diagnosed with NHL from 1980 to 1986 and frequency-matched controls (n = 2,381) randomly selected from the same geographic areas as the cases were included. Information on use of pesticides and history of asthma was based on interviews. Unconditional logistic regression was used to calculate ORs, adjusted for age, state and vital status. Of all subjects, 177 (45 cases, 132 controls) reported having been told by their doctor that they had asthma. Subjects with an asthma history had a nonsignificantly lower risk of NHL than nonasthmatics (OR = 0.6, 95% CI 0.3–1.4), and there was no main effect of pesticide exposure (OR = 1.0, 95% CI 0.8–1.2). However, asthmatics tended to have larger ORs associated with exposure to pesticides than nonasthmatics. The OR among asthmatics was 1.8 (95% CI 1.1–3.2) for ever-use of crop insecticides, 2.7 (95% CI 1.0–7.2) for chlordane, 2.4 (95% CI 1.0–5.7) for lindane and 3.7 (95% CI 1.3–10.9) for fonofos. Among nonasthmatics, ORs were 1.1 (0.9–1.3), 1.5 (1.1–2.2), 1.3 (0.97–1.8) and 1.6 (1.0–2.4), respectively. Although there is limited power for assessing interaction, our results suggest that the risk of NHL among asthmatics with pesticide exposure may be higher than among nonasthmatics with pesticide exposure.

Key words: *asthma; insecticide; farmer; non-Hodgkin's lymphoma; pesticide exposure*

Incidence and mortality rates for non-Hodgkin's lymphoma (NHL) have been increasing worldwide over the past several decades.[1] Although the reasons for this increase are not fully understood, NHL is known to be associated with a compromised immune system, particularly acquired or genetic immunodeficiencies.[2,3] Medical conditions related to more subtle immune alteration, such as asthma and other allergic conditions, have also been studied as potential risk factors for NHL.[4–10] These reports have described a decreased risk for NHL among persons with a history of asthma or allergies,[4,5] no association[6–8] or an increase in risk.[9,10] Exposure to pesticides has also been suggested as a possible risk factor for NHL.[11–15] Pesticides may increase cancer risk by altering the immune system.[16–19] Because both asthma and pesticide exposure may change the risk of NHL by immunologic alterations, we investigated the relation between pesticide exposure, asthma and risk of NHL.

MATERIAL AND METHODS

Study population

We pooled data from 2 population-based case-control studies of NHL in 3 midwestern states in the United States, which have been described in detail previously.[20,21] In Iowa and Minnesota, all newly diagnosed cases of NHL among white men aged ≥30 were ascertained from records of the Iowa State Health Registry and a special surveillance system of Minnesota hospitals and pathology laboratories from 1980 to 1983 (n = 530). In Nebraska, all cases of NHL diagnosed between July 1983 and June 1986 among white men and women aged ≥21 in 45 eastern counties were identified through the Nebraska Lymphoma Study Group and area hospitals (n = 346). All cases were reviewed by pathologists, and only histologically confirmed cases were included in this analysis. Controls were randomly selected from the same geographic areas as cases with frequency matching by race, gender, age (5-year age group) and vital status at the time of interview. Control/case matching ratios were approximately 2:1 in Iowa and Minnesota and 4:1 in Nebraska. For living cases under the age of 65, controls were selected by 2-stage random digit dialing.[22] For living cases aged 65 and over, controls were selected from the records of the Health Care Financing Administration. Controls for deceased cases were selected from death records in each state, with additional matching for year of death. Persons whose underlying cause of death was NHL, Hodgkin's lymphoma, multiple myeloma, leukemia or malignancy of unknown sites were excluded as controls. A total of 2,357 controls (Nebraska 1,318, Iowa and Minnesota 1,039) were identified.

Interview

Interviews were conducted with subjects or their next-of-kin if subjects were dead or incapacitated. Interviews were held in person in Iowa and Minnesota and by telephone in Nebraska. Participation rates among cases were 89% in Iowa and Minnesota and 91% in Nebraska. Among controls, rates were 78% in Iowa and Minnesota and 85% in Nebraska. We used standardized and structured questionnaires to collect information on use of pesticides and other known or suspected risk factors for NHL. Questions included personal handling of groups of pesticides and individual pesticides used on crops or animals, with year of first and last use. We also asked whether subjects had ever been told by a doctor that they had asthma and, if so, their age at first diagnosis.

Statistical analysis

Subjects who did not have any information on asthma (n = 25) were excluded from the pooled data set, leaving 872 cases and 2,336 controls eligible for analysis. We used unconditional logistic regression to obtain odds ratios (ORs) and 95% confidence intervals (CIs) with Stata software (version 7.0).[23] The ORs for NHL among farmers exposed to pesticides with asthma were compared to those of nonfarmers without asthma (*i.e.*, individuals who had never lived or worked on a farm and did not have asthma) and to those of farmers without asthma. We estimated the risk of NHL by reported use of individual pesticides where sufficient numbers of exposed subjects were available. We present ORs for pesticides

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that were personally handled by at least 5 exposed cases. The logistic model included age (<60, 60–75, >75), state (Iowa, Minnesota, Nebraska) and vital status (alive, dead). Other variables, such as gender, smoking, having a first-degree relative with lymphohematopoietic cancer, ever having a job correlated with lymphohematopoietic cancers (*e.g.*, painting or welding) and use of protective equipment, were also evaluated as possible confounders. Adjustments of ORs for these variables had minimal impact on risk estimates of NHL, and the latter 2 variables have some missing cases. These variables were not included in the final model. To assess possible reporting bias, risks were estimated including and excluding proxy respondents. We also explored the risk of NHL by age at first diagnosis of asthma and duration of pesticide use.

RESULTS

Table I shows the distribution of the 872 cases and 2,336 controls by asthma history, age, gender, vital status, state of residence, having a first-degree relative with lymphohematopoietic cancer and type of NHL. Of the total subjects, 177 (5.5%) reported having been told by their doctor that they had asthma. Asthmatic NHL cases were more likely than asthmatic controls to be younger, male, alive at the time of interview and residing in Iowa. Nonasthmatic NHL cases were more likely than nonasthmatic controls to be male, to have family history of lymphohematopoietic cancer and to reside in Iowa/Minnesota.

We evaluated ORs for NHL by pesticide groups and asthma history (Table II). Among nonfarmers, subjects with asthma had a lower risk for NHL (not statistically significant) compared to nonfarmers without asthma (OR = 0.6, 95% CI 0.3–1.4). ORs for NHL among farmers without asthma were near 1.0 for all pesticide categories except chemical classes of insecticide. The risk of NHL was significantly increased for exposure to crop insecticides (OR = 1.8, 95% CI 1.1–3.2) and nonsignificantly increased for exposure to livestock insecticides (OR = 1.4, 95% CI 0.9–2.3), herbicides (OR = 1.5, 95% CI 0.9–2.5) and fungicides (OR = 1.4, 95% CI 0.5–4.3) among farmers with asthma. Only organophosphate insecticides had significant ORs among both asthmatics and nonasthmatics. The pattern was consistent by state of residence or interview type, although the results were limited by small numbers of cases (data not shown).

Table III presents ORs for NHL among farmers exposed to individual pesticides by asthma history. Among insecticides, risk of NHL was significantly elevated with exposure to chlordane (OR = 2.7, 95% CI 1.0–7.2), fonofos (OR = 3.7, 95% CI 1.3–10.9) and lindane (OR = 2.4, 95% CI 1.0–5.7) in asthmatics compared to nonfarmers without asthma. Many other insecticides (aldrin, carbaryl, carbofuran, diazinon, dieldrin, flyspray, heptachlor, malathion) also had larger ORs among farmers with a history of asthma than among those without asthma. However, none of these was significantly different from the risks in nonasthmatics. Among nonasthmatics, risk of NHL was also significantly elevated with exposure to chlordane, diazinon, fonofos and malathion; but the magnitude of risk was smaller than that among asthmatics. Use of individual herbicides was also associated with increased risk of NHL among asthmatics compared to nonasthmatics, but only cyanazine had a significant OR. No fungicide had 5 or more exposed cases and was significantly associated with NHL.

Analyses of pesticide exposure and asthma history among farmers only are presented in Table IV. The reference category was nonasthmatic farmers not exposed to each pesticide. Asthmatics with exposure to crop insecticides had significantly elevated risk of NHL (OR = 2.0, 95% CI 1.1–3.5), but the interaction risk for pesticide exposure and asthma was not statistically significant.

We explored the potential modifying effects of age at first diagnosis of asthma and duration of pesticide use on risk of NHL (Table V). Only asthmatic farmers exposed to pesticides were included in this analysis. Risks among subjects diagnosed with asthma after age 30 tended to be higher for all types of pesticide than those among subjects who had developed asthma relatively early. There was no clear pattern of ORs for NHL by duration of pesticide use and age at diagnosis of asthma. The results were limited due to the small number of asthmatic NHL cases, and further studies are needed to investigate these findings.

DISCUSSION

We found that farmers with potential exposure to pesticides and a history of asthma tended to have higher relative risks for NHL than pesticide-exposed farmers not reporting asthma. The excess risks among asthmatics with pesticide exposure were generally more pronounced when we analyzed by individual pesticides (*e.g.*,

TABLE I – CHARACTERISTICS OF CASES AND CONTROLS BY ASTHMA HISTORY

Characteristics	Nonasthmatics (n = 3,031)		Asthmatics (n = 177)	
	Cases (n = 827)	Controls (n = 2,204)	Cases (n = 45)	Controls (n = 132)
Age (years)				
<60	231 (27.9)[2]	585 (26.5)	18 (40.0)	24 (18.2)
60–75	348 (42.1)	875 (39.7)	17 (37.8)	51 (38.6)
>75	248 (30.0)	744 (33.8)	10 (22.2)	57 (43.2)
Gender				
Male	676 (81.7)	1,594 (72.3)	38 (84.4)	100 (75.8)
Female	151 (18.3)	610 (27.7)	7 (15.6)	32 (24.2)
Vital status				
Alive	572 (69.2)	1,486 (67.4)	34 (75.6)	71 (53.8)
Dead	255 (30.8)	718 (32.6)	11 (24.4)	61 (46.2)
State of residence				
Iowa	238 (28.8)	483 (21.9)	15 (33.3)	26 (19.7)
Minnesota	264 (31.9)	491 (22.3)	10 (22.2)	28 (21.2)
Nebraska	325 (39.3)	1,230 (55.8)	20 (44.5)	78 (59.1)
Family history of cancer[1]				
No	733 (90.7)	2,072 (95.4)	42 (93.3)	120 (92.3)
Yes	75 (9.3)	99 (4.6)	3 (6.7)	10 (7.7)
Histologic type				
Follicular	243 (29.5)	—	18 (40.9)	—
Diffuse	298 (36.1)	—	16 (36.4)	—
Small lymphocytic	90 (10.9)	—	4 (9.1)	—
Other	194 (23.5)	—	6 (13.6)	—

[1]Lymphohematopoietic cancers diagnosed in any first-degree relative.–[2]Percentage in parentheses.

TABLE II – RISKS OF NHL BY FARMING HISTORY, PESTICIDE USE AND ASTHMA HISTORY

	Nonasthmatics				Asthmatics			
	Cases	Controls	OR[1]	95% CI	Cases	Controls	OR	95% CI
Nonfarmers	259	684	1.0	Ref[2]	9	37	0.6	0.3–1.4
Farmers	560	1,510	1.0	0.8–1.2	36	95	1.1	0.7–1.6
No pesticide use	137	419	1.0	0.8–1.3	3	14	0.7	0.2–2.6
Pesticide use	423	1,091	1.0	0.8–1.2	33	81	1.1	0.7–1.7
Animal insecticides	363	900	1.0	0.8–1.2	28	52	1.4	0.9–2.3
Crop insecticides	239	572	1.1	0.9–1.3	23	32	1.8	1.1–3.2
Organochlorine	205	412	1.2	0.9–1.5	17	28	1.5	0.8–2.8
Organophosphate	149	269	1.4	1.1–1.7	14	17	2.0	1.0–4.2
Carbamate	79	154	1.3	0.9–1.7	8	9	2.2	0.8–5.9
Herbicides	260	639	1.0	0.8–1.3	23	43	1.5	0.9–2.5
Phenoxyacetic acid	176	409	1.0	0.8–1.3	17	33	1.3	0.7–2.4
Triazine	131	268	1.1	0.9–1.5	12	17	1.7	0.8–3.7
Amides	105	231	1.1	0.8–1.4	11	15	1.8	0.8–3.9
Fungicides	44	110	1.0	0.7–1.4	5	10	1.4	0.5–4.3

[1]OR adjusted for age, vital status and state.–[2]Ref, reference category was nonfarmers without asthma (259 cases, 684 controls) for all ORs.

TABLE III – RISKS OF NHL AMONG FARMERS EXPOSED TO INDIVIDUAL PESTICIDES[1] BY ASTHMA HISTORY

	Nonasthmatics				Asthmatics			
	Cases	Controls	OR[2]	95% CI	Cases	Controls	OR	95% CI
Nonfarmers	259	684	1.0	Ref[3]	9	37	0.6	0.3–1.4
Insecticides								
Aldrin	66	148	1.0	0.7–1.5	10	11	2.1	0.9–5.1
Carbaryl	42	77	1.4	0.9–2.0	6	6	2.4	0.8–7.6
Carbofuran	56	117	1.2	0.8–1.7	6	8	1.9	0.7–5.6
Chlordane	67	108	1.5	1.1–2.2	9	8	2.7	1.0–7.2
DDT	158	313	1.2	0.9–1.5	11	24	1.2	0.6–2.4
Diazinon	58	98	1.6	1.1–2.3	7	9	1.9	0.7–5.3
Dieldrin	30	63	1.2	0.7–1.9	5	3	4.2	0.98–18.2
Flyspray	189	442	0.9	0.7–1.1	14	27	1.1	0.6–2.2
Fonofos	41	69	1.6	1.0–2.4	8	6	3.7	1.3–10.9
Heptachlor	44	84	1.3	0.9–2.0	6	6	2.6	0.8–8.4
Lindane	84	146	1.3	0.97–1.8	11	11	2.4	1.0–5.7
Malathion	89	141	1.5	1.1–2.1	7	9	1.9	0.7–5.1
Herbicides								
2,4-D	172	402	1.0	0.8–1.3	17	33	1.3	0.7–2.5
2,4,5,-T	36	77	1.1	0.7–1.8	7	8	2.2	0.8–6.1
Alachlor	96	210	1.1	0.8–1.4	10	14	1.7	0.8–4.0
Atrazine	119	225	1.3	0.96–1.6	9	16	1.4	0.6–3.3
Butylate	38	75	1.1	0.7–1.7	5	6	2.0	0.6–6.9
Chloroamben	52	103	1.1	0.8–1.6	9	10	2.3	0.9–5.7
Cyanazine	53	131	0.9	0.6–1.3	8	7	2.8	1.0–8.1
Dicamba	49	106	1.0	0.7–1.5	6	7	2.0	0.6–6.0
Glyphosate	53	91	1.4	0.98–2.1	6	12	1.2	0.4–3.3
Trifluralin	73	168	1.0	0.7–1.3	8	10	1.9	0.7–4.8

[1]At least 5 cases handled each individual pesticide were included in this analysis.–[2]OR adjusted for age, vital status and state.–[3]Ref, reference category was nonfarmers without asthma (259 cases, 684 controls) for all ORs.

chlordane, fonofos, lindane, cyanazine) and occurred when either "nonfarmers" or "farmers" was used as the reference.

Although we had limited power for assessing effect modification, there might be synergism between asthma and pesticide exposure for developing NHL. One possible explanation is that there is immune deviation in asthma toward T-helper 2 (Th2) predominance, with elevated IL-4, IL-5 and IL-13, which might inhibit Th1 responses that could protect against cancer.[24,25] This skewing of the immune response toward the Th2 phenotype could exacerbate the effects of the pesticides, which may partly act as carcinogens, and may also inhibit the immune response, acting synergistically with the asthma. Some pesticides might also inhibit a different arm of the immune response, *e.g.*, cytotoxic T lymphocytes or natural killer (NK) cells,[26,27] so that the combination of asthma and pesticides exposure eliminates more than one mechanism of immunosurveillance. Moreover, IL-13, which is prominent in asthma, can also downregulate cytotoxic T lymphocyte–mediated tumor immunosurveillance,[28] reducing 2 arms of the immune response to cancer and specifically crippling immunosurveillance against cancer in a murine tumor model.

Various characteristics, such as history of allergy and serum IgE levels, between late-onset and early-onset asthma[29–31] might be related to higher risk of NHL among individuals diagnosed with asthma over age 30. Exposure to pesticides may influence the induction and aggravation of asthma through modification of autonomic control of airways.[32] Associations between asthma and use of cholinesterase-inhibiting pesticides were observed among Canadian farmers[33] and U.S. pesticide applicators.[34]

The strengths of our pooled study are a population-based design, high response rates and detailed information on pesticide use and potential etiologic factors for NHL. The relatively large sample size facilitated the simultaneous evaluation of asthma and pesticide use but was still not enough to carefully evaluate individual pesticides and asthma in relation to NHL.

We used self-reported information concerning prior asthma history. The sensitivity of ascertainment of physician-diagnosed asthma has been estimated at about 68% and the specificity at about 94% when validated against clinical diagnosis.[35] This type of misclassification is likely to cause underestimation of the asso-

TABLE IV – RISKS OF NHL AMONG FARMERS BY PESTICIDE EXPOSURE AND ASTHMA HISTORY[1]

	Nonasthmatics			Asthmatics			Interaction OR (95% CI)
	Cases	OR[2]	95% CI	Cases	OR	95% CI	
Any pesticide							
No	137	1.0	Ref[3]	3	0.7	0.2–2.5	
Yes	423	1.0	0.8–1.2	33	1.1	0.7–1.7	1.6 (0.4–6.2)
Crop insecticides							
No	252	1.0	Ref	12	0.9	0.5–1.8	
Yes	239	1.2	0.9–1.4	23	2.0	1.1–3.5	1.9 (0.8–4.6)
Animal insecticides							
No	143	1.0	Ref	6	0.8	0.3–2.1	
Yes	363	1.0	0.8–1.3	28	1.4	0.9–2.4	1.7 (0.6–4.9)
Herbicides							
No	232	1.0	Ref	12	1.0	0.5–1.9	
Yes	260	1.1	0.9–1.4	23	1.6	0.9–2.8	1.4 (0.6–3.4)
Fungicides							
No	433	1.0	Ref	28	1.2	0.8–1.9	
Yes	44	1.0	0.7–1.5	5	1.5	0.5–4.5	1.2 (0.4–4.2)

[1]Nonfarmers were excluded from this analysis.–[2]OR, adjusted for age, vital status and state.–[3]Ref, reference category was nonasthmatic farmers not exposed to each pesticide.

TABLE V – RISKS OF NHL AMONG ASTHMATIC FARMERS BY AGE AT FIRST DIAGNOSIS OF ASTHMA AND DURATION OF PESTICIDE USE[1]

Age at first diagnosis (years)	Duration of pesticide use					
	≤50th percentile			>50th percentile		
	Cases	OR[2]	95% CI	Cases	OR	95% CI
Any pesticide						
≤30	3	1.0	Ref[3]	8	4.5	0.7–27.3
>30	6	16.3	1.7–156.8	6	5.0	0.7–37.1
Crop insecticides						
≤30	4	1.0	Ref	6	2.5	0.3–19.6
>30	3	2.3	0.2–31.1	4	14.1	0.8–257.7
Animal insecticides						
≤30	3	1.0	Ref	6	2.8	0.4–19.5
>30	4	15.1	0.95–240.2	8	5.0	0.7–37.8
Herbicides						
≤30	2	1.0	Ref	6	1.7	0.1–29.4
>30	4	3.2	0.1–99.5	4	2.3	0.1–51.3

[1]Only asthmatic farmers exposed to pesticides were included in this analysis.–[2]OR adjusted for age, vital status and state.–[3]Ref, reference category was asthmatic farmers in the category of ≤30 years of age at first diagnosis of asthma and ≤50th percentile of each pesticide use.

ciation between asthma history and NHL risk. However, we think misclassification *per se* is unlikely to explain the observed effect of asthma because the reported prevalence of asthma in our study (5.5%) was consistent with that reported in other populations, ranging from 5% in the Agricultural Health Study in the United States[34] to 4–6% in rural Saskatchewan in Canada.[33,36] Asthma prevalence was also similar by self (5%) and proxy (6%) respondents.

Although farmers provide considerably accurate detail regarding past pesticide use,[37–39] misclassification of exposure is a concern. Use of proxy respondents may introduce nondifferential misclassification bias;[40] however, responses from proxies are reported to be adequate for epidemiologic studies of pesticides and cancer.[41] Our analyses based on direct interviews found the same pattern of results as seen for proxy respondents (data not shown). Based on a study of the quality of information on pesticide use provided by farmers or their proxy respondents,[42] the degree of misclassification was generally in the range observed for other factors obtained by interview in epidemiologic studies of such factors as diet and use of tobacco and alcohol. Therefore, it appears unlikely that misclassification of exposure could explain the observed increase in the risk of NHL among asthmatics exposed to pesticides.

Differential reporting bias is also a concern in case-control studies and could have resulted from an increased likelihood of cases to remember pesticide exposures compared to controls. However, comparison of reporting by cases and controls regarding pesticide use among our subjects provided no evidence of differential response bias.[37]

In summary, our findings suggest that the risk of NHL among asthmatics with pesticide exposure may be higher than that among nonasthmatics with pesticide exposure. Considering the widespread use of pesticides and the relatively high prevalence of asthma, further studies, particularly with carefully defined asthma diagnosis and biomarkers, such as cytokine levels and activity of different T and NK cells, are needed to confirm these findings and clarify the mechanisms involved.

REFERENCES

1. Parker DM, Whelan SL, Ferlay J, Raymond L, Young J. Cancer incidence in five continents. vol. VII. Lyon: IARC, 1997.
2. Hoover RN. Lymphoma risks in populations with altered immunity—a search for mechanism. Cancer Res 1992;52(Suppl 19): S5477–8.
3. Scherr PA, Mueller NE. Non-Hodgkin's lymphomas. In: Schottenfeld D, Fraumeni JF Jr, eds. Cancer epidemiology and prevention, 2nd ed. New York: Oxford University Press, 1996. 920–45.
4. Bernstein L, Ross RK. Prior medication use and health history as risk factors for non- Hodgkin's lymphoma: preliminary results from a

case-control study in Los Angeles County. Cancer Res 1992;52(Suppl 19):S5510–5.
5. Holly EA, Lele C, Bracci PM, McGrath MS. Case-control study of non-Hodgkin's lymphoma among women and heterosexual men in the San Francisco Bay area, California. Am J Epidemiol 1999;150:375–89.
6. La Vecchia C, Negri E, Franceschi S. Medical history and the risk of non-Hodgkin's lymphomas. Cancer Epidemiol Biomarkers Prev 1992;1:533–6.
7. Vesterinen E, Pukkala E, Timonen T, Aromaa A. Cancer incidence among 78,000 asthmatic patients. Int J Epidemiol 1993;22:976–82.
8. Briggs NC, Levine RS, Brann EA. Allergies and risk of non-Hodgkin's lymphoma by subtype. Cancer Epidemiol Biomarkers Prev 2002;11:401–7.
9. McWhorter WP. Allergy and risk of cancer. A prospective study using NHANESI follow-up data. Cancer 1988;62:451–5.
10. Mills PK, Beeson WL, Fraser GE, Phillips RL. Allergy and cancer: organ site-specific results from the Adventist Health Study. Am J Epidemiol 1992;136:287–95.
11. Pearce N, Bethwaite P. Increasing incidence of non-Hodgkin's lymphoma: occupational and environmental factors. Cancer Res 1992; 52(Suppl 19):S5496–500.
12. Zahm SH, Blair A. Pesticides and non-Hodgkin's lymphoma. Cancer Res 1992;52(Suppl 19):S5485–8.
13. McDuffie HH, Pahwa P, McLaughlin JR, Spinelli JJ, Fincham S, Dosman JA, Robson D, Skinnider LF, Choi NW. Non-Hodgkin's lymphoma and specific pesticide exposures in men: cross-Canada study of pesticides and health. Cancer Epidemiol Biomarkers Prev 2001;10:1155–63.
14. Zheng T, Zahm SH, Cantor KP, Weisenburger DD, Zhang Y, Blair A. Agricultural exposure to carbamate pesticides and risk of non-Hodgkin lymphoma. J Occup Environ Med 2001;43:641–9.
15. Hardell L, Eriksson M, Nordstrom M. Exposure to pesticides as risk factor for non-Hodgkin's lymphoma and hairy cell leukemia: pooled analysis of two Swedish case-control studies. Leuk Lymphoma 2002; 43:1043–9.
16. Colosio C, Corsini E, Barcellini W, Maroni M. Immune parameters in biological monitoring of pesticide exposure: current knowledge and perspectives. Toxicol Lett 1999;108:285–95.
17. Voccia I, Blakley B, Brousseau P, Fournier M. Immunotoxicity of pesticides: a review. Toxicol Ind Health 1999;15:119–32.
18. Klucinski P, Kossmann S, Tustanowski J, Friedek D, Kaminska-Kolodziej B. Humoral and cellular immunity rates in chemical plant workers producing dust pesticides. Med Sci Monit 2001;7:1270–4.
19. Thrasher JD, Heuser G, Broughton A. Immunological abnormalities in humans chronically exposed to chlorpyrifos. Arch Environ Health 2002;57:181–7.
20. Zahm SH, Weisenburger DD, Babbitt PA, Saal RC, Vaught JB, Cantor KP, Blair A. A case-control study of non-Hodgkin's lymphoma and the herbicide 2,4- dichlorophenoxyacetic acid (2,4-D) in eastern Nebraska. Epidemiology 1990;1:349–56.
21. Cantor KP, Blair A, Everett G, Gibson R, Burmeister LF, Brown LM, Schuman L, Dick FR. Pesticides and other agricultural risk factors for non-Hodgkin's lymphoma among men in Iowa and Minnesota. Cancer Res 1992;52:2447–55.
22. Hartge P, Brinton LA, Rosenthal JF, Cahill JI, Hoover RN, Waksberg J. Random digit dialing in selecting a population-based control group. Am J Epidemiol 1984;120:825–33.
23. StataCorp. Stata reference manual: release 7. College Station, TX: Stata Press, 2001.
24. Grunig G, Warnock M, Wakil AE, Venkayya R, Brombacher F, Rennick DM, Sheppard D, Mohrs M, Donaldson DD, Locksley RM, Corry DB. Requirement for IL-13 independently of IL-4 in experimental asthma. Science 1998;282:2261–3.
25. Finotto S, Neurath MF, Glickman JN, Qin S, Lehr HA, Green FH, Ackerman K, Haley K, Galle PR, Szabo SJ, Drazen JM, De Sanctis GT, et al. Development of spontaneous airway changes consistent with human asthma in mice lacking T-bet. Science 2002;295:336–8.
26. Whalen MM, Hariharan S, Loganathan BG. Phenyltin inhibition of the cytotoxic function of human natural killer cells. Environ Res 2000;84:162–9.
27. Li Q, Nagahara N, Takahashi H, Takeda K, Okumura K, Minami M. Organophosphorus pesticides markedly inhibit the activities of natural killer, cytotoxic T lymphocyte and lymphokine-activated killer: a proposed inhibiting mechanism via granzyme inhibition. Toxicology 2002;172:181–90.
28. Terabe M, Matsui S, Noben-Trauth N, Chen H, Watson C, Donaldson DD, Carbone DP, Paul WE, Berzofsky JA. NKT cell–mediated repression of tumor immunosurveillance by IL-13 and the IL-4R-STAT6 pathway. Nat Immunol 2000;1:515–20.
29. Bauer BA, Reed CE, Yunginger JW, Wollan PC, Silverstein MD. Incidence and outcomes of asthma in the elderly. A population-based study in Rochester, Minnesota. Chest 1997;111:303–10.
30. Papi A, Corbetta L, Fabbri LM. What can we learn from late-onset and occupational asthma? Clin Exp Allergy 1998;28(Suppl 5):S174–80.
31. Kitch BT, Levy BD, Fanta CH. Late onset asthma: epidemiology, diagnosis and treatment. Drugs Aging 2000;17:385–97.
32. Barnes PJ. Is asthma a nervous disease? The Parker B. Francis Lectureship. Chest 1995;107(Suppl 3):S119–25.
33. Senthilselvan A, McDuffie HH, Dosman JA. Association of asthma with use of pesticides. Results of a cross-sectional survey of farmers. Am Rev Respir Dis 1992;146:884–7.
34. Hoppin JA, Umbach DM, London SJ, Alavanja MC, Sandler DP. Chemical predictors of wheeze among farmer pesticide applicators in the Agricultural Health Study. Am J Respir Crit Care Med 2002;165: 683–9.
35. Toren K, Brisman J, Jarvholm B. Asthma and asthma-like symptoms in adults assessed by questionnaires. A literature review. Chest 1993; 104:600–8.
36. Masley ML, Semchuk KM, Senthilselvan A, McDuffie HH, Hanke P, Dosman JA, Cessna AJ, Crossley MF, Irvine DG, Rosenberg AM, Hagel LM. Health and environment of rural families: results of a Community Canvass survey in the Prairie Ecosystem Study (PECOS). J Agric Saf Health 2000;6:103–15.
37. Blair A, Zahm SH. Patterns of pesticide use among farmers: implications for epidemiologic research. Epidemiology 1993;4:55–62.
38. Blair A, Tarone R, Sandler D, Lynch CF, Rowland A, Wintersteen W, Steen WC, Samanic C, Dosemeci M, Alavanja MC. Reliability of reporting on life-style and agricultural factors by a sample of participants in the Agricultural Health Study from Iowa. Epidemiology 2002;13:94–9.
39. Hoppin JA, Yucel F, Dosemeci M, Sandler DP. Accuracy of self-reported pesticide use duration information from licensed pesticide applicators in the Agricultural Health Study. J Expo Anal Environ Epidemiol 2002;12:313–8.
40. Johnson RA, Mandel JS, Gibson RW, Mandel JH, Bender AP, Gunderson PD, Renier CM. Data on prior pesticide use collected from self- and proxy respondents. Epidemiology 1993;4:157–64.
41. Brown LM, Dosemeci M, Blair A, Burmeister L. Comparability of data obtained from farmers and surrogate respondents on use of agricultural pesticides. Am J Epidemiol 1991;134:348–55.
42. Blair A, Kross B, Stewart PA, Ogilivie L, Falk R, Popendorf W, Ward MH, Zahm SH. Comparability of information on pesticide use obtained from farmers and their proxy respondents. J Agric Saf Health 1995;1:165–76.

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Non-Hodgkin's Lymphoma and Specific Pesticide Exposures in Men: Cross-Canada Study of Pesticides and Health[1]

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Abstract

Our objective in the study was to investigate the putative associations of specific pesticides with non-Hodgkin's Lymphoma [NHL; International Classification of Diseases, version 9 (ICD-9) 200, 202]. We conducted a Canadian multicenter population-based incident, case (n = 517)-control (n = 1506) study among men in a diversity of occupations using an initial postal questionnaire followed by a telephone interview for those reporting pesticide exposure of 10 h/year or more, and a 15% random sample of the remainder. Adjusted odds ratios (ORs) were computed using conditional logistic regression stratified by the matching variables of age and province of residence, and subsequently adjusted for statistically significant medical variables (history of measles, mumps, cancer, allergy desensitization treatment, and a positive history of cancer in first-degree relatives). We found that among major chemical classes of herbicides, the risk of NHL was statistically significantly increased by exposure to phenoxyherbicides [OR, 1.38; 95% confidence interval (CI), 1.06–1.81] and to dicamba (OR, 1.88; 95% CI, 1.32–2.68). Exposure to carbamate (OR, 1.92; 95% CI, 1.22–3.04) and to organophosphorus insecticides (OR, 1.73; 95% CI, 1.27–2.36), amide fungicides, and the fumigant carbon tetrachloride (OR, 2.42; 95% CI, 1.19–5.14) statistically significantly increased risk. Among individual compounds, in multivariate analyses, the risk of NHL was statistically significantly increased by exposure to the herbicides 2,4-dichlorophenoxyacetic acid (2,4-D; OR, 1.32; 95% CI, 1.01–1.73), mecoprop (OR, 2.33; 95% CI, 1.58–3.44), and dicamba (OR, 1.68; 95% CI, 1.00–2.81); to the insecticides malathion (OR, 1.83; 95% CI, 1.31–2.55), 1,1,1-trichloro-2,2-bis (4-chlorophenyl) ethane (DDT), carbaryl (OR, 2.11; 95% CI, 1.21–3.69), aldrin, and lindane; and to the fungicides captan and sulfur compounds. In additional multivariate models, which included exposure to other major chemical classes or individual pesticides, personal antecedent cancer, a history of cancer among first-degree relatives, and exposure to mixtures containing dicamba (OR, 1.96; 95% CI, 1.40–2.75) or to mecoprop (OR, 2.22; 95% CI, 1.49–3.29) and to aldrin (OR, 3.42; 95% CI, 1.18–9.95) were significant independent predictors of an increased risk for NHL, whereas a personal history of measles and of allergy desensitization treatments lowered the risk. We concluded that NHL was associated with specific pesticides after adjustment for other independent predictors.

Introduction

NHL[4] has been epidemiologically associated with farming (1–8), with certain farm practices (9), with pesticide exposure (10–13), and with certain other occupations (14–17). The term pesticide is used to denote a wide variety of chemicals used to destroy weeds (herbicides), insects (insecticides), and mold (fungicides). Such chemicals are widely used in agriculture, horticulture, and forestry, and in the secondary processing of the products of these primary industries. Many of the NHL and pesticide case-control or cohort studies focused either on a small geographical area (1, 2, 4) or on one occupational group (2, 4, 5, 9). Our study encompassed six provinces of Canada with diverse agricultural practices and a number of different types of occupational and nonoccupational exposures to pesticides. Non-Hodgkin's lymphoma incidence rates have been increasing in Canada for the last 25 years reflecting a worldwide trend (18) that has not been explained by improved diagnostic (19) methods or record-keeping (20).

Materials and Methods

Study Population. We conducted a population-based case-control study among men resident in six Canadian provinces to

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[3] Dr. Choi was a collaborator who is now deceased.

[4] The abbreviations used are: NHL, non-Hodgkin's lymphoma; DDT, 1,1,1-trichloro-2,2-bis (4-chlorophenyl) ethane; STS, soft tissue sarcoma; HD, Hodgkin's disease; MM, multiple myeloma; 2,4-D, 2,4-dichlorophenoxyacetic acid; MCPA, 4-chloro-2-methylphenoxyacetic acid; 2,4,5-T, 2,4,5-trichlorophenoxyacetic acid; OR, odds ratio; OR_{adj}, adjusted OR; 95% CI, 95% confidence interval.

test the pesticide-exposure hypothesis related to four rare tumors. Incident cases among men, ages 19 years or over, with a first diagnosis of STS, HD, NHL [International Classification of Diseases, version 9 (ICD-9), code 200 or 202], or MM diagnosed between September 1, 1991, and December 31, 1994, were eligible. To balance the number of cases by geographical regions, each province was assigned a target number of cases in each tumor category. Each province ceased to ascertain cases when their preassigned target was reached. This report is based solely on cases diagnosed with NHL. Cases were ascertained from provincial Cancer Registries except in Quebec, for which hospital ascertainment was used. The Cancer Registries and hospitals provided information, including pathology reports, to confirm the diagnosis. Pathological material was reviewed and classified according to the working formulation by the reference pathologist. Misclassified and ineligible (*e.g.*, Kaposi's sarcoma, known HIV-positive) cases were excluded. Subjects for whom pathological material was unavailable remained in the study. After physician consent was received, postal questionnaires and informed consent forms were mailed to potential cases. Surrogates for deceased cases were not contacted.

Men, ages 19 years and older, selected at random within age constraints from the provincial Health Insurance records (Alberta, Saskatchewan, Manitoba, Quebec), computerized telephone listings (Ontario), or voters' lists (British Columbia) were potential controls. The random control subject selection was stratified by age ± 2 years to be comparable with the age distribution of the entire case group (STS, HD, NHL, and MM) within each province. Postal questionnaires and informed consent forms were mailed to potential controls. Surrogates for deceased persons were ineligible as controls. All of the participating control subjects were used in the statistical analyses of each cancer site.

Pilot Study. We conducted a pilot study (21) in each provincial region to test study procedures and to determine an operational definition of pesticide exposure to distinguish between environmental (which includes bystander and incidental) and more intensive exposure. Nonoccupational use of pesticides (home, garden, hobby) was included. There were few individuals who were completely free of being exposed to pesticides. Therefore, we constructed graphs that demonstrated that the most efficient definition of pesticide exposure, which discriminated (*a*) between incidental, bystander, and environmental exposure as compared with more intensive exposure and (*b*) between cases and controls, was a cumulative total of 10 h per year to any combination of pesticides. The screening questions in the postal questionnaire were used to trigger telephone interviews among those with cumulative exposure of ≥10 h/year to any combination of herbicides, insecticides, fungicides, fumigants, and/or algicides. The 68 cases and 103 controls who participated in the pilot study are not included in this report.

Pesticides. Pesticide is a generic term describing a variety of compounds of diverse chemical structures and biological modes of action. In this study, the term pesticide refers primarily to herbicides, insecticides, fungicides, and fumigants.

We conducted a validation pilot study of the modified questionnaires (21). Volunteer farmers ($n = 27$) completed the questionnaires and granted permission for us to access their records of purchases through their local agrochemical supplier. The concordance between the two sources was excellent and discordance was explainable by (*a*) the farmer paid in cash and the supplier discarded the record; (*b*) the farmer purchased the agrochemical in the United States, and, therefore, the local supplier did not have a record; (*c*) the farmer paid for professional ground or aerial spraying, and the account was listed in another name; or (*d*) the supplier had destroyed the records.

Questionnaires. The questionnaires were modified versions of the telephone interview questionnaire that was used in studies of pesticide exposure and rare tumors in Kansas (11) and Nebraska (13). With permission, we modified the questionnaire to create postal and telephone interview questionnaires. To control for the effects of other variables known or suspected to be associated with the development of NHL after conducting an extensive literature review, we used the postal questionnaire to capture demographic characteristics, antecedent medical history, family history of cancer, detailed lifetime job history, and occupational exposure history to selected substances, accidental pesticide spills, and use of protective equipment, as well as details of cigarette smoking history. The telephone questionnaire characterized exposure to individual pesticides. The pesticide data were collected at several levels beginning with the broadest categories (*e.g.*, minimal exposure, occupations with potential pesticide exposure) and progressing sequentially to major classes (*e.g.*, herbicides); to chemical groups (*e.g.*, phenoxy herbicides); and finally to individual compounds (*e.g.*, 2,4-D, MCPA, and 2,4,5-T).

In this report, we focus on lifetime exposure to individual pesticides classified by active ingredients and to major chemical classes of herbicides, insecticides, fungicides, and fumigants. We classified exposure by the number of herbicides, insecticides, fungicides, and fumigants reported by cases and controls as well as by the number of days per year of exposure to individual compounds.

Each subject who reported 10 h per year or more of exposure to pesticides (any combination of compounds) as defined by the screening questions, and a 15% random sample of the remainder was mailed a list of pesticides (both chemical and brand names) and an information letter. Each subject was subsequently telephoned to obtain details of pesticide use.

The listed pesticides were chosen for inclusion (22–25): (*a*) if the compound was ever registered for use in Canada and reviewed by the IARC; (*b*) if the pesticide was recently banned or restricted in Canada by the federal licensing agency; or (*c*) if the pesticide was commonly used in Canada for specific purposes.

To ensure consistency, we developed and distributed manuals for provincial study coordinators, interviewers, and data managers. Before commencing data collection, we held a 2-day workshop with provincial coordinators to review data collection procedures and policies, to practice interviewing skills, and to review SPSS-DE (Statistical Packages for the Social Sciences-Data Entry),[5] the custom data entry program that we used. On receipt of a postal questionnaire, the provincial coordinator reviewed it for internal consistency and completeness. Data were computer-entered and verified in the province of origin, transported to the coordinating center, and rechecked for completeness, after which statistical analyses were performed.

Copies of the questionnaires and additional information on pesticides that were not included in this report are available from the corresponding author.

Pathology Review. Pathologists in participating provinces were requested to send blocks or slides of tumor tissue removed at surgery to the reference pathologist. Ten subjects with Ka-

[5] SPSS-Data Entry II Statistical Package for the Social Sciences: Statistical Data Analysis. SPSS Inc., Chicago, Illinois, 1998.

Table 1 Comparisons of demographic, antecedent personal medical, general pesticide exposures and cigarette smoking history between cases of NHL and control subjects based on the postal questionnaire

	NHL, n = 517		Controls, n = 1506		OR[a] (95% CI)
	n	%	n	%	
Age, yr					
<30	64	12.4	356	23.6	
30–39	87	16.8	255	16.9	
40–49	111	21.5	238	15.8	
50–59	143	27.7	370	25.6	
>60	112	21.7	287	19.0	
Mean ± SD	57.7 ± 14		55.0 ± 16		
Residence on a farm at any time					
Yes	235	45.5	673	44.7	
No (reference)	279	54.0	828	55.0	1.06 (0.86–1.20)
Missing	3	0.6	5	0.3	
Pesticide exposure (screening question)					
<10 h/yr (reference)	379	73.3	1142	75.8	
≥10 h/yr	138	26.7	364	24.2	1.22 (0.96–1.55)
Smoking History					
Nonsmoker (reference)	160	30.9	526	34.9	
Ex-smoker	254	49.1	648	43.0	1.10 (0.86–1.41)
Current smoker	91	17.6	298	19.8	0.98 (0.72–1.33)
Missing data	12	2.3	34	2.3	
Current or ex-smoker	345	66.7	946	62.8	1.06 (0.86–1.20)
Medical History[b]					
Measles (yes)	251	48.5	888	59.0	**0.64 (0.51–0.79)**
Mumps (yes)	194	37.5	588	39.0	**0.75 (0.60–0.93)**
Previous cancer (yes)	73	14.1	87	5.8	**2.43 (1.71–3.44)**
Skin-prick allergy test	34	6.6	196	13.0	**0.52 (0.34–0.76)**
Allergy desensitization shots (yes)	18	3.5	114	7.6	**0.49 (0.29–0.83)**
Family history of cancer any first-degree relative (yes)	219	42.4	497	33.0	**1.31 (1.05–1.62)**

[a] OR stratified by age and by province of residence.

[b] Also tested and found to be unassociated: acne; asthma; celiac disease; chickenpox; diabetes; hay fever; mononucleosis; rheumatic fever; rheumatoid arthritis; ringworm; shingles; syphilis; tuberculosis; urinary tract infections; whooping cough; allergies; drug treatment for overactive thyroid; treatment for head lice, body lice, or scabies; medical implants; drug treatment for epilepsy; tonsillectomy; positive allergy prick skin test, patch skin test, or positive patch skin test for allergy.

posi's sarcoma were omitted on the basis of the etiological association with HIV infection. Any other known HIV-positive subjects had been previously excluded. Eighty-four % (436 of 517) of the NHL tumors were validated. Because of a change midstudy in some hospitals' policies regarding supplying pathological material without charge, we were unable to obtain the remaining samples.

Statistical Analyses. Data from the postal and telephone interviews were merged by using the identification number. Of the individuals selected randomly for a telephone interview, most had used one or no chemical pesticides. We reviewed these data and decided to include them in the statistical analyses because they might be informative with respect to low levels of exposure to pesticides and their inclusion maximized our sample size with respect to other known or suspected risk factors for NHL. We conducted descriptive analyses of each variable, which included, where applicable, frequencies, rangcs, means ± SD, and median values for cases and controls separately.

To evaluate putative risk factors for NHL, conditional logistic regression was used to compute ORs and 95% CIs, stratifying by age groups and province of residence.[6] ORs were calculated for categorical variables related to medical history that were selected based on previous studies (*e.g.*, measles, mumps, previous cancer, allergy desensitization treatment, skin prick allergy test); pesticide exposure (<10 and ≥10 h per year); and smoking history. Using conditional logistic regression, ORs were also calculated for (*a*) major chemical classes of herbicides, insecticides, fungicides, and fumigants; and (*b*) for individual active chemicals. The statistically significant ($P < 0.05$) medical variables were used to adjust the effect of exposure to pesticides classified by major chemical group and by individual active chemical. Given the study sample size and the case-control ratio, *a priori* power calculations indicated that we had sufficient statistical power to detect an OR of 2 when at least 1% of the controls was exposed to a specific pesticide or chemical class of pesticide. Conditional logistic analyses (26) were conducted that retained in the model, all covariates for which the P was ≤.05. The criterion for entry into models was a $P \leq 0.20$ in bivariate age and province stratified analyses.

We created dose-response levels based on days/year of personally mixing or applying selected herbicides, insecticides, fungicides, and fumigants. We reported ORs stratified by age and province of residence. We created exposure categories for exposures to multiple different herbicides, insecticides, fungicides, and fumigants. For these analyses, the unexposed category was specific to the class of pesticide. We also created exposure categories for exposures to combinations of herbicides, insecticides, fungicides, and fumigants for which the reference group did not report exposure to any of those classes of pesticides.

[6] EGRET Intuitive Software for DOS Micros Statistics and Epidemiology Research Corporation, 1993.

Table 2 Herbicides: frequency of exposure to herbicides classified into major chemical classes and as individual compounds

The list includes only those reported by 1% or more of responders.

Major chemical classes	NHL n = 517		Controls n = 1506		OR[a] (95% CI)	OR_{adj}[b] (95% CI)
	n exposed	% exposed	n exposed	% exposed		
Phenoxyherbicides,[c] exposed	131	25.3	319	21.2	**1.46 (1.09–1.82)**	**1.38 (1.06–1.81)**
Individual phenoxyherbicides						
2,4-D	111	21.5	293	19.5	1.26 (0.97–1.64)	**1.32 (1.01–1.73)**
Mecoprop	53	10.2	81	5.4	**2.23 (1.38–3.07)**	**2.33 (1.58–3.44)**
MCPA	17	3.3	46	3.1	1.08 (0.59–1.94)	1.10 (0.60–2.00)
Diclofopmethyl	9	1.7	25	1.7	0.96 (0.42–2.20)	0.95 (0.41–2.22)
Phosphonic acid,[d] exposed	63	12.2	147	9.8	1.42 (0.95–1.90)	1.40 (0.94–1.89)
Individual phosphonic herbicides						
Glyphosate (Round-up)	51	9.9	133	8.8	1.26 (0.87–1.80)	1.20 (0.83–1.74)
Thiocarbamates,[e] exposed	21	4.1	49	3.3	1.41 (0.62–2.20)	1.46 (0.82–2.58)
Individual thiocarbamate herbicides						
Diallate (n exposed)	11	2.1	29	1.9	1.26 (0.59–2.67)	1.46 (0.68–3.14)
Phenols: Bromoxynil,[f] exposed	16	3.1	48	3.2	1.05 (0.41 1.69)	1.07 (0.58–1.99)
Dicamba,[g] exposed	73	14.1	131	8.7	**1.92 (1.39–2.66)**	**1.88 (1.32–2.68)**
Individual dicamba herbicides						
Dicamba (Banvel or Target)	26	5.0	50	3.3	1.59 (0.95–2.63)	**1.68 (1.00–2.81)**
Dinitroaniline,[h] exposed	11	2.1	31	2.1	1.17 (0.56–2.41)	1.20 (0.61–2.35)
Individual dinitroaniline herbicides						
Trifluralin	11	2.1	31	2.1	1.17 (0.56–2.41)	1.06 (0.50–2.22)

[a] ORs calculated with strata for the variables of age and province of residence.
[b] ORs adjusted for statistically significant medical variables (history of measles, mumps, cancer, allergy desensitization shots, and a positive family history of cancer in a first-degree relative), and with strata for the variables of age and province of residence.
[c] Phenoxyherbicides include the phenoxyacetic acids (*e.g.*, 2,4-D and MCPA), the phenoxy-2-propionic acids (*e.g.*, mecoprop); the phenoxybutanoic acids (*e.g.*, 2,4-DB) and other phenoxyalkanoic acids (*e.g.*, diclofopmethyl).
[d] Glyphosate is the only phosphonic acid herbicide reported by more than 1% of responders. Round-up, Touchdown, Victor, Wrangler, Laredo do not include dicamba, and Rustler is a mixture of dicamba and glyphosate.
[e] Thiocarbamate herbicides include diallate and triallate.
[f] Bromoxynil is the only phenol herbicide included.
[g] Dicamba as a major chemical class includes Banvel, and Target, and a mixture of dicamba and glyphosate (Rustler), or mixtures of dicamba, 2,4-D, and mecoprop (Dynel DS, Killex).
[h] Dinitroaniline herbicides include ethalfluralin and trifluralin.

Ethics. The protocol, letters of informed consent, questionnaires, and all other correspondence with potential subjects were approved by the relevant agencies in each province. All of the information that could be used to identify individuals remained within the province of origin under the control of the provincial principal investigators.

Results

Data from postal questionnaires based on responses from 517 NHL cases (67.1% of those contacted) and 1506 control subjects (48.0% of those contacted) were analyzed. Similar percentages of potential subjects resident in rural and urban areas responded. There were higher percentages of responders in the middle-age group than at either extreme among both cases and controls. Detailed information related to their pesticide exposure history was obtained by telephone interview from 119 NHL cases and 301 control subjects who indicated pesticide exposure of 10 h per year or more. A 15% random sample of cases and controls who indicated pesticide exposure of less than 10 h/year was also interviewed by telephone, resulting in detailed pesticide exposure information on 60 cases of NHL and on 155 controls. The total telephone interviewed sample consisted of 179 cases of NHL and 456 controls.

A summary of selected demographic, antecedent personal and familial medical history, general pesticide exposure as measured by the screening questions, and cigarette smoking history comparisons of NHL cases and population-based controls is shown in Table 1. Because all of the controls (age-matched for STS, MM, HD, and NHL) were used in the analysis, cases were older than controls. Cases and controls were similar in their smoking patterns. Cases were less likely to have a history of measles or mumps and more likely to have a personal history of a previous primary cancer. Cases were more likely than controls to have a positive family history of cancer, whereas more controls had undergone allergy desensitization injections. A slightly higher proportion of cases than controls indicated cumulative exposure to pesticides of ≥10 h per year.

Table 2 summarizes reported exposure to herbicides classified by major chemical classes (phenoxy, phosphonic acid, thiocarbamates, phenols, dicamba, and dinitroaniline) and by individual compounds for which at least 1% of responders reported exposure. ORs are also shown after adjustment for the statistically significant ($P < 0.05$) variables reviewed in Table 1, which included a history of measles, mumps, cancer, and allergy desensitization shots and a positive history of cancer in a first-degree relative. Cases experienced a significantly higher frequency of exposure to phenoxyherbicides, to dicamba or a mixture including dicamba, to 2,4-D, and to mecoprop.

Table 3 summarizes the insecticide exposure data. Exposure to two major chemical classes, carbamates and organophosphates, was statistically significantly associated with NHL, whereas exposure to organochlorines as a group was not.

Table 3 Insecticides: frequency of exposure to insecticides classified into major chemical classes and as individual compounds

Major chemical classes	NHL n = 517		Controls n = 1506		OR[a] (95% CI)	OR_{adj}[b] (95% CI)
	n exposed	% exposed	n exposed	% exposed		
Carbamates,[c] exposed	37	7.2	60	4.0	**1.95 (1.25–3.05)**	**1.92 (1.22–3.04)**
Individual carbamate insecticides						
Carbaryl	25	4.8	34	2.3	**2.05 (1.18–3.55)**	**2.11 (1.21–3.69)**
Carbofuran	9	1.7	18	1.2	1.58 (0.68–3.67)	1.64 (0.70–3.85)
Methomyl	6	1.2	13	0.9	1.86 (0.67–5.17)	1.65 (0.54–5.03)
Organochlorine, (1)[d] exposed	50	9.7	134	8.9	1.16 (0.81–1.66)	1.27 (0.87–1.84)
Individual organochlorine (1) insecticides						
Chlordane	36	7.0	105	7.0	1.06 (0.71–1.59)	1.11 (0.74–1.69)
Lindane	15	2.9	23	1.5	**2.05 (1.01–4.16)**	**2.06 (1.01–4.22)**
Aldrin	10	1.9	6	0.4	**3.81 (1.34–10.79)**	**4.19 (1.48–11.96)**
Organochlorine (2) diphenylchlorides[e] exposed	86	16.6	233	15.5	1.24 (0.94–1.65)	1.21 (0.90–1.62)
Individual organochlorine (2) diphenylchlorides						
Methoxychlor	65	12.6	201	13.3	1.08 (0.79–1.47)	1.02 (0.74–1.41)
DDT	32	6.2	59	3.9	**1.63 (1.03–2.57)**	**1.73 (1.08–2.76)**
Organophosphorus,[f] exposed	90	17.4	167	11.1	**1.69 (1.26–2.27)**	**1.73 (1.27–2.36)**
Individual organophosphorus insecticides						
Malathion	72	13.9	127	8.4	**1.77 (1.28–2.46)**	**1.83 (1.31–2.55)**
Dimethoate	22	4.3	50	3.3	1.20 (0.71–2.03)	1.20 (0.70–2.06)
Diazinon	18	3.5	28	1.9	1.72 (0.92–3.19)	1.69 (0.88–3.24)

[a] ORs calculated with strata for the variables of age and province of residence.
[b] ORs adjusted for statistically significant medical variables (history of measles, mumps, cancer, allergy desensitization shots and a positive family history of cancer in a first-degree relative), and with strata for the variables of age and province of residence.
[c] Carbamate insecticides include carbaryl, carbofuran, and methomyl.
[d] Organochlorine insecticides class one includes aldrin; chlordane; dieldrin; endrin; heptachlor; lindane; and a mixture of lindane, carbathiin, and thiram (Vitavex).
[e] Organochlorine (2) diphenylchloride insecticides include DDT and methoxychlor.
[f] Organophosphorus insecticides include malathion, chlorpyrifos, diazinon, dimethoate, parathion, methidathion, and trichlorfon.

Table 4 Fungicides: frequency of exposure to fungicides classified into major chemical classes and as individual compounds

Major chemical classes	NHL n = 517		Controls n = 1506		OR[a] (95% CI)	OR_{adj}[b] (95% CI)
	n exposed	% exposed	n exposed	% exposed		
Amide,[c] exposed	30	5.8	58	3.9	**1.69 (1.05–2.73)**	**1.70 (1.04–2.78)**
Individual amide fungicides						
Captan	20	3.9	24	1.6	**2.48 (1.33–4.63)**	**2.51 (1.32–4.76)**
Vitavax	10	1.9	39	2.6	0.88 (0.42–1.85)	0.88 (0.41–1.87)
Aldehyde,[d] exposed	7	1.4	25	1.7	0.85 (0.35–2.07)	0.92 (0.37–2.29)
Individual aldehyde fungicides						
Formaldehyde	7	1.4	255	1.7	0.85 (0.35–2.07)	0.92 (0.37–2.29)
Mercury Containing,[e] exposed	18	3.5	48	3.2	1.09 (0.61–1.95)	1.28 (0.70–2.27)
Mercury-containing fungicides						
Mercury dust (n exposed)	15	2.9	39	2.6	1.08 (0.57–2.04)	1.23 (0.64–2.35)
Mercury liquid (n exposed)	8	1.5	22	1.5	1.15 (0.49–2.69)	1.40 (0.74–3.22)
Sulphur Compounds	17	3.3	21	1.4	**2.26 (1.16–4.40)**	**2.80 (1.41–5.57)**

[a] ORs calculated with strata for the variables of age and province of residence.
[b] ORs adjusted for statistically significant medical variables (history of measles, mumps, cancer, allergy desensitization shots, and a positive family history of cancer in a first-degree relative), and with strata for the variables of age and province of residence.
[c] Amide fungicides include captan and a mixture of carbathiin, thiram, and lindane (Vitavax).
[d] Aldehyde fungicides include formaldehyde and a mixture of formaldehyde and iprodione (Rovral Flo).
[e] Mercury-containing fungicides include mercury dusts (Ceresan, Reytosan, and Agrox) and mercury liquids (Panogen, Leytosol, and PMAS).

Among individual carbamate compounds, exposure to carbaryl was statistically significantly associated with NHL. Among organochlorines, exposure to lindane, to aldrin, and to DDT was significantly associated with NHL. Malathion was the only individual organophosphate exposure statistically significantly associated with NHL.

Exposure to fungicides is summarized in Table 4. The fungicides with an amide group (OR_{adj}, 1.70; 95% CI, 1.04–2.78) were associated with NHL, whereas aldehydes and those containing mercury were not. Among individual amide-containing compounds, exposure to captan (OR_{adj}, 2.51; 95% CI, 1.32–4.76) was associated with NHL.

Malathion used as a fumigant was not associated with NHL (Table 5). There were fewer users of malathion as a fumigant compared with its use on crops. Carbon tetrachloride fumigant exposure (OR_{adj}, 2.42; 95% CI, 1.19–5.14) was associated with NHL.

Table 6 shows the results of a conditional logistic regres-

Table 5 Frequency of exposure to fumigants: individual compounds

Individual compounds+	NHL n = 517		Controls n = 1506		OR[a] (95% CI)	OR_{adj}[b] (95% CI)
	n exposed	% exposed	n exposed	% exposed		
Malathion[c]	12	2.3	23	1.5	1.49 (0.72–3.11)	1.54 (0.74–3.22)
Carbon tetrachloride[d]	13	2.5	18	1.2	**2.13 (1.02–4.47)**	**2.42 (1.19–5.14)**

[a] ORs calculated with strata for the variables age and province of residence.
[b] ORs adjusted for statistically significant medical variables (history of measles, mumps, cancer, allergy desensitization shots, and a positive family history of cancer in a first-degree relative) and with strata for the variables age and province of residence.
[c] Malathion is an organophosphorus insecticide which has been used indoors as a fumigant.
[d] Carbon tetrachloride was used as a grain fumigant.

Table 6 Most parsimonious model: conditional logistic regression analyses that contained major chemical classes of pesticides and important covariates ($P < 0.05$)

Phenoxyherbicides as a group, carbamate, and organophosphate insecticides, amide group containing fungicides, and carbon tetrachloride users/nonusers were included in the initial multivariate model and found not to contribute significantly to the risk of NHL.

Variable	Parameter Estimate ± SE	OR (95% CI)
Measles (yes)	−0.47 ± 0.11	**0.62 (0.50–0.78)**
Previous cancer (yes)	0.79 ± 0.18	**2.20 (1.54–3.15)**
First-degree relative with cancer (yes)	0.32 ± 0.11	**1.37 (1.10–1.71)**
Allergy desensitization shots (yes)	−0.65 ± 0.27	**0.52 (0.31–0.89)**
Dicamba mixtures (user)	0.67 ± 0.17	**1.96 (1.40–2.75)**

Table 7 Most parsimonious model: conditional logistic regression analyses that contained individual chemical pesticides and important covariates ($P < 0.05$)

Among individual pesticides, carbaryl, lindane, DDT, and malathion insecticides, and captan fungicide user/nonuser were included in the initial multivariate model and found not to contribute significantly to the risk of NHL.

Variable	Parameter estimate ± SE	OR (95% CI)
Measles (yes)	−0.48 ± 0.11	**0.50 (0.45–0.83)**
Previous cancer (yes)	0.80 ± 0.18	**2.23 (1.56–3.19)**
First-degree relative with cancer (yes)	0.32 ± 0.11	**1.38 (1.11–1.72)**
Allergy desensitization shots (yes)	−0.68 ± 0.27	**0.51 (0.30–0.87)**
Mecoprop (user)	0.80 ± 0.20	**2.22 (1.49–3.29)**
Aldrin (user)	1.23 ± 0.54	**3.42 (1.18–9.95)**

sion model that included major chemical classes of pesticides and all other covariates for which $P < 0.05$. The variables that remained statistically significantly associated with increased risk of NHL were a previous personal history of another malignancy, a history of cancer among first-degree relatives, and exposure to dicamba and mixtures containing dicamba. ORs for a personal history of measles or of allergy desensitization injections were significantly lower than those without this history. Table 7 summarizes a similar model that included individual pesticides and all of the other covariates for which $P <$ 0.05 and in which mecoprop and aldrin exposure as well as the same covariates as in Table 6 were associated with NHL.

Table 8 shows the frequency of exposure to selected individual herbicides, insecticides, fungicides, and fumigants, stratified by the average number of days per year of exposure. In general, the results of these dose-response analyses are consistent with the exposed/nonexposed findings. Those compounds for which we found statistically significant case-control differences also have elevated ORs based on strata of the variable "days per year of exposure" (mecoprop, dicamba, malathion, DDT, captan, carbon tetrachloride, and sulfur). The exceptions were 2,4-D, for which there was no dose-response relationship, and glyphosate, which was not significant for exposure but for which we demonstrated a dose-response relationship.

Table 9 compares the frequencies of multiple herbicide, insecticide, fungicide, and fumigant use among cases and controls. Cases are significantly more likely to report exposure to between two and four herbicides or insecticides but not to five and more of either. An elevated OR was found for exposure to two or more fungicides. Table 9 also shows a dose-response relationship in comparisons of subjects who reported no pesticide exposure and those who reported using five or more pesticides.

Discussion

The hypothesis that farming (1–8), agricultural practices (9), and pesticide exposure (10–13, 22–25) are associated with NHL has been tested in a number of occupational studies. Not all of the studies confirm an association (27–29). Pesticides have diverse chemistry and biological modes of action. In addition to the active ingredients, there are emulsifiers, carriers, dispersants, and a variety of agents used to formulate liquids, granular and mists. The major chemical classes of *a priori* interest based on epidemiological studies (10–13, 22–25) were phenoxyherbicides, organophosphorus, organochlorines, aldehydes, and carbon tetrachloride. Occupational exposure to 2,4-D, 2,4,5-T, carbaryl, chlordane, DDT, diazinon, dichlorvos, lindane, malathion, nicotine, and toxaphene has been reported to be associated with NHL. In addition, our interest focused on pesticides classified as possibly or probably carcinogenic to humans based on evaluations by the IARC expert panels (Refs. 22–25; phenoxyherbicides including 2,4-D, MCPA, and 2,4,5-T as a group, atrazine, chlordane, DDT, dichlorvos, heptachlor, and pentachlorophenol). Our bivariate results for exposure to groups of phenoxyherbicides or dicamba-containing herbicides, for carbamates and organophosphorus insecticides, and for amide fungicides and for carbon tetrachloride were not attenuated when simultaneously adjusted for the important medical covariates (history of measles, mumps, cancer, allergy desensitization shots, and a positive history of cancer in a first-degree relative).

Among individual compounds, our results that related to exposure to 2,4-D, mecoprop, dicamba, malathion, DDT, carbaryl, lindane, aldrin, captan, and sulfur compounds were not attenuated after simultaneous adjustment for the same medical covariates. Clearly, we had few exposed men whose exposure was limited to one pesticide or to one class of pesticides. Our results show elevated risk for exposure to multiple herbicides, insecticides, and fungicides.

Table 8 Frequency of exposure to selected herbicides, insecticides, fungicides, and fumigants stratified by the number of days per year of exposure

Models that included the time variable "days per year" and stratification for age and province of residence were also assessed for the individual herbicide compounds bromoxynil, 2,4-DB, diallate, MCPA, triallate, and treflan. No significant associations were found.

Individual compounds	Days/yr	NHL		Controls		OR[a] (95% CI)
		n	%	*n*	%	
Herbicides						
2,4-D	Unexposed	406	78.5	1213	80.5	1
	>0 and ≤2	55	10.6	160	10.6	1.17 (0.83–1.64)
	>2 and ≤5	36	7.0	82	5.4	1.39 (0.91–2.13)
	>5 and ≤7	9	1.7	20	1.3	1.38 (0.60–3.15)
	>7	11	2.1	31	2.1	1.22 (0.60–2.49)
Mecoprop	Unexposed	464	89.8	1425	94.6	1
	>0 and ≤2	31	6.0	48	3.2	**2.27 (1.40–3.68)**
	≥2	22	4.3	33	2.2	**2.06 (1.17–3.61)**
Phosphonic acid: glyphosate	Unexposed	466	90.1	1373	91.2	1
	>0 and ≤2	28	5.4	97	6.4	1.00 (0.63–1.57)
	>2	23	4.5	36	2.4	**2.12 (1.20–3.73)**
Dicamba	Unexposed	491	95.0	1456	96.7	1
	≥1	26	5.0	50	3.3	1.58 (0.96–2.62)
Insecticides						
Malathion	Unexposed	445	87.0	1379	91.6	1.00
	>0 and ≤2	50	9.7	88	5.8	**1.82 (1.25–2.68)**
	≥2	22	4.3	39	2.6	**1.75 (1.02–3.03)**
DDT	Unexposed	485	93.8	1447	96.1	1.00
	>0 and ≤2	18	3.5	32	2.1	1.75 (0.96–3.21)
	>2	14	2.7	27	1.8	1.50 (0.77–2.91)
Fungicides						
Captan	Unexposed	497	96.1	1482	98.4	1.00
	>0 and ≤2	11	2.1	12	0.8	**2.69 (1.17–6.19)**
	>2	9	1.7	12	0.8	**2.80 (1.13–6.90)**
Sulphur	Unexposed	500	96.7	1485	98.6	1.00
	Exposed ≥1	17	3.3	21	1.4	**2.26 (1.16–4.40)**
Fumigant						
Carbon tetrachloride	Unexposed	504	97.5	1488	98.8	1.00
	>0 and ≤2	13	2.5	18	1.2	**2.13 (1.02–4.47)**

[a] ORs calculated with strata for the variables age and province of residence.

The strength of our results is enhanced by their internal consistency as we applied the strategy of assessing risk by different analytic approaches progressing from exposure to: (*a*) major chemical classes of herbicides, insecticides, fungicides, and fumigants; (*b*) individual compounds within those major chemical classes; and (*c*) individual compounds stratified by days per year of exposure. We constructed models that included potential confounders (*e.g.*, positive history of cancer in a first-degree relative). Generally, the same individual compounds or class of compounds was associated with case status. The risk estimates based on exposure to major chemical classes or to individual compounds tended to be precise, as indicated by the 95% CIs.

Our results confirm previously reported associations of NHL and a personal history of cancer (30, 31), of NHL and a history of cancer among first-degree relatives (32, 33), and of NHL and exposure to selected pesticides (1, 3, 5, 9–13). We were unable to find a previous report suggesting a protective effect of allergy desensitization shots. Koepsell *et al.* reported little association of the number of allergy desensitization shots and MM (34). The relationship between allergy and cancer is complex with well-designed studies reporting opposite results (35–38). Cigarette smoking was not a risk factor overall, confirming one study (39) and contradicting others (40, 41), although certain subtypes (39, 40) of NHL may be associated with cigarette smoking.

The limitations of this study relate to those inherent in the case-control design, specifically the potential for recall bias and for misclassification of pesticide exposure. Hoar *et al.* and Zahm *et al.* (11, 13), as well as others (27–29, 42–45), have dealt extensively with these issues among farmers. We have included individuals in many different occupations as well as home and garden users. These are groups for whom we did not find extensive validation studies. Their inclusion may have biased our dose-response findings toward the null, although the yes/no responses to individual pesticides would be less affected. We reduced the number of surrogate responders by excluding deceased persons from our definition of eligible subjects. This strategy was useful in decreasing the potential for misclassification of exposure.

A second limitation is the less-than-optimal response rates. We continued to recruit subjects in each province until the target numbers were achieved. We compared respondents to nonrespondents using postal codes as an indicator of rural residence, and we did not find a rural bias among respondents.

We reported results for a number of chemical agents and exposures, not all of which were specified in the hypothesis. Therefore, the statistical analyses related to these unspecified agents should be considered exploratory. As a consequence of conducting multiple comparisons, a small number of statistically significant results may be attributable to chance.

The two-tiered study design permitted us to obtain detailed information related to factors other than pesticides that are known or suspected of being etiologically associated with NHL. The mailing of a list of pesticides with both trade and generic chemical names followed by a telephone interview

Table 9 Distribution of numbers of exposures to multiple types of pesticides among cases and controls

	NHL		Controls		OR[a] (95% CI)
	n	%	*n*	%	
Multiple herbicide use					
Unexposed[b]	374	72.3	1148	76.2	1.00
Exposed 1	45	8.7	146	9.7	1.02 (0.70–1.47)
Exposed 2–4	73	14.1	151	10.0	**1.75 (1.27–2.42)**
Exposed ≥5	25	4.8	61	4.1	1.41 (0.84–2.35)
Multiple insecticide use					
Unexposed	370	71.6	1154	76.6	1.00
Exposed 1	44	8.5	127	8.4	1.24 (0.85–1.80)
Exposed 2–4	86	16.6	189	12.6	**1.58 (1.17–2.13)**
Exposed ≥5	17	3.3	36	2.4	1.46 (0.79–2.69)
Multiple fungicide use					
Unexposed	457	88.4	1361	90.4	1.00
Exposed 1	32	6.2	90	6.0	1.08 (0.70–1.67)
Exposed ≥2	28	5.4	55	3.7	1.61 (.99–2.63)
Multiple fumigant use					
Unexposed	487	94.2	1440	95.6	1.00
Exposed ≥1	30	5.8	66	4.4	1.45 (0.91–2.63)
Multiple pesticide use[c]					
Unexposed	357	69.1	1095	72.7	1.00
Exposed 1–4	77	14.9	230	15.3	1.09 (0.81–1.46)
Exposed ≥5	83	16.1	181	12.0	**1.57 (1.16–2.14)**

[a] ORs calculated with strata for the variables age and province of residence.
[b] With the exception of the variable multiple pesticide use, the "unexposed" referent category is specific to the class of pesticides.
[c] The unexposed referent category contains those who did not report exposure to herbicides, insecticides, fungicides, or fumigants.

allowed the collection of detailed information concerning pesticide exposure. The statistical power of our study was enhanced by the large number of cases and controls. In instances of rare exposures (<1% exposed), we had limited statistical power to detect associations. We restricted our analyses of individual pesticide compounds to those for which at least 1% of respondents indicated exposure.

The study was not restricted to pesticide exposure experienced by a specific occupational group. Occupational exposure was quite diverse; single *versus* multiple pesticides; indoor *versus* outdoor applications. For example, men who work in animal confinement buildings, grain elevators, and pesticide manufacturing have different exposure patterns in comparison with grain farmers and commercial applicators. Because this study encompassed a large geographical area of Canada, there was substantial diversity among agricultural enterprises and in the patterns and types of pesticide exposure.

Delineating the putative relationship between exposure to pesticides and NHL is complicated: (*a*) by the subject's exposure to a variety of different pesticides many of which are not mutagenic, teratogenic, or carcinogenic when tested as a single compound; (*b*) by the complexity of formulations of pesticides, the details of which are privileged proprietary information; (*c*) by the diversity of routes of possible exposure, which include ingestion, dermal, inhalation, and ocular; (*d*) by unexpected interactions among seemingly unrelated exposures, such as the increased permeability of rubber gloves to 2,4-D when exposed simultaneously to the insect repellent DEET and sunlight (46); and (*e*) by the role of differential genetic susceptibility.

Garry *et al.* (47) describe a potential mechanism to explain the relationship between exposure to specific pesticides and an increased risk of developing NHL. They have demonstrated specific chromosomal alterations in the peripheral lymphocytes of pesticide applicators exposed to a variety of pesticide classes. A higher frequency of chromosomal breaks involving band 18q21 was found in men who applied only herbicides compared with nonoccupationally exposed controls. Higher frequencies of rearrangements and breaks involving band 14q32 were found among men who applied herbicides, insecticides, and fumigants compared with controls. Reciprocal translocations between chromosomes 14q32 and 18q21 are frequently found in NHL patients.

Our results support previous findings of an association between NHL and specific pesticide exposures. Our strategy of assessing risk by several different approaches, beginning with general categories (*e.g.*, herbicides), proceeding through cumulative pesticide exposure to specific chemical classes, and proceeding further to specific chemicals, proved effective in delineating complex relationships. In our final models, NHL was associated with a personal history of cancer; a history of cancer in first-degree relatives; and exposure to dicamba-containing herbicides, to mecoprop, and to aldrin. A personal history of measles and of allergy desensitization treatments lowered risk.

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References

1. Cantor, K. P., Blair, A., Everett, G., Gibson, R., Burmeister, L. F., Brown, L. M., Schuman, L., and Dick, F. R. Pesticides and other agricultural risk factors for non-Hodgkin's lymphoma among men in Iowa, and Minnesota. Cancer Res., *52:* 2447–2455, 1992.

2. Saftlas, A. F., Blair, A., Cantor, K. P., Hanrahan, L., and Anderson, H. A. Cancer and other causes of death among Wisconsin farmers. Am. J. Ind. Med., *11:* 119–129, 1987.

3. Pearce, N. E., Smith, A. H., and Fisher, D. O. Malignant lymphoma and multiple myeloma linked with agricultural occupation in a New Zealand cancer registration-based study. Am. J. Epidemiol., *121:* 225–237, 1985.

4. Burmeister, L. F., Everett, G. D., Van Lier, S. F., and Isacson, P. Selected cancer mortality and farm practices in Iowa. Am. J. Epidemiol., *118:* 72–77, 1983.

5. Cantor, K. P. Farming and mortality from non-Hodgkin's lymphoma: a case-control study. Int. J. Cancer, *29:* 239–247, 1982.

6. Delzell, E., and Grufferman, S. Mortality among white and non-white farmers in North Carolina 1976–78. Am. J. Epidemiol., *121:* 391–402, 1985.

7. Buesching, D. P., and Wallstadt, L. Cancer mortality among farmers. J. Natl. Cancer Inst. (Bethesda), *72:* 503–504, 1984.

8. Schumacher, M. C. Farming occupations and mortality from non-Hodgkin's lymphoma in Utah: a case-control study. J. Occup. Med., *27:* 580–584, 1985.

9. Wigle, D. T., Semenciw, R. M., Wilkins, K., Riedel, D., Ritter, L., Morrison, H., and Mao, Y. Mortality study of Canadian farm operators: non-Hodgkin's lymphoma mortality and agricultural practices in Saskatchewan. J. Natl. Cancer Inst. (Bethesda), *82:* 575–580, 1990.

10. Hardell, L., Eriksson, M., Lenner, P., and Lundgren, E. Malignant lymphoma and exposure to chemicals especially organic solvents, chlorophenols and phenoxy acids: a case-control study. Br. J. Cancer, *43:* 169–176, 1981.

11. Hoar, S. K., Blair, A., Holmes, F., Boysen, C., Robel, R. J., Hoover, R., and Fraumeni, J. F. Agricultural herbicide use and risk of lymphoma and soft tissue sarcoma. J. Am. Med. Assn., *256:* 1141–1147, 1986.

12. Woods, J. S., Polissar, L., Severson, R. K., Heuser, L. S., and Kulander, E. G. Soft tissue sarcoma and non-Hodgkin's lymphoma in relation to phenoxyherbicide and chlorinated phenol exposure. J. Natl. Cancer Inst., *78:* 899–910, 1987.

13. Zahm, S. H., Weisenburger, D. D., Babbit, P. A., Saal, R. C., Vaught, J. B., Cantor, K. P., and Blair, A. A case control study of non-Hodgkin's lymphoma and agricultural factors in Eastern Nebraska. Epidemiology, *1:* 349–356, 1990.

14. Alavanja, M. C. R., Blair, A., Merkle, S., Teske, J., Eaton, B., and Reed, B. Mortality among forest and soil conservationists. Arch. Environ. Health, *44:* 94–101, 1989.

15. Gallagher, R. P., Threlfall, W. J., Band, P. R., and Spinelli, J. J. Cancer mortality experience of woodworkers, loggers, fishermen, farmers and miners in British Columbia. Natl. Cancer Inst. Monogr., *69:* 163–167, 1985.

16. Kross, B. C., Burmeister, L. F., Ogilvie, L. K., Fuortes, L. J., and Fu, C. M. Proportionate mortality study of golf course superintendents. Am. J. Ind. Med., *29:* 501–506, 1996.

17. Scherr, P. A., Hutchison, G. B., and Neiman, R. S. Non-Hodgkin's lymphoma and occupational exposure. Cancer Res., *52* (Suppl.): 5503s–5509s, 1992.

18. Devesa, S. S., and Fears, T. Non-Hodgkin's lymphoma time trends: United States and international data. Cancer Res., *52* (Suppl.): 5432s–5440s, 1992.

19. Banks, P. M. Changes in diagnosis of non-Hodgkin's lymphoma over time. Cancer Res., *52* (Suppl.): 5453s–5455s, 1992.

20. Holford, T. R., Zheng, T., Magne, S. T., and McKay, L. A. Time trends of non-Hodgkin's lymphoma: are they real? what do they mean? Cancer Res., *52* (Suppl.): 5443s–5446s, 1992.

21. Dosman, J. A., McDuffie, H. H., Pahwa, P., Fincham, S., McLaughlin, J. R., Robson, D., and Theriault, G. Pesticides, Soft Tissue Sarcoma, Lymphoma, and Multiple Myeloma. A Case Control Study in Three Regions of Canada. Report to Health and Welfare Canada on Project 6008-1223. Saskatoon, Canada: University of Saskatchewan, 1990.

22. IARC Working Group. An evaluation of chemicals and industrial processes associated with cancer in humans based on human and animal data. Cancer Res., *40:* 1–12, 1980.

23. IARC. Some halogenated hydrocarbons and pesticide exposures. *In:* Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans, Vol. 41. Lyon, France: IARC, 1986.

24. IARC. Overall Evaluation of Carcinogenicity: An Updating of IARC Monographs, Volumes 1–42, Suppl. 7. Lyon, France: IARC, 1987.

25. IARC. Occupational exposures in insecticide application and some pesticides. *In:* Monographs on the Evaluation of Carcinogenic Risks to Humans, Vol. 53. Lyon, France: IARC, 1991.

26. Breslow, N. E., and Day, N. E. The analysis of case-control studies. *In:* Statistical Methods in Cancer Research, Vol. 1, IARC Sci. Publ. 32. Lyon, France: IARC, 1980.

27. Bond, G. C., Bodner, K. M., and Cook, R. R. Phenoxy herbicides and cancer: insufficient epidemiologic evidence for a causal relationship. Fundam. Appl. Toxicol., *12:* 172–188, 1989.

28. Wiklund, K., Dich, J., and Holm, L-E. Risk of malignant lymphoma in Swedish pesticide appliers. Br. J. Cancer, *56:* 505–508, 1987.

29. Wiklund, K., and Holm, L-E. Trends in cancer risks among Swedish agricultural workers. J. Natl. Cancer Inst. (Bethesda), *77:* 657–664, 1986.

30. Cerhan, J. R., Wallace, R. B., Folsom, A. R., Potter, J. D., Sellers, T. A., Zheng, W., and Lutz, C. T. Medical history risk factors for non-Hodgkin's lymphoma in older women. J. Natl. Cancer Inst. (Bethesda), *89:* 314–318, 1997.

31. Berstein, R., and Ross, R. K. Prior medication use and health history as risk factors for non-Hodgkin's lymphoma: preliminary results from a case-control study in Los Angeles County. Cancer Res., *52* (Suppl.): 5510s–5515s, 1992.

32. Linet, M. S., and Pottern, L. M. Familial aggregation of hematopoietic malignancies and risk of non-Hodgkin's lymphoma. Cancer Res., *52* (Suppl.): 5465s–5473s, 1992.

33. Goldgar, D. E., Easton, D. F., Cannon-Allright, L. A., and Skolnick, M. H. Systematic population-based assessment of cancer risk in first degree relatives of cancer probands. J Natl Cancer Inst. (Bethesda), *86:* 1600–1608, 1994.

34. Koepsell, T. D., Daling, J. R., Weiss, N. S., Taylor, S. W., Olshan, A. F., Swanson, G. M., and Child, M. Antigenic stimulation and the occurrence of multiple myeloma. Am. J. Epidemiol., *126:* 1051–1062, 1987.

35. Vena, J. E., Bona, J. R., Byers, T. E., Middleton, E., Swanson, M. K., and Graham, S. Allergy-related diseases and cancer: an inverse association. Am. J. Epidemiol., *122:* 66–74, 1985.

36. Mills, P. K., Beeson, W. L., Fraser, G. E., and Phillips, R. L. Allergy and cancer: organ site-specific results from the Adventist health study. Am. J. Epidemiol., *136:* 287–295, 1992.

37. Severson, R. K., Davis S., Thomas, D. B., Stevens, R. G., Heuser, L., and Sever, L. E. Acute myelocytic leukemia and prior allergies. J Clin. Epidemiol., *42:* 995–1001, 1989.

38. McDuffie, H. H., Cockcroft, D. W., Talebi, Z., Klaassen, D. J., and Dosman, J. A. Lower prevalence of positive atopic skin tests in lung cancer patients. Chest, *93:* 241–246, 1988.

39. Herrinton, L. J., and Friedman, G. D. Cigarette smoking and risk of non-Hodgkin's lymphoma subtypes. Cancer Epidemiol. Biomark. Prev., *7:* 25–28, 1998.

40. Brown, L. M., Everett, G. D., Gibson, R., Burmeister, L. F., Schuman, L. M., and Blair, A. Smoking and risk of non-Hodgkin's lymphoma, and multiple myeloma. Cancer Causes Control, *3:* 49–55, 1992.

41. Linet, M. S., McLaughlin, J. K., Hsing, A. W., Wacholder, S., CoChien, H. T., Schuman, L. M., Bjelke, E., and Blot, W. J. Is cigarette smoking a risk factor for non-Hodgkin's lymphoma? results from the Lutheran Brotherhood Cohort Study. Leuk. Res., *16:* 621–624, 1992.

42. Blair, A., and Zahm, S. H. Epidemiologic studies of cancer among agricultural populations. *In:* H. H. McDuffie, J. A. Dosman, K. M. Semchuk, S. Olenchock, and A. Senthilselvan (eds.), Agricultural Health and Safety: Workplace, Environment, Sustainability, pp. 111–117. Boca Raton, FL: CRC Lewis Publishers, 1994.

43. Brown, L. M., Dosemeci, M., Blair, A., and Burmeister, L. Comparability of data obtained from farmers and surrogate respondents on use of agricultural pesticides. Am. J. Epidemiol., *134:* 348–355, 1991.

44. Blair, A., and Zahm, S. H. Herbicides and cancer: a review and discussion of methodologic issues. Recent Results Cancer Res., *120:* 132–145, 1990.

45. Blair, and A., Zahm, S. H. Methodologic issues in exposure assessment for case-control studies of cancer and herbicides. Am. J. Ind. Med., *18:* 285–293, 1990.

46. Moody, R. P., and Nadeau, B. Effect of the mosquito repellent DEET and long-wave ultraviolet radiation on permeation of the herbicide 2,4-D and the insecticide DDT in natural rubber gloves. Am. Ind. Hyg. Assn. J., *53:* 436–441, 1992.

47. Garry, V. F., Tarone, R. E., Long, L., Griffith, J., Kelly, J. T., and Burroughs, B. Pesticide appliers with mixed pesticide exposure: G-banded analysis and possible relationship to non-Hodgkin's lymphoma. Cancer Epidemiol. Biomark. Prev., *5:* 11–16, 1996.

Occupational Cancer Research Centre

An Evaluation of Glyphosate Use and the Risk of Non-Hodgkin Lymphoma Major Histological Sub-Types in the North American Pooled Project

Manisha Pahwa, John J. Spinelli, Laura Beane Freeman, Paul A. Demers, Aaron Blair, Punam Pahwa, James A. Dosman, John R. McLaughlin, Shelia Hoar Zahm, Kenneth P. Cantor, Dennis D. Weisenburger, Shelley A. Harris

International Society for Environmental Epidemiology Conference | Sao Paulo, Brazil | August 31, 2015
#868 (Pesticides and Other POPs)

Towards a cancer-free workplace

Disclosure of Competing Financial Interests

None

IARC Evaluation of Glyphosate

- Limited evidence of NHL in humans and sufficient evidence of cancer in animals
- Mechanistic evidence of genotoxicity and oxidative stress
- Classified as Group 2A (probably carcinogenic)

Carcinogenicity of tetrachlorvinphos, parathion, malathion, diazinon, and glyphosate

In March, 2015, 17 experts from 11 countries met at the International Agency for Research on Cancer (IARC; Lyon, France) to assess the carcinogenicity of the organophosphate pesticides tetrachlorvinphos, parathion, malathion, diazinon, and glyphosate (table). These assessments will be published as volume 112 of the IARC Monographs.[1]

The insecticides tetrachlorvinphos

to the bioactive metabolite, paraoxon, is similar across species. Although bacterial mutagenesis tests were negative, parathion induced DNA and chromosomal damage in human cells in vitro. Parathion markedly increased rat mammary gland terminal end bud density.[4] Parathion use has been severely restricted since the 1980s.

The insecticides malathion and diazinon were classified as "probably

aggressive cancers after adjustment for other pesticides.[3] In mice, malathion increased hepatocellular adenoma or carcinoma (combined).[10] In rats, it increased thyroid carcinoma in males, hepatocellular adenoma or carcinoma (combined) in females, and mammary gland adenocarcinoma after subcutaneous injection in females.[4] Malathion is rapidly absorbed and distributed. Metabolism to the

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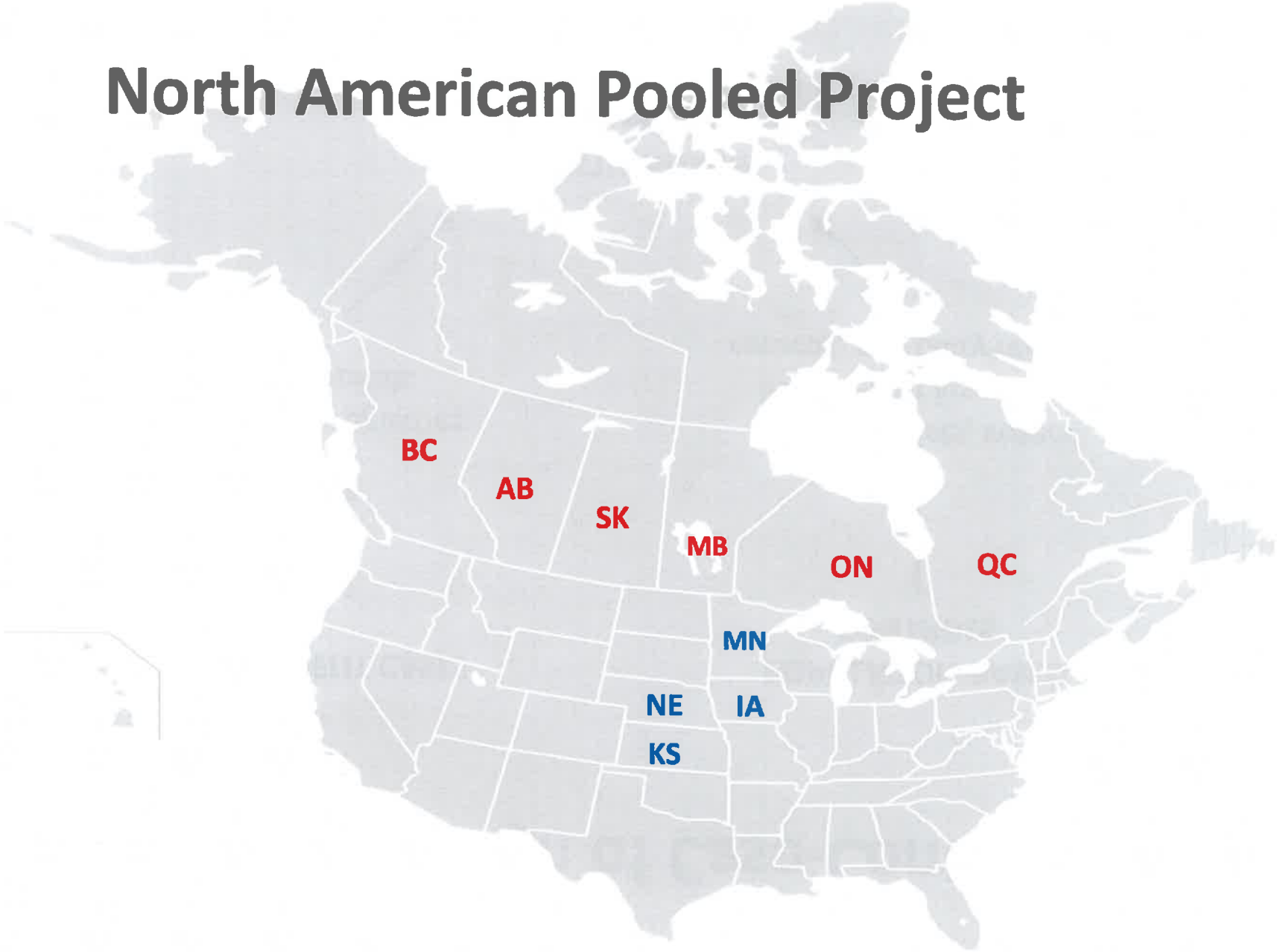
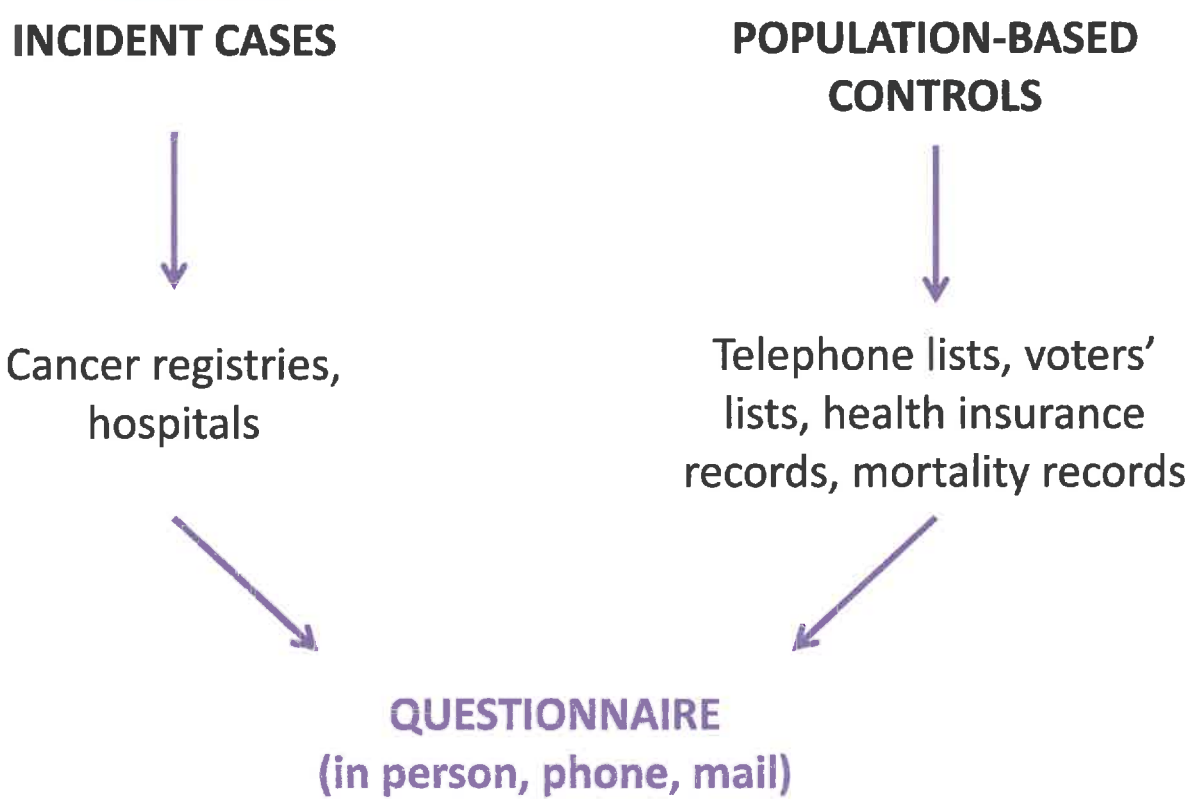
Towards a cancer-free workplace

International Survey of Herbicide Resistant Weeds: http://weedscience.org/graphs/geochart.aspx

North American Pooled Project



General Design of Case-Control Studies



Glyphosate Use Information

	EVER/NEVER	DURATION # Years	FREQUENCY # Days/Year	LIFETIME DAYS # Years x # Days/Year
Iowa/Minnesota	✓	✓	X	X
Kansas	✓	X	X	X
Nebraska	✓	✓	✓	✓
Canada	✓	✓	✓	✓

Conceptual Framework for Analysis

Glyphosate Use

Ever/Never
Duration
Frequency
Lifetime days

NHL Risk

Overall
FL
DLBCL
SLL
Other

Covariates

Age, sex, state/province, lymphatic/hematopoietic cancer in a first-degree relative, proxy respondent use, any PPE use; *2,4-D, dicamba, malathion use*

Selected Characteristics of NHL Cases and Controls

Variable	Cases (N)	Controls (N)	OR* (95% CI)
N	1690	5131	
Histological sub-type			
Follicular (FL)	468		
Diffuse (DLBCL)	647		
Small lymphocytic (SLL)	171		
Other	404		
Location			
U.S.	1177	3625	
Canada	513	1506	
Respondent type			
Self	1140	3372	1
Proxy	533	1692	1.01 (0.89, 1.15)
Unknown/missing	17	67	
Lymphatic or hematopoietic cancer in a first-degree relative			
No	1493	4790	1
Yes	139	202	2.13 (1.69, 2.67)
Unknown/missing	58	139	

*ORs adjusted for age and location

Glyphosate Use and NHL Risks

NHL sub-type	Number of cases who reportedly ever used glyphosate	OR[a] (95% CI)	OR[b] (95% CI)
Overall	113	1.43 (1.11, 1.83)	1.13 (0.84, 1.51)
FL	28	1.00 (0.65, 1.54)	0.69 (0.41, 1.15)
DLBCL	45	1.60 (1.12, 2.29)	1.23 (0.81, 1.88)
SLL	15	1.77 (0.98, 3.22)	1.79 (0.87, 3.69)
Other	25	1.66 (1.04, 2.63)	1.51 (0.87, 2.60)

a. ORs adjusted for age, sex, state/province, lymphatic or hematopoietic cancer in a first-degree relative, use of a proxy respondent, use of any personal protective equipment; b. ORs adjusted for all covariates in model (a) plus use of 2,4-D, use of dicamba, use of malathion

Duration (#Years) of Glyphosate Use and NHL Risks

# years	OR* (95% CI)				
	Overall	FL	DLBCL	SLL	Other
0	1	1	1	1	1
>0 and ≤3.5	1.59 (1.13, 2.22)	0.95 (0.52, 1.74)	2.02 (1.28, 3.21)	1.49 (0.63, 3.58)	2.08 (1.14, 3.78)
>3.5	1.20 (0.82, 1.75)	0.88 (0.46, 1.71)	1.19 (0.67, 2.12)	1.98 (0.89, 4.39)	1.32 (0.64, 2.71)
P-trend	0.03	0.96	0.03	0.08	0.14

*ORs adjusted for age, sex, state/province, lymphatic or hematopoietic cancer in a first-degree relative, use of a proxy respondent, use of any personal protective equipment

Frequency (#Days/Year) of Glyphosate Handling and NHL Risks

# days/year handled	OR* (95% CI)				
	Overall	FL	DLBCL	SLL	Other
0	1	1	1	1	1
>0 and ≤2	1.03 (0.67, 1.60)	0.81 (0.35, 1.84)	0.95 (0.49, 1.81)	1.27 (0.42, 3.89)	1.49 (0.66, 3.32)
>2	2.42 (1.48, 3.96)	2.21 (0.99, 4.93)	2.83 (1.48, 5.41)	2.29 (0.66, 7.98)	2.26 (0.85, 5.99)
P-trend	0.02	0.07	0.04	0.21	0.85

*ORs adjusted for age, sex, state/province, lymphatic or hematopoietic cancer in a first-degree relative, use of a proxy respondent, use of any personal protective equipment

Lifetime Days (#Years x #Days/Year) of Glyphosate Use and NHL Risks

Lifetime days	OR* (95% CI)				
	Overall	FL	DLBCL	SLL	Other
0	1	1	1	1	1
>0 and ≤7	1.20 (0.74, 1.95)	1.03 (0.43, 2.48)	1.14 (0.56, 2.30)	1.04 (0.24, 4.58)	1.93 (0.82, 4.51)
>7	1.55 (0.99, 2.44)	1.33 (0.60, 2.94)	1.51 (0.79, 2.88)	2.13 (0.76, 5.96)	1.69 (0.68, 4.15)
P-trend	0.02	0.02	0.10	0.01	0.33

*ORs adjusted for age, sex, state/province, lymphatic or hematopoietic cancer in a first-degree relative, use of a proxy respondent, use of any personal protective equipment

Challenges

- Uncollected information about duration and frequency of glyphosate use in some locations
- Small numbers for certain stratified analyses
- Measurement error
- Potential recall bias and unmeasured confounding

Strengths

- Larger sample size = more statistical power to incorporate evaluations of NHL sub-types with detailed glyphosate use metrics
- Risk estimates adjusted for other pesticide uses *(results not presented)*
- Evaluated ORs based on data from self-respondents only and assessed effect modification of PPE use on glyphosate-NHL associations *(results not presented)*

Conclusions

- Glyphosate use may be associated with ↑ risk of NHL
- Some differences in risk by sub-type, but not consistent across different glyphosate use metrics
- Large sample size yielded more precise results than possible in previous smaller studies

Further Considerations

- Glyphosate use is projected to increase worldwide, especially in emerging large-scale agricultural economies in Latin America, Asia, and South Africa
- Use of glyphosate is important for global food supply

BUT…

- Glyphosate-resistant weeds are a concern and threat to its prolonged and isolated use
- The human (and environmental) health effects of newer herbicide formulations that contain glyphosate with ≥1 other active ingredient are largely unknown

Acknowledgements

- **Canadian investigators:** Drs. Shelley A. Harris, John J. Spinelli, Paul A. Demers, Punam Pahwa, James A. Dosman, John R. McLaughlin
- **U.S. investigators:** Drs. Laura Beane Freeman, Aaron Blair, Shelia Hoar Zahm, Kenneth P. Cantor, Dennis D. Weisenburger
- **NAPP Executive Committee:** Drs. Shelley A. Harris, Laura Beane Freeman, John J. Spinelli
- **Data pooling:** Mr. Joe Barker (IMS Inc.)

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Towards a cancer free workplace

www.occupationalcancer.ca

About NHL and Glyphosate

NHL

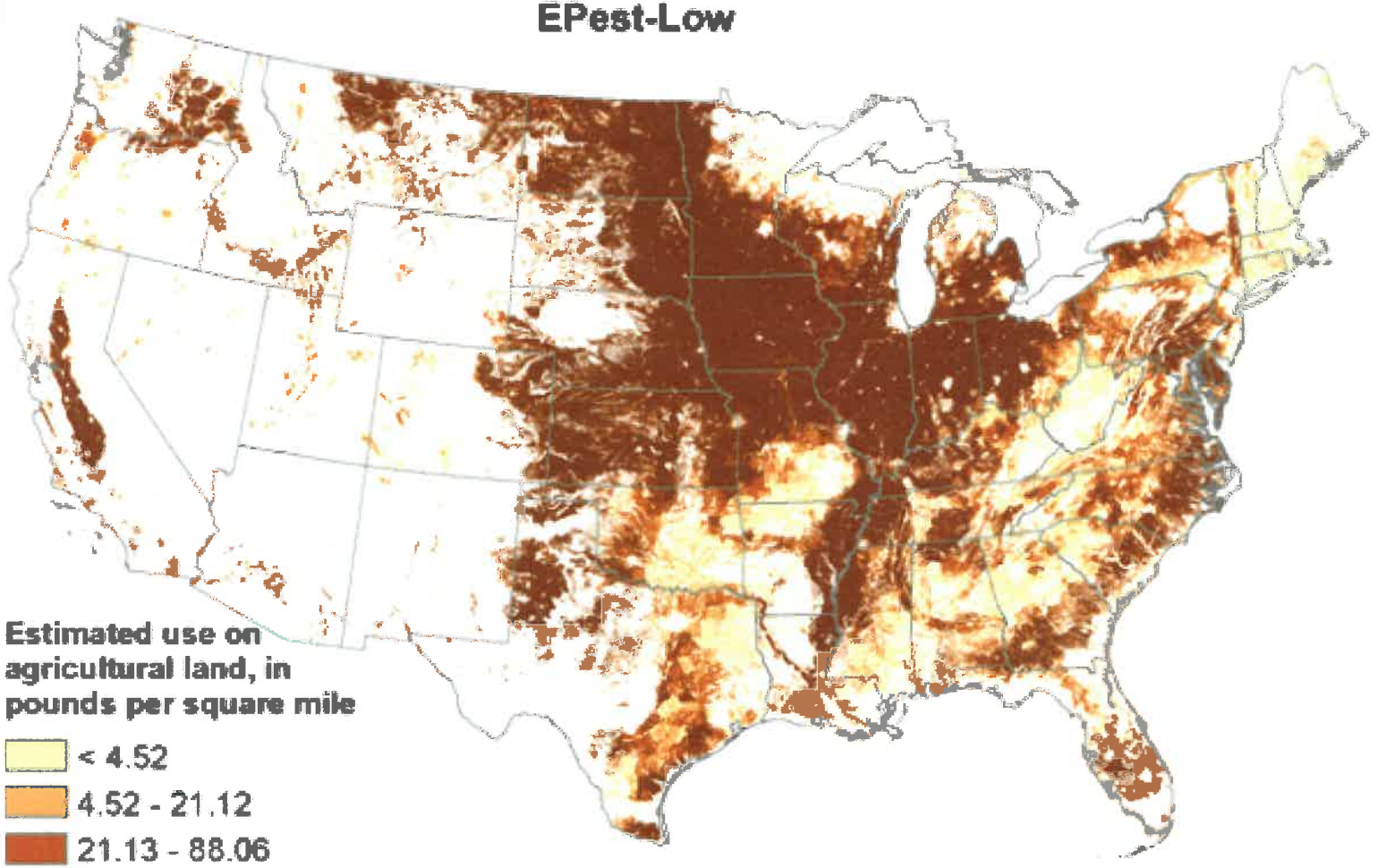
- A cancer that starts in the lymphocytes
- Heterogeneous, according to type of cell affected

Glyphosate

- A broad-spectrum herbicide
- Commonly known as “Roundup”
- The most frequently used herbicide in the world

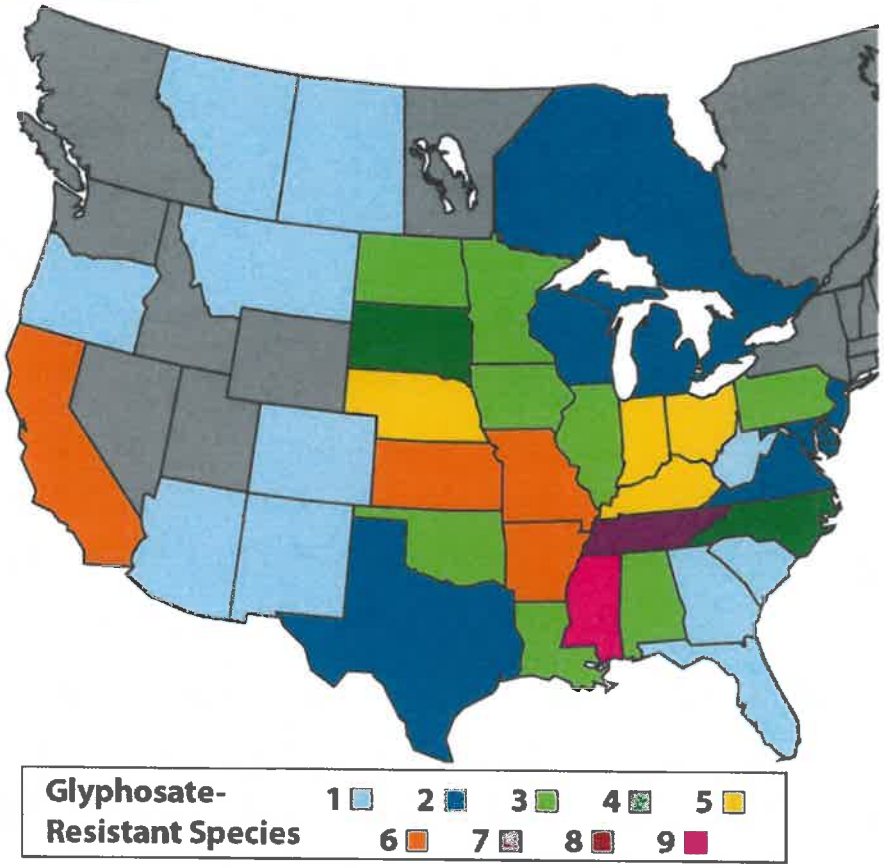
Estimated Agricultural Use for Glyphosate, 2012

EPest-Low



Source: U.S. Geological Survey. 2012 Pesticide Use Maps.
https://water.usgs.gov/nawqa/pnsp/usage/maps/show_map.php?year=2012&map=GLYPHOSATE&hilo=L

Glyphosate-Resistant Weed Species in North America



https://www.pioneer.com/home/site/mobile/plan/soybeans/weed-mgmt/

Proxy Respondent Analysis

Glyphosate Use

Ever/Never
Duration
Frequency
Lifetime days

Proxy and self-respondents
Self-respondents only

NHL Risk

Overall
FL
DLBCL
SLL
Other

Age, sex, state/province, lymphatic/hematopoietic cancer in a first-degree relative, use of any PPE, use of 2,4-D, use of dicamba, use of malathion

Covariates

Selected Characteristics of NHL Cases and Controls (Continued)

Variable	Cases (N)	Controls (N)	OR (95% CI)
Ever lived or worked on a farm or ranch			
No	577	1840	1
Yes	1102	3276	1.06 (0.94, 1.20)
Unknown/missing	11	15	
Ever used any type of PPE			
No	374	1127	1
Yes	105	310	1.12 (0.86, 1.45)
Unknown/missing	1211	3694	

Proxy vs. Self Respondents

	OR (95% CI) for NHL Overall	
Glyphosate Use	**Proxy and Self Respondents[a]**	**Self Respondents Only[b]**
Never used	1	1
Ever used	1.13 (0.84, 1.51)	0.95 (0.69, 1.32)
Duration (# years)		
>0 and ≤3.5	1.28 (0.88, 1.84)	1.17 (0.79, 1.74)
>3.5	0.94 (0.62, 1.42)	0.78 (0.49, 1.24)
Frequency (# days/year)		
>0 and ≤2	0.74 (0.46, 1.19)	0.66 (0.39, 1.12)
>2	1.73 (1.02, 2.94)	1.77 (0.99, 3.17)
Lifetime days (# years x # days/year)		
0 and ≤7	0.87 (0.52, 1.45)	0.82 (0.46, 1.44)
>7	1.08 (0.66, 1.77)	1.06 (0.62, 1.81)

a. ORs adjusted for age, sex, state/province, lymphatic or hematopoietic cancer in a first-degree relative, use of a proxy respondent, use of any PPE, use of 2,4-D, use of dicamba, use of malathion; b. ORs adjusted for age, sex, state/province, lymphatic or hematopoietic cancer in a first-degree relative, use of any PPE, use of 2,4-D, use of dicamba, use of malathion

Future Research Priorities

- Evaluation of other agricultural exposures, confounding, and interactions
- Non-occupational exposures
- Factors that modify exposure, e.g. immune conditions

Acknowledgements

Canadian investigators

- Shelley A. Harris
- John J. Spinelli
- Paul A. Demers
- Punam Pahwa
- James A. Dosman
- John R. McLaughlin

U.S. investigators

- Laura Beane Freeman
- Aaron Blair
- Shelia Hoar Zahm
- Kenneth P. Cantor
- Dennis D. Weisenburger

Introduction to Cohort Studies

Beate Ritz MD PhD
Epi 200A
Fall 2012

Table 1. Validity for etiologic inference according to study designs

Validity ranking	Types of study design
Highest	Randomized clinical trial
	Prospective cohort study
	Retrospective cohort study
	Nested case–control study
	Time–series analysis
	Cross-sectional study
	Ecologic study
	Cluster analysis
	Case study
Lowest	Anecdote

Source: Kunzli et al. The Semi-individual Study in Air Pollution Epidemiology: A Valid Design as Compared to Ecologic Studies. *EHP* 1997. 105 (10)

MacMahon and Pugh, 1970
Definition of cohort studies (in public health epidemiology)

- The group or groups of persons to be studied are defined in terms of **characteristics manifest prior to the appearance of the disease** under investigation
- The study group so defined are observed over a period of time to determine the **frequency of disease** among them

Cohort studies

Simplistic description

- A cause 'looking' for a disease
- (*versus* case-control study: "A disease 'looking' for a cause")

Cohort design:

Retrospective (historical) in terms of
a) timing of events *or*
b) data collection

Cohort is enumerated some time in the past and followed over *historical* time (to today)
- time of follow-up long (20-40 years), often extends across decades
- cohort can be large i.e. 10,000+ members

But, how do we:
- "reconstruct" the cohort - who belongs into the cohort?
- Obtain exposure and outcome information
  - Note: a historical cohort is often restricted to investigations of fatal disease (why!)

Cohort design:

Prospective in terms of
a) timing of events *or*
b) data collected

This design is best to be used for
- short-term (common) health outcomes; e.g. for:
  - physiological changes (blood pressure and noise)
  - acute neurotoxic effects (OP pesticides)
  - pulmonary function (cotton dust)
  - skin rashes (irritants, e.g. solvents, metals)
  - injuries
  - allergic reactions, asthma attacks
- prospective medical surveillance

Cohort design:

Prospective *or* retrospective in terms of

a) timing of events *or*
b) data collected

The major issue we want to convey is whether disease status could have influenced exposure measurement/information (such as via recall of exposure by a diseased subject)

Note that retrospective often is considered a 'less reliable' design; thus, be clear about how you use this term

Cohort study: examples

Cohort: "Any designated group of individuals who are followed or traced over a period of time"

Historically:

- John Snow: Cholera in London (1854)
- Panum: Measles on the Faroe Islands (1846)

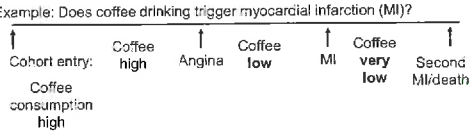
More recent

- Framingham: cardiovascular diseases (N=5,209); bi-annual exams, medical records and deaths info
- British doctors: smoking and lung cancer among British doctors (N=34,439 male British doctors in 1951; Doll)
- Perinatal collaborative study: pregnancy and child health, cerebral palsy and allied neurological defects (N=42,000 pregnant women enrolled 1959–1966 at 12 hospitals across the United States)
- Nurses Health Study: established in 1976 from female US registered nurses ages 30-55 years who responded to a mailed questionnaire that inquired about risk factors for cancer and heart disease (N=121,700)
- HIV cohorts: 1984-2005, Multicenter AIDS Cohort Study (N=4,955 homosexual men who volunteered in Baltimore, Chicago, Los Angeles, and Pittsburgh)
- EPIC study: cancer
- California Teachers Cohort (125,000 in 1995): Breast cancer
- And many more

Causal Inferences in Cohort Studies

- Since the only *sine qua non* causal criteria states that **a cause precedes its effect,** it is logical to start with the exposure and follow exposed people forward in time to study the occurrence of the health endpoint of interest
- This was hardly done *prospectively* before the Framingham cohort study (baseline 1948); too expensive, too time consuming
- A cohort study is a logical design to study determinants of the changes from not having a disease to having a disease. The study can guarantee that exposure precedes the onset of clinical diagnosis (but perhaps not the real onset of pathological changes).

Example: Does coffee drinking trigger myocardial infarction (MI)?



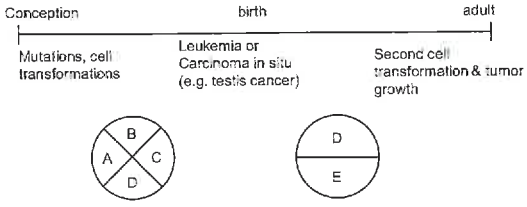
Experimental *vs.* Observational Studies:

Why not conduct a randomized trial?

Trials

- cannot obtain evidence for harmful agents (and sometimes for beneficial ones as well)
- deal by nature with (very) selected populations
- not practical for
  - rare outcomes (Note: we would expect only 50-200 lung or colon cancers and 16 Parkinson's cases per 100,000 person years of observation in most working age cohorts)
  - long follow-up times that allow for latency
  - effects that occur late in disease progression
- focus on one (or several) specific doses only
- expensive to conduct

Life course perspective



Different causal components may be operating

Note: many cohorts recruit at entry only few of those eligible (% of all eligible often not known):

- What is the impact on internal validity and external validity?

Cohort studies: recruitment

- Recruitment to the cohort may be mandatory/ automatic
  - All in public registers = mortality, births, deaths, cancer (without informed consent)
  - Occupational cohorts using employment data from occupational plants (assess exposures retrospectively from records and outcomes from registers)
- NOTE: cohorts using "primary" data (i.e. collected during/for the investigation) are usually based upon **informed consent**

Examples:

- via General Practitioner – e.g. Danish National Birth Cohort
- Letters – e.g. to members of an organization (British doctors, CA Teachers, Nurses Health Study, Harvard Alumni)
- Advertisements – e.g. people with a given disease
- Local community: ALSPAC, Framingham
- Visitors to a website
- Participants in L.A. Marathon

Cohort studies: follow-up

- Compliance to follow-up procedures
  - frequent contacts needed!
  - Are (health) benefit incentives given?
- Recording of endpoints
  - rely on diagnoses made by the health care system
  - repeated measurements necessary?
- Changes in other determinants/ covariates
  - questionnaires
  - interviews
  - measurements
- Participation is voluntary, participants are free to leave the cohort at any point in time
  - right to remove data from the study?

TABLE 1. Types of outcomes for cohort

- Discrete events
  - Single events
    - Mortality
    - First occurrence of a disease or health-related outcome
      - Incidence (density)
      - Cumulative incidence (risk)
      - Ratios (incidence density and cumulative incidence)
  - Multiple occurrences:
    - Of disease outcome
    - Of transitions between states of health/disease
    - Of transitions between functional states
- Level of a marker for disease or state of health
- Change in a functional/physiologic/biochemical/anatomic marker for disease or health
  - Rate of change
    - Patterns of growth and/or decline
    - "Tracking" of markers of disease/health
  - Change in level with time (age)

Source: Tager IB. Outcomes in cohort studies. *Epidemiologic Reviews* 1998, 20(1).

TABLE 1. Types of outcomes in cohort morbidity studies

Induction period/ reversibility	Event (dichotomous)	Change in status (continuous)
Short (days to months)		
Reversible	Asthma attack Tendonitis Contact dermatitis	Cross-shift function (FEV_1*) Temporary threshold hearing
Irreversible	Asthma diagnosis Spontaneous abortion Amputation	Annual change in FEV_1
Long (years)		
Reversible	Chronic bronchitis Endometriosis Carpal tunnel syndrome	Sperm count Blood pressure
Irreversible	Silicosis Myocardial infarction Infertility	Noise-induced hearing loss Atherosclerosis Hepatic fibrosis

*FEV_1, forced expiratory volume in 1 second.

Source: Checkoway H and Eisen EA. Developments in Occupational Cohort Studies. *Epidemiologic Reviews* 1998, 20(1).

Cohort Entry Definitions

Entry to a cohort can be defined at a fixed point in time:

- All subjects are selected at a given point (range) in time, e.g. from a registry of a type of people
  - All atomic bomb survivors in Japan on Jan 1st 1950 living in Nagasaki and Hiroshima
  - European Prospective Investigation into Cancer and Nutrition (EPIC), a multi-centre prospective cohort study in 23 study centers in ten European countries
    - E.g in Germany, recruitment was based on a random sample of subjects in targeted age range (women aged 35–65, men 40-65) from population registers between 1994 and 1998
    - participation rate was 38.5% (i.e. observed cohort is a self-selected subgroup of the underlying population)

or

- subjects enter the cohort at different points in time; *e.g.*: all inhabitants of Framingham/MA that reach a certain age

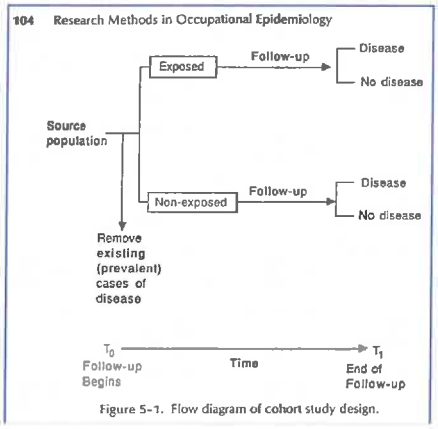


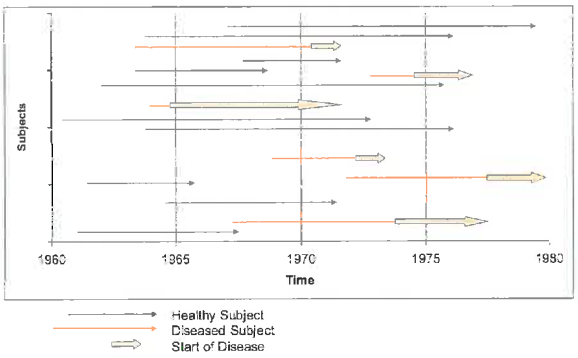
Figure 5-1. Flow diagram of cohort study design.

Cohort Exit Definitions

Subjects can be follow-up

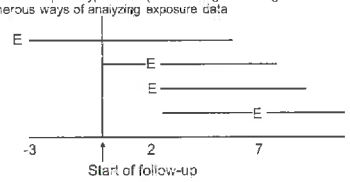
- until a fixed point in calendar time (end of study);
  - note: some subjects are observed for a shorter time i.e. due
    - incidence of the disease under investigations,
    - death,
    - migration or
    - loss of follow-up
- or as long as they are
  - employed
  - live in the city
  - have the exposure (are "right censored" when this changes) (e.g. use of a certain type of medication)

Study Design Overview: Identifying Diseased Subjects in a Population



Cohort studies: exposure assessment

- Exposure may have started at a given point in time:
  - E.g. at baseline or any other measurement point
  - and remains fixed ("ever smoker")
  - or changes over time (amount of smoking)
- Exposure can be measured as:
  - Average or cumulative exposure over time
  - exposure level at baseline
  - Note: without a prior hypothesis (or knowledge of biological mechanism) there may be numerous ways of analyzing exposure data



Person time 'lagged' by x years (after time of hire) – immortal PT

Cohort studies: exposure assessment

- Exposures can be lagged (i.e. exclude exposure during time irrelevant for the disease)
  - E.g. exposure too close to disease onset
- Exposure contrast
  - Generally we like to examine as large an exposure contrast as possible - thus, we want to establish a cohort with different exposure levels (e.g. workers in a copper-smelter compared to the general population)
- Select the non-exposed subjects as close to the **counterfactual** ideal as possible
  - Non-exposed subjects should have the same disease risk as the exposed had they not been exposed

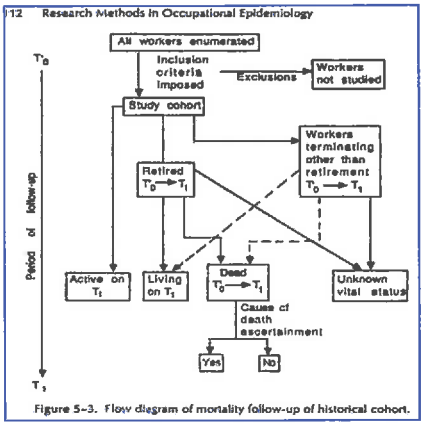


Figure 5-3. Flow diagram of mortality follow-up of historical cohort.

Start of follow-up in a cohort study

- hire date or fixed time/date after hiring
- first monitoring date (e.g. radiation monitoring, blood lead monitoring)
- fixed date (such as Jan 1970)

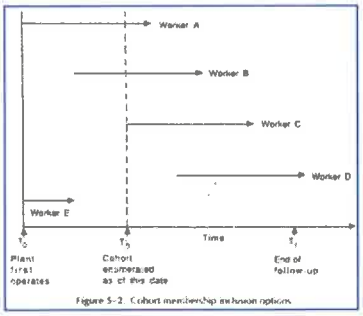


Figure 5-2. Cohort membership and human options.

End of follow-up in a cohort study

- end of follow-up for the cohort reached
- death or incidence from outcome of interest
- death from competing causes
- last known date alive (after that we call them 'lost to follow up')

Or

- should we assume a worker is alive if no information is found that indicates that the subject died (and thus continues to add person-time)?

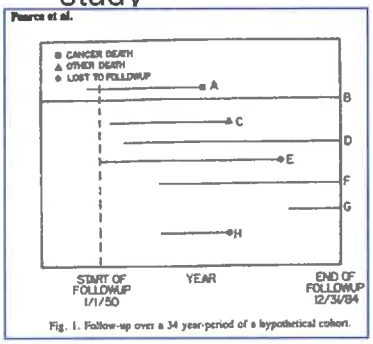


Fig. 1. Follow-up over a 34 year-period of a hypothetical cohort.

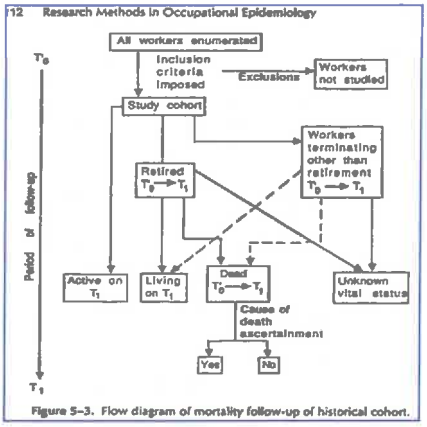


Figure 5–3. Flow diagram of mortality follow-up of historical cohort.

Summary: Cohort Studies

- Generally most accepted in scientific community
- Include the entire available study population
- Most similar to standard experimental strategies
  - determine (rather than apply) a toxin or preventative agent among subjects disease-free at baseline
  - follow-up subjects over time
  - observe adverse or positive health effects in exposed and non-exposed subjects

The goal is to estimate the risk of (various or one) disease/s among the exposed subjects relative to the background risk experienced by "comparable" unexposed persons:
- comparable refers to the "exchangeability assumption" or "counterfactual"
  - *what would have happened to this group of exposed subjects if they had NOT been exposed?*

Summary: Cohort Studies

- Select non-exposed as close to the counterfactual ideal as possible:
  - Non-exposed should have the same disease risk as the exposed had they not been exposed
- Recruitment to the cohort
  - based upon informed consent if primary data are collected
  - Without informed consent if all are followed in public registers = mortality, births, deaths
- Historical cohorts: e.g. use existing data but need not be 'retrospective'

Advantages of the cohort method

- In principle, can provide a **complete description of experience of cohort members** subsequent to exposure, including rates of progression to and staging of disease, and natural history of disease
- Allows study of **multiple potential effects** of a given exposure, thereby obtaining information on potential benefits as well as risks
- Allows for the **calculation of rates** of disease in exposed and unexposed individuals and time to event
- Permits **flexibility in choosing variables** to be systematically recorded
- Allows for **thorough quality control in measurement** of study variables (not in historical cohort studies though)

Disadvantages of the cohort method

- Large numbers of subjects required (thus, low feasibility to study rare diseases)
- Relatively expensive to conduct
- Potentially long duration for follow-up necessary
- Exposures may change, making findings irrelevant unless the exposure assessment is adapted
- Maintaining follow-up may be difficult
- The cohort is generally not representative of the general population

Example: The Agricultural Health Study Cohort (AHS)

- Collaborative effort to study the effects of pesticide exposures among farmers
  - National Cancer Society (NCI)
  - National Institute of Environmental Health Sciences (NIEHS)
  - U.S. Environmental Protection Agency (EPA)

http://aghealth.nci.nih.gov/

The AHS Cohort study:
Retro- and prospective data collection

- Phase I, initial cohort recruitment, 1994-1997:
- 89,658
  - private pesticide applicators, and
  - spouses of private applicators, and
  - commercial pesticide applicators
- Recruited at Iowa and North Carolina state pesticide applicator licensing facilities
- Each pesticide applicator asked to complete a 21-page enrollment questionnaire
  a. Demographic data
  b. Pesticides used (50 pesticides), other pesticide-related questions
  c. Lifestyle (i.e., smoking, alcohol, vegetable, and fruit consumption)
  d. Brief medical history
  e. Family history of cancer, kidney failure, diabetes, and heart disease
  f. Farm exposures other than pesticides (not in commercial pesticide applicator version)
  g. Personal identifiers, spouse identifiers, children identifiers

Farmer applicators completing the enrollment questionnaire are given three take-home questionnaires (scannable) for
- the applicator (licensing exam taker)
- spouse, and
- female and family health questionnaires

The AHS Cohort

Take Home Questionnaires:
Farmer Applicator/Commercial Applicator

a. Farm exposures (comprehensive)
b. Pesticide use information (i.e., methods of application, additional pesticides used)
c. Work practices used currently versus those used 10 years ago
d. Other occupational exposures
e. Leisure and work physical activity, physical attributes (e.g., height, weight, eye color, skin pigmentation category)
f. Dietary and cooking practices
g. Medical history (comprehensive)
f. Personal identifiers

The AHS Cohort

- Cancer and non-cancer outcomes
  - Linkage with
    - » cancer registries
    - » vital statistics
    - » United States Renal Data System (USRDS)
  - Exposure data collection
    - » Baseline questionnaire at licensing exam
      At follow-up
    - » telephone interviews (CATI)
    - » food frequency questionnaire and
    - » cheek cell collection
- Phase II: follow-up in 1999-2003
- Phase III: follow-up in 2004-2008

The AHS Cohort

1. Cohort studies
   - All cause and cancer mortality
   - cancer incidence
2. Cross-sectional studies:
   - Using questionnaire data, functional measures, biomarkers, and GIS
   - E.g. cross sectional immunology study of atrazine applicators/corn farmers in Iowa
3. Nested case-control studies
   - High pesticide exposure events
   - Parkinson's disease study
4. Exposure assessment and validation studies

The AHS Cohort

Table 1. Composition of Cohort and Data Collection Progress

	Phase I (Complete)	Phase II (In Progress) [2]		
	Contacts Completed	Main Qx Admin	Buccal Cell Collection	Dietary Health Qx Admin
Private Applicators	52,395	26,575	14,577	14,882
Spouses	32,347	20,856	12,030	13,224
Commercial Applicators [1]	4,916	0	0	0
Total	89,658	47,431	26,607	28,106

[1] Phase II data collection on Commercial Applicators not yet begun
[2] Progress through October 12, 2001

The AHS Cohort

Table 2a: Post-enrollment (incident only) Malignant Cancer Cases by Site and Phase II Data Collection progress [1,2,3]

	Post-enrollment Cases Only			
Cancer Site	Total with Cancer	Completed Phase II Qx	Returned Buccal Sample	Returned Dietary History Qx
Breast	268	181	131	142
Prostate	572	337	215	210
Colon	224	106	64	73
Lung	180	41	21	23
NHL	79	29	23	25
Other [4]	789	320	217	216
Total	2112	1014	671	689

Table 2b: Pre- and Post-enrollment (Prevalent and Incident) Malignant Cancer Cases by Site and Phase II Data Collection progress [1,2,3]

Ag-Health study topics

Cancer mortality and incidence in Applicators and Spouses
Pesticide Exposure Assessment, Applicators, Spouses and Children – questionnaires
Pesticide Exposure Assessment - Field Studies – Acute exposures
Biologic and Functional Effects of Chronic Pesticide Exposure
Biomarkers and Molecular Genetics
Injury
Lifestyle and Diet
Non-pesticide Exposures, Exposure to Animals
Respiratory Disease and Function
Neurological Disease and Function
Reproductive Health, Child and Adolescent Health
Autoimmune Disease and Immune Function
Other Non-cancer Chronic Disease

Pooling of cohorts

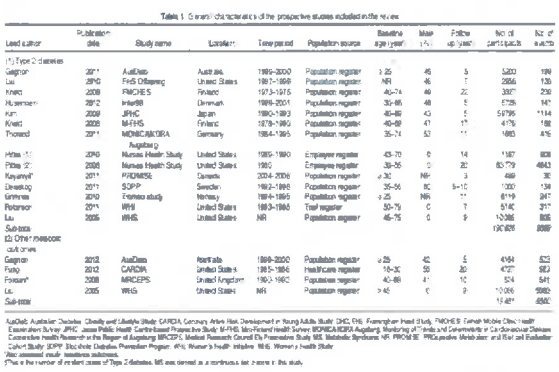
Advantages:

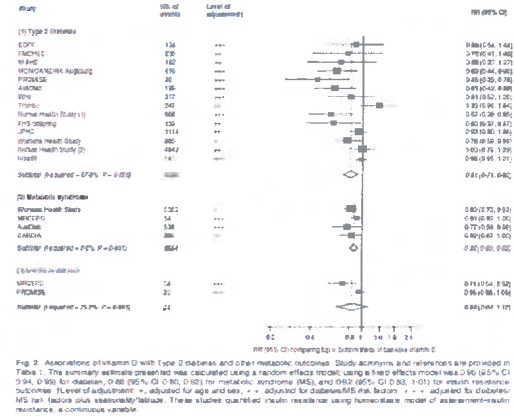
- Can study rare outcomes
- Conduct subgroup analyses for effect measure modifiers (e.g. sex, race etc)
- Wide geographic distribution allows spread of exposures
- Availability of prospective data; stored serum blood samples can be analyzed by same lab

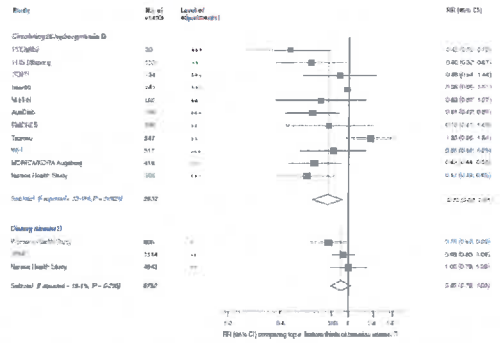
Disadvantages

- Usually no common data elements, i.e. diverse data collection methods need to be reconciled
- Some variables may not have been collected at all; how to handle missing data?

Vid D and type 2 diabetes: meta-analysis







Person time

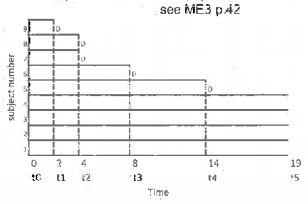
Incidence Proportion: A/N A= case number N=initial population size
Person-time instead of persons:
A/T observed rate [A= observed cases and T= person-time units in study group]

Poisson model
$Pr(A=a) = \exp(-l^*T)(l^*T)^a/a!$
l = the rate parameter (average rate we would observe if we repeated the study over and over under the same conditions with the same amount of person-time T observed each time(i.e. end the follow-up when we reach T)
Note: Under the Poisson model A/T is the MLE estimator of l

Immortal person time
The study has a criterion for a minimum of time before a subject is eligible to be in the study:
E.g. in occupational cohort studies when workers are required to have worked for a minimum of x-years. All workers who did not work for this length of time are automatically not enrolled in this cohort and all of those who are could not be censored prior to 2 years i.e. could not have died if included in the cohort.

This time should not be used to calculate person-time for those included in the cohort

Figure 3-4: Example of a small closed population with end of follow-up at 19 years
see ME3 p.42



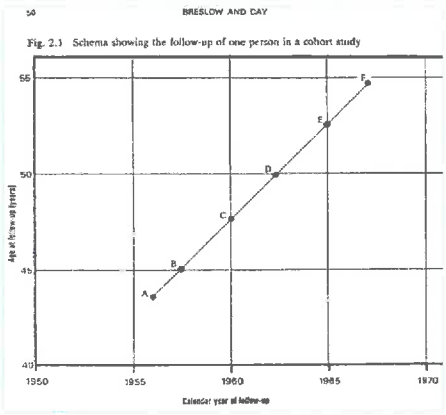
108 PY total

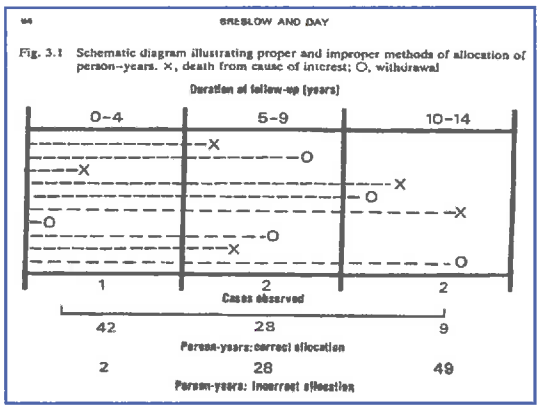
	Start	Outcome event times (tk)				End
	0	2	4	8	14	19
Index (k)	0	1	2	3	4	5
No. of outcome events (Ak)	0	1	2	1	1	0
No. at risk (Nk)	9	9	8	6	5	4
Prop. Surviving (Sk)		8/9	6/8	5/6	4/5	4/4
Length of interval (Δtk)		2	2	4	6	5
Person time(NkΔtk)		18	16	24	30	20
Incidence rate (Ik)		1/18	2/16	1/24	1/30	0/20

EXAMPLE:
Incidence rate ratios (IRR) for epilepsy among children exposed to pre-eclampsia or eclampsia

Pre-eclampsia or Eclampsia	Entire Birth Cohort: Person years	No. of epilepsy cases	IR	Crude IRR (95%CI)	Adjusted* IRR (95%CI)	Cohort of children without cerebral palsy or a low Apgar score† : Person years	No. of epilepsy cases	IR	Adjusted* IRR (95%CI)
Non-exposed	17,650,197	19,441	108.9	1.00	1.00 (Ref)	16,651,803	15,734	94.5	1.00 (Ref)
Pre-eclampsia									
Mild	458,558	620	135.2	1.27	1.20 (1.11-1.30)	418,764	485	115.8	1.20 (1.10-1.32)
Severe	78,386	135	172.2	1.54	1.14 (0.96-1.36)	68,957	94	136.3	1.22 (0.99-1.49)
Eclampsia	7,672	15	195.5	1.78	1.35 (0.81-2.24)	6,604	10	151.4	1.35 (0.73-2.52)
Unspec.	43,328	49	113.1	1.04	0.95 (0.72-1.26)	40,002	42	105.0	1.05 (0.77-1.42)

IR: incidence rate /100,000 person years





Person-time calculations

Table 2.1 Calculation of exact and approximate age- and year-specific person-years at risk

Point*	Coordinates (year, age)	Quinquinquennium: Year	Quinquinquennium: Age	Person-years: Exact	Person-years: Approximate
A	(1956.03, 43.71)				
B	(1957.32, 45.00)	1955–1959	40–44	1.29	1.50
C	(1960.00, 47.68)	1955–1959	45–49	2.68	2.00
D	(1962.32, 50.00)	1960–1964	45–49	2.32	3.00
E	(1965.00, 52.68)	1960–1964	50–54	2.68	2.00
F	(1967.15, 54.83)	1965–1969	50–54	2.15	2.50
Total				11.12	11.00

*See Figure 2.1

Incorrect *vs.* correct person-time calculations

Table 3.1 Reanalysis of data by Duck *et al.* showing original *versus* revised numbers of expected deaths and SMRs by duration of exposure and cause of death*

Cause of death	Duration of exposure (years)	No. of observed deaths	No. of expected deaths: Original	No. of expected deaths: Revised	SMR: Original	SMR: Revised
All causes	0–14	111	100.92	118.97	110	94
	15+	25	41.30	24.15	61	104
Total cancers	0–14	27	25.55	29.93	106	90
	15+	8	10.89	6.51	73	123
Digestive system cancers	0–14	7	7.77	9.10	90	77
	15+	4	3.31	1.98	121	202
Lung cancer	0–14	13	10.73	12.57	121	103
	15+	3	4.80	2.96	62	101

*From Duck *et al.* (1975); Duck & Carter (1976)

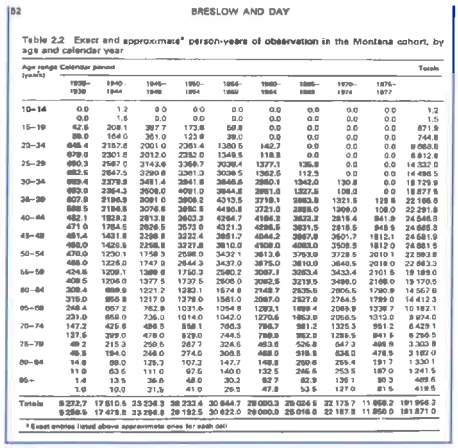


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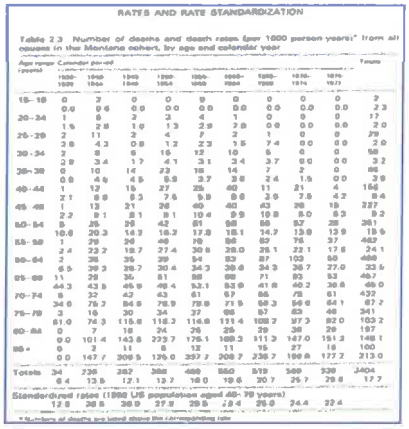
Table 2.2 Exact and approximate* person-years of observation in the Montana cohort, by age and calendar year

Age range (years)	Calendar period 1938–1939	1940–1944	1945–1949	1950–1954	1955–1959	1960–1964	1965–1969	1970–1974	1975–1977	Totals
10–14	0.0	1.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	1.2
	0.0	1.5	0.0	0.0	0.0	0.0	0.0	0.0	0.0	1.5
15–19	42.5	208.1	367.7	173.8	59.8	0.0	0.0	0.0	0.0	851.9
	39.0	164.0	351.0	123.8	39.0	0.0	0.0	0.0	0.0	744.8
20–24	648.4	2157.8	2001.0	2361.4	1380.5	142.7	0.0	0.0	0.0	8690.8
	679.0	2301.8	2012.0	2352.0	1349.5	118.5	0.0	0.0	0.0	8812.8
25–29	690.3	2587.0	3143.6	3368.7	2038.4	1377.1	135.8	0.0	0.0	14332.0
	682.5	2647.5	3290.8	3361.3	3039.5	1362.5	112.5	0.0	0.0	14496.5
30–34	669.4	2379.8	3481.4	3841.8	3646.6	2880.1	1342.0	130.8	0.0	18729.9
	693.0	2364.3	3606.0	4091.0	3644.8	2881.0	1327.6	108.0	0.0	18877.5
35–39	607.8	2186.9	3091.0	3806.2	4313.5	3719.1	2863.8	1321.5	128.8	22186.6
	588.5	2186.5	3076.8	3892.8	4480.8	3721.0	2888.0	1309.0	108.0	22291.8
40–44	482.1	1828.2	2813.8	3603.3	4264.7	4186.2	3622.2	2818.4	841.9	24566.8
	471.0	1784.5	2826.5	3573.0	4321.3	4296.5	3631.5	2818.5	848.5	24666.3
45–49	451.4	1431.8	2298.8	3222.4	3851.7	4044.2	3867.8	3601.7	1812.1	24681.9
	466.0	1426.5	2298.8	3277.8	3810.0	4109.0	4083.0	3509.5	1812.0	24891.5
50–54	470.0	1230.1	1758.3	2598.0	3432.1	3812.6	3763.9	3728.5	2010.1	22593.8
	488.0	1226.0	1747.0	2644.3	3437.0	3875.0	3810.0	3840.5	2018.0	22883.3
55–59	424.5	1209.1	1389.6	1750.3	2560.2	3087.1	3083.4	3433.4	2101.5	18189.0
	409.5	1206.0	1377.5	1737.5	2605.0	3082.5	3219.5	3496.0	2168.0	19170.0
60–64	308.4	999.9	1221.2	1282.1	1574.9	2148.7	2535.5	2805.5	1780.9	14557.9
	319.0	955.8	1217.0	1278.0	1561.0	2097.0	2527.0	2764.5	1799.0	14412.3
65–69	248.4	657.2	762.9	1031.6	1054.8	1293.1	1699.4	2069.9	1397.7	10182.1
	231.0	668.0	736.0	1014.0	1042.0	1270.5	1663.0	2056.5	1312.0	9974.0
70–74	147.2	425.6	486.5	598.1	766.3	786.7	981.2	1325.3	951.2	6429.1
	137.5	399.0	478.0	529.0	744.5	788.8	982.0	1289.5	841.5	6295.5
75–79	49.2	215.3	250.5	267.7	324.6	463.6	526.8	647.3	466.9	3303.9
	48.5	194.0	248.0	274.0	308.5	468.0	518.5	634.0	478.5	3169.0
80–84	14.8	88.0	125.3	107.2	147.7	148.8	209.6	259.4	191.7	1301.1
	11.0	83.5	111.0	97.5	140.0	132.5	246.5	253.5	187.0	1261.5
85+	1.4	13.5	36.6	48.0	30.3	82.7	62.9	136.1	90.3	469.6
	1.0	10.0	31.5	41.0	29.5	47.8	53.5	127.0	81.5	419.5
Totals	5 232.7	17 610.5	23 234.3	28 232.4	30 644.7	28 080.3	25 634.5	22 175.7	11 868.2	191 956.3
	5 256.5	17 478.5	23 294.8	28 182.5	30 622.0	28 060.0	25 618.0	22 187.5	11 850.0	191 871.0

* Exact entries listed above approximate ones for each cell



RATES AND RATE STANDARDIZATION

Table 2.3 Number of deaths and death rates (per 1000 person-years)* from all causes in the Montana cohort, by age and calendar year

Age range (years)	Calendar period 1938–1939	1940–1944	1945–1949	1950–1954	1955–1959	1960–1964	1965–1969	1970–1974	1975–1977	Totals
10–14	0	2	0	0	0	0	0	0	0	2
	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	2.3
15–19	1	0	2	2	4	1	0	0	0	10
	1.9	2.8	1.9	1.3	2.9	2.9	0.0	0.0	0.0	2.0
20–24	2	11	2	4	7	2	1	0	0	29
	2.8	4.3	0.8	1.2	2.3	1.5	7.4	0.0	0.0	2.0
25–29	2	8	6	10	12	10	5	0	0	53
	2.9	3.4	1.7	4.1	3.1	3.4	3.7	0.0	0.0	3.2
30–34	0	10	14	23	18	14	7	2	0	88
	0.0	4.6	4.5	5.8	3.7	3.8	2.4	1.5	0.0	3.9
35–39	1	12	15	27	25	40	11	21	4	156
	2.1	8.8	5.3	7.6	5.9	8.8	3.8	7.8	4.2	8.4
40–44	1	13	21	26	40	40	43	28	15	227
	2.2	8.1	8.1	10.4	9.9	10.8	8.0	6.3	5.3	9.2
45–49	5	25	26	42	61	98	58	57	28	381
	10.8	20.3	14.2	16.2	17.8	18.1	14.7	13.8	13.9	15.5
50–54	1	29	26	46	78	96	82	76	37	482
	2.4	23.7	18.7	27.4	30.8	28.0	25.1	22.1	17.6	24.1
55–59	2	38	35	39	94	83	87	103	58	499
	6.5	39.3	28.7	30.4	34.3	30.8	34.3	38.7	27.0	33.5
60–64	11	28	35	51	88	88	71	83	53	497
	44.3	43.5	45.9	49.4	63.1	53.9	41.6	40.2	38.6	46.0
65–69	9	32	42	43	61	67	66	78	61	432
	54.6	76.2	84.6	76.9	78.8	71.5	68.3	56.6	64.1	67.7
70–74	3	16	30	34	37	66	57	83	46	341
	31.0	74.3	115.8	116.2	116.8	111.4	108.7	97.3	82.0	103.2
80–84	0	7	18	24	26	25	29	38	29	197
	0.0	101.4	143.8	223.7	175.1	169.3	111.3	147.0	151.3	148.1
85+	0	2	11	6	12	11	15	27	16	100
	0.0	147.7	309.5	125.0	397.7	208.7	238.7	198.8	177.2	213.0
Totals	34	236	282	388	486	550	519	569	329	3404
	6.4	13.5	12.1	13.7	16.0	19.6	20.7	25.7	29.8	17.7
Standardized rates (1960 US population aged 40–79 years)	12.8	26.8	26.9	27.8	29.5	28.4	25.0	24.4	22.4	

* Numbers of deaths are listed above the corresponding rate

Role of Statistical Modeling

Construction of a probability model that explicitly recognizes

- the role of chance mechanism in producing some variation in the rates;
- i.e. observed rates are regarded as just one of the many possible realizations of an underlying random process.

Parameters in the model describe systematic effects of

- exposure of interest
- confounding variables such as age, period, length of follow-up etc.

Estimates of these parameters, obtained during the process of fitting the model, serve as summary statistics analogous to SMR or MH estimates of relative risk.

Role of Statistical Modeling

Advantage of model fitting over standardization:

- facilitates simultaneous consideration of several different exposure variables at risk
- estimates of relative risk obtained by model fitting generally have greater numerical stability than those computed from standardized rates.

Disadvantage of model fitting:

- parametric specification of the model due to statistical rather than biological criteria. Note: epidemiologic data are rarely extensive enough to allow to discriminate between closely related models (according to model fit criteria).

Risk set approach in a cohort study

- each subject that enters the cohort at some *entry time* is *at risk*
- each subject exits the study either as a ***failure*** i.e. contracting or dying of the disease of interest or is *censored*, i.e. is alive at the end of study, is lost to follow-up or does not contract the disease
- associated with each subject is a covariate history – fixed or time-dependent --, including factors that are known or believed to be related to the rate of the disease of interest

- At each failure a *risk set* is formed of the size *m* that included the *case* (failure at that failure time) and all *controls*, i.e. any other cohort member who is at *risk* at the failure time.

Note: The approach that organizes the cohort data by risk sets leads to data which looks just like a matched case-control study and hence we can use the conditional logistic likelihood for the analysis

***also note*:** the risk sets are not independent, i.e. subjects can be sampled as controls in multiple risk sets and failures can serve as controls in risk sets prior to their failure times.

Risk set approach in a cohort study

Confounder control can be achieved by either

- Modeling the effect of the confounder
- Restricting each risk set to those who have similar (or the same) confounder values (=matching).

Note: if the matching factors are categorical this approach corresponds to stratification in the Cox model

Sampling from Risk Sets

- Risk set sampling designs are intrinsically related to semiparametric estimation methods for parameters in the Cox proportional hazards model used in the analysis of full cohort data.
- A sampled risk set of size *m* is a subset of the risk set that contains
  - the case and *m-1* sampled controls
  - e.g. 1:1 simple nested case-control sampling: each risk set consists of the case and one control randomly sampled from all the controls in the risk set.

  note: one can use the *'(m-1)/m'* relative efficiency rule for control sampling versus full cohort analysis for testing associations between single exposures and diseases (Breslow and Patton , 1979)
  - Thus, we have for 1 case and 4 controls (or 4/5=0.8 or 80% efficiency but then for one case and 5 controls 5/6=0.83 or 83% power, and for 9/10=0.90 or 90% power, thus, we need to add 4 controls to gain10% efficiency, i.e. double your efforts to increase efficiency only slightly; it gets worse after that add another 10 controls and you get 19/20=0.95 only 5% efficiency added

Cancer Incidence among Glyphosate-Exposed Pesticide Applicators in the Agricultural Health Study

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Glyphosate is a broad-spectrum herbicide that is one of the most frequently applied pesticides in the world. Although there has been little consistent evidence of genotoxicity or carcinogenicity from *in vitro* and animal studies, a few epidemiologic reports have indicated potential health effects of glyphosate. We evaluated associations between glyphosate exposure and cancer incidence in the Agricultural Health Study (AHS), a prospective cohort study of 57,311 licensed pesticide applicators in Iowa and North Carolina. Detailed information on pesticide use and other factors was obtained from a self-administered questionnaire completed at time of enrollment (1993–1997). Among private and commercial applicators, 75.5% reported having ever used glyphosate, of which > 97% were men. In this analysis, glyphosate exposure was defined as *a*) ever personally mixed or applied products containing glyphosate; *b*) cumulative lifetime days of use, or "cumulative exposure days" (years of use × days/year); and *c*) intensity-weighted cumulative exposure days (years of use × days/year × estimated intensity level). Poisson regression was used to estimate exposure–response relations between glyphosate and incidence of all cancers combined and 12 relatively common cancer subtypes. Glyphosate exposure was not associated with cancer incidence overall or with most of the cancer subtypes we studied. There was a suggested association with multiple myeloma incidence that should be followed up as more cases occur in the AHS. Given the widespread use of glyphosate, future analyses of the AHS will allow further examination of long-term health effects, including less common cancers. *Key words:* cancer, cohort study, farming, glyphosate, pesticide. *Environ Health Perspect* 113:49–54 (2005). doi:10.1289/ehp.7340 available via *http://dx.doi.org/* [Online 4 November 2004]

Glyphosate [*N*-(phosphonomethyl)glycine], commonly sold in the commercial formulation named Roundup (Monsanto Company, St. Louis, MO), has been a frequently used herbicide on both cropland and noncropland areas of the world since its introduction in the 1970s (Williams et al. 2000). Roundup is a combination of the acrive ingredient and other chemicals, including a surfactant (polyoxyethyleneamine) that enhances the spreading of spray droplets when they contact foliage. Glyphosate is a broad-spectrum herbicide of which the primary mechanism is inhibition of the enzyme 5-enolpyruvoylshikimate 3-phosphate synthase, which is essential for the formation of aromatic amino acids in plants (Steinrucken and Amrhein 1980). Because this specific biologic pathway operates only in plants and microorganisms, the mechanism is not considered to be a risk for humans. Nevertheless, genotoxic, hormonal, and enzymatic effects in mammals have been reported (Bolognesi et al. 1997; Daruich et al. 2001; El Demerdash et al. 2001; Hietanen et al. 1983; Lioi et al. 1998a, 1998b; Olorunsogo et al. 1979; Peluso et al. 1998; Walsh et al. 2000; Yousef et al. 1995).

Results from genotoxicity studies of glyphosate have been conflicting. Glyphosate did not show any genotoxic activity in a battery of assays (Garry et al. 1999; Grisolia 2002; Li and Long 1988; Wildeman and Nazar 1982). However, other studies observed that glyphosate treatment of human lymphocytes *in vitro* resulted in increased sister chromatid exchanges (Bolognesi et al. 1997), chromosomal aberrations (Lioi et al. 1998b), and indicators of oxidative stress (Lioi et al. 1998b). Some studies found slightly greater toxicity of the Roundup formulation compared with glyphosate, in terms of both acute toxicity (Folmar et al. 1979; Martinez et al. 1990; Mitchell et al. 1987) and genotoxicity (Bolognesi et al. 1997; Vigfusson and Vyse 1980). Roundup was associated with increased DNA adducts in mice (Peluso et al. 1998) and a weak mutagenic effect in the *Salmonella* assay (Kale et al. 1995; Moriya et al. 1983; Rank et al. 1993), whereas glyphosate alone did not show these effects. Chronic feeding studies of glyphosate have not provided evidence of a carcinogenic effect in mice or rats (Williams et al. 2000).

The U.S. Environmental Protection Agency (U.S. EPA 1993) and the World Health Organization (WHO 1994) reviewed the toxicology data on glyphosate and concluded that glyphosate is not mutagenic or carcinogenic. The U.S. EPA classified glyphosate as category E, indicating "evidence of noncarcinogenicity for humans" (U.S. EPA 1993). Despite this conclusion, three recent case–control studies suggested an association between reported glyphosate use and the risk of non-Hodgkin lymphoma (NHL) (De Roos et al. 2003b; Hardell and Eriksson 1999; Hardell et al. 2002; McDuffie et al. 2001). Considering the widespread and frequent use of glyphosate in both the United States and the rest of the world, ongoing risk assessment is of importance. We studied site-specific cancer incidence associated with glyphosate use among pesticide applicators in the Agricultural Health Study (AHS) cohort.

Materials and Methods

Cohort enrollment and follow-up. The AHS is a prospective cohort study in Iowa and North Carolina, which includes 57,311 private and commercial applicators who were licensed to apply restricted-use pesticides at the time of enrollment. Recruitment of the applicators occurred between 1993 and 1997 (Alavanja et al. 1996). Cohort members were matched to cancer registry files in Iowa and North Carolina for case identificarion and to the state death registries and the National Death Index (National Center for Health Statistics 1999) to ascertain vital status. Incident cancers were identified for the time period from the date of enrollment until 31 December 2001 and were coded according to the *International Classification of Diseases*, 9th Revision (WHO 1977). If cohort members had moved from the state, they were censored in the year they left. The median time of follow-up was 6.7 years.

Exposure assessment. Using a self-administered enrollment questionnaire, we collected comprehensive-use data on 22 pesticides, ever/never use information for 28 additional pesticides, and general information on pesticide application methods, personal protective equipment, pesticide mixing, and equipment repair. Data were also collected on basic demographic

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and lifestyle factors. Applicators who completed this questionnaire were given a self-administered take-home questionnaire, which contained additional questions on occupational exposures and lifestyle factors. The questionnaires are available from the AHS website (National Institutes of Health 2004).

We constructed three glyphosate exposure metrics for this analysis: *a*) ever personally mixed or applied products containing glyphosate (ever/never); *b*) cumulative lifetime days of use, or "cumulative exposure days" (years of use × days per year, categorized in tertiles among users: 1–20, 21–56, 57–2,678); and *c*) intensity-weighted cumulative exposure days (years of use × days per year × intensity level, categorized in tertiles: 0.1–79.5, 79.6–337.1, 337.2–18,241). Tertiles were chosen *a priori* as the cut points with which to categorize exposure data, to avoid sparse data for rare cancers in the high-exposure categories. Intensity levels were estimated using questionnaire data from enrollment and measurement data from the published pesticide exposure literature, as follows: intensity level = [(mixing status + application method + equipment repair status) × personal protective equipment use] (Dosemeci et al. 2002).

Data analysis. Persons whose first primary cancer occurred before the time of enrollment (n = 1,074) were excluded from analyses, as were subjects who were lost to follow-up or otherwise did not contribute any person-time (n = 298) and applicators who did not provide any information on age (n = 7) or whether they had ever used glyphosate (n = 1,678). After exclusions, 54,315 subjects were available for inclusion in the age-adjusted analyses of cancer incidence in relation to glyphosate use; however, other analyses contained fewer observations because of missing data for duration and frequency of glyphosate use or for covariates.

We compared certain baseline characteristics among three types of pesticide applicators: *a*) those applicators who never personally used glyphosate; *b*) applicators with the lowest glyphosate exposure, defined as being in the lowest tertile of cumulative exposure days; and *c*) those with higher glyphosate exposure, defined as being in the middle or highest tertile of cumulative exposure days. The purpose of the comparison was to identify potential confounders of glyphosate exposure–disease associations for the various analyses we conducted. Differences between the exposure groups were tested using the chi-square statistics and associated p-values.

Poisson regression analyses were carried out for all cancers combined and specific cancer sites to estimate rate ratios (RRs) and 95% confidence inrervals (CIs) associated with glyphosate exposure metrics; the effect of each metric was evaluated in a separate model for each cancer. We analyzed tertile exposure variables in separate models using either the lowest-tertile–exposed or never-exposed subjects as the reference category. We investigated specific cancer sites for which there were at least 30 cases with sufficient information for inclusion in age-adjusted analyses. These cancers were then evaluated for all the exposure metrics and in adjusted analyses, despite smaller numbers of cases upon further adjustment. For each exposure metric, RRs were adjusted for demographic and lifesryle factors, including age at enrollment (continuous), education (dichotomous: ≤ high school graduate or GED/education beyond high school), pack-years of cigarette smoking [indicator variables: never, pack-years at or below the median (12 pack-years), pack-years above the median], alcohol consumprion in the past year [indicator variables: none, frequency at or below the median (72 drinks), frequency above the median], family history of cancer in first-degree relatives (dichotomous: yes/no), and state of residence (dichotomous: Iowa/North Carolina). There was insufficient variability in sex or applicator type to adjust for these factors.

Potential confounding from exposure to other pesticides was explored by adjusting for the five pesticides for which cumulative-exposure-day variables were most highly associated with glyphosate cumulative exposure days [(2,4-dichlorophenoxy)acetic acid (2,4-D), alachlor, atrazine, metolachlor, trifluralin]; these pesticide exposures were coded as variables indicating never, low, and high, with the split between low and high as the median of their cumulative exposure days. Additionally, of the pesticides for which only ever/never use

Table 1. Selected characteristics of applicators in the AHS by glyphosate exposure, based on data from the enrollment questionnaire (1993–1997).[a]

Characteristic	Never exposed (n = 13,280) No. (%)	Lowest exposed (n = 15,911)[b] No. (%)	Higher exposed (n = 24,465)[c] No. (%)
State of residence			
Iowa	9,987 (75.2)	9,785 (61.5)	15,336 (62.7)
North Carolina	3,293 (24.8)	6,126 (38.5)	9,129 (37.3)
Age (years)			
< 40	2,279 (17.2)	2,226 (14.0)	4,190 (17.1)
40–49	3,420 (25.8)	4,279 (26.9)	7,899 (32.3)
50–59	2,989 (22.5)	3,931 (24.7)	6,035 (24.7)
60–69	2,715 (20.4)	3,266 (20.5)	3,997 (16.3)
70	1,877 (14.1)	2,209 (13.9)	2,344 (9.6)
Sex			
Male	12,778 (96.2)	15,505 (97.5)	23,924 (97.8)
Female	502 (3.8)	406 (2.6)	541 (2.2)
Applicator type[d]			
Private	12,067 (90.9)	15,008 (94.3)	21,938 (89.7)
Commercial	1,213 (9.1)	903 (5.7)	2,527 (10.3)
Education			
High school graduate or GED	8,898 (68.7)	8,997 (57.9)	11,975 (50.1)
Beyond high school	4,060 (31.3)	6,530 (42.1)	11,936 (49.9)
Smoking history			
Never	7,298 (57.3)	8,241 (53.2)	12,751 (53.7)
≤ 12 pack-years	2,866 (22.5)	3,597 (23.2)	5,572 (23.5)
> 12 pack-years	2,567 (20.2)	3,643 (23.5)	5,439 (22.9)
Alcohol consumption in past year			
None	4,087 (32.7)	5,352 (35.6)	7,023 (29.8)
≤ 6 drinks/month	4,461 (35.7)	5,291 (35.2)	8,149 (34.5)
> 6 drinks/month	3,936 (31.5)	4,387 (29.2)	8,422 (35.7)
Family history of cancer			
No	8,701 (65.5)	9,520 (59.8)	14,668 (60.0)
Yes	4,579 (34.5)	6,391 (40.2)	9,797 (40.0)
Use of other common pesticides			
2,4-D	7,030 (53.3)	11,879 (75.2)	20,699 (85.1)
Alachlor	4,896 (39.7)	7,321 (50.9)	13,790 (59.7)
Atrazine	7,707 (58.5)	10,533 (66.6)	18,237 (75.0)
Metolachlor	3,890 (31.6)	6,172 (43.1)	12,952 (56.2)
Trifluralin	4,239 (34.0)	7,109 (49.7)	14,675 (63.5)
Carbaryl	4,110 (33.7)	8,515 (58.1)	15,139 (64.8)
Benomyl	510 (4.3)	1,418 (9.9)	3,391 (14.8)
Maneb	492 (4.1)	1,412 (9.9)	2,929 (12.9)
Paraquat	1,067 (9.0)	3,021 (21.2)	8,031 (35.2)
Diazinon	1,906 (16.0)	4,615 (32.4)	9,107 (40.0)

[a]Includes observations for subjects included in age-adjusted Poisson regression models of cancer incidence (n = 54,315). [b]Lowest tertile of cumulative exposure days. [c]Highest two tertiles of cumulative exposure days; the sum of the three tertiles of cumulative exposure days (n = 40,376) does not equal the total number of subjects who reported having ever used glyphosate (n = 41,035) because of missing data on duration and frequency of use. [d]"Private" refers primarily to individual farmers, and "commercial" refers to professional pesticide applicators.

information was available, we adjusted for the five pesticides that were most highly associated with ever use of glyphosate (benomyl, maneb, paraquat, carbaryl, diazinon). Where inclusion of all 10 other pesticides in a model changed a glyphosate exposure estimate by at least 20% (compared with a model restricted to the same observations), these results were presented as the final results for that cancer; otherwise, estimates adjusted only for demographic and lifestyle factors are presented.

Tests for trend across tertiles were conducted by creating a continuous variable with assigned values equal to the median value of cumulative exposure days (or intensity-weighted exposure days) within each tertile; the p-value for the trend test was that from the Poisson model coefficient for this continuous variable. We considered p-values < 0.10 as indicative of a trend.

Additional analyses were conducted for cancers for which we observed elevated RRs, and for NHL because of its association with glyphosate in previous studies. These included analyses stratified by state and analyses across quartiles and quintiles (where numbers allowed) of exposure days metrics.

Results

Selected characteristics of the glyphosate-exposed and never-exposed applicators are presented in Table 1. Among 54,315 subjects included in age-adjusted analyses, 41,035 (75.5%) reported having ever personally mixed or applied products containing glyphosate, and 13,280 (24.5%) did not. The cohort, both exposed and never exposed, was composed of primarily of male, middle-aged, private applicators. This is a population with relatively low smoking prevalence; in both the exposed and never-exposed groups, more than half of the subjects reported that they had never smoked. Significant differences ($p < 0.05$) existed between never-exposed and lowest-exposed subjects for all of the characteristics in Table 1. Lowest- and higher-exposed subjects ($p < 0.05$) also differed on several factors, the most notable being that higher-exposed subjects were more likely to be commercial applicators, to have consumed greater amounts of alcohol in the past year, and to have used other specific pesticides. However, lowest- and higher-exposed subjects were similar to each other ($p \geq 0.05$) in characteristics including smoking and family history of cancer in a first-degree relative. In addition, lowest- and higher-exposed subjects were more similar to each other than to their never-exposed counterparts (by qualitative comparison of percentages only) in factors including North Carolina residence, education beyond high school, and use of other pesticides. Because of relative similarities between lowest- and higher-exposed in factors associated with socioeconomic status and other exposures, we decided to conduct some analyses using lowest-exposed rather than never-exposed applicators as the reference group, in order to avoid residual confounding by unmeasured covariates. However, we decided *a priori* that any association should be apparent regardless of which reference group was used.

RRs for the association of all cancers combined and specific cancers with having ever used glyphosate are presented in Table 2. RRs adjusted for age only are presented, as well as RRs adjusted for demographic and lifestyle factors and, in some cases, for other pesticides. The incidence of all cancers combined was not associated with glyphosate use, nor were most specific cancers. There was an 80% increased risk of melanoma associated with glyphosate use in the age-adjusted analysis, which diminished slightly upon further adjustment. Adjusted risk estimates for colon, rectum, kidney, and bladder cancers were elevated by 30–60%, but these estimates were not statistically significant. There was more than 2-fold increased risk of multiple myeloma associated with ever use of glyphosate in adjusted analyses, although this is based on a small number of cases. The association between myeloma incidence and glyphosate exposure was consistent in both states (ever used glyphosate, fully adjusted analyses: Iowa RR = 2.6; North Carolina RR = 2.7).

Results from analyses of tertiles of increasing glyphosate exposure level are presented in Table 3. A decreased risk of lung cancer was suggested for the highest tertile of both cumulative and intensity-weighted exposure days (p-value for trend = 0.02); however, a similar trend was not observed in analyses using never exposed as the referent (results not shown). There was a 40% increased risk of colon cancer for the highest tertile of intensity-weighted exposure; however, no clear monotonic trend was observed for either exposure metric. Elevated risks of leukemia and pancreas cancer were observed only for the middle tertiles of both cumulative and intensity-weighted exposure days, with no increased risk among those with the highest exposure. The associations we observed in the analysis of ever use of glyphosate (Table 2) for melanoma, rectum, kidney, and bladder cancers were not confirmed in analyses based on exposure-day metrics; similarly, no exposure–response patterns were observed in analyses using never exposed as the referent or in analyses across quintiles of exposure (results not shown). No association was observed between NHL and glyphosate exposure in any analysis, including an analysis comparing the highest with the lowest quintile of exposure (> 108 vs. > 0–9 cumulative exposure days: RR = 0.9; 95% CI, 0.4–2.1).

Elevated RRs were estimated for multiple myeloma, with an approximate 2-fold increased risk for the highest tertile of both cumulative and intensity-weighted exposure days (Table 3); however, small numbers precluded precise effect estimation ($n = 19$ in adjusted analyses of exposure-day metrics). The estimated intensity-level component of the intensity-weighted exposure-day metric was not associated with multiple myeloma (highest vs. lowest tertile: RR = 0.6; 95% CI, 0.2–1.8), and observed positive associations of the intensity-weighted exposure-day metric with myeloma relied solely

Table 2. Association of glyphosate exposure (ever/never used) with common cancers[a] among AHS applicators.

Cancer site	Total no. of cancers[c]	Ever used glyphosate (% of total)	RR (95% CI)[b] Effect estimates adjusted for age ($n = 54,315$)[d]	RR (95% CI)[b] Adjusted for age, demographic and lifestyle factors, and other pesticides[d]
All cancers	2,088	73.6	1.0 (0.9–1.1)	1.0 (0.9–1.2)
Lung	204	72.1	1.0 (0.7–1.3)	0.9 (0.6–1.3)
Oral cavity	59	76.3	1.1 (0.6–2.0)	1.0 (0.5–1.8)
Colon	174	75.3	1.1 (0.8–1.6)	1.4 (0.8–2.2)[e]
Rectum	76	77.6	1.2 (0.7–2.1)	1.3 (0.7–2.3)
Pancreas	38	76.3	1.2 (0.6–2.5)	0.7 (0.3–2.0)[e]
Kidney	63	73.0	1.0 (0.6–1.7)	1.6 (0.7–3.8)[e]
Bladder	79	76.0	1.2 (0.7–2.0)	1.5 (0.7–3.2)[e]
Prostate	825	72.5	1.0 (0.8–1.1)	1.1 (0.9–1.3)
Melanoma	75	84.0	1.8 (1.0–3.4)	1.6 (0.8–3.0)
All lymphohematopoietic cancers	190	75.3	1.1 (0.8–1.5)	1.1 (0.8–1.6)
NHL	92	77.2	1.2 (0.7–1.9)	1.1 (0.7–1.9)
Leukemia	57	75.4	1.1 (0.6–2.0)	1.0 (0.5–1.9)
Multiple myeloma	32	75.0	1.1 (0.5–2.4)	2.6 (0.7–9.4)[f]

[a]Cancers for which at least 30 subjects had sufficient information for inclusion in age-adjusted analyses. [b]RRs and 95% CIs from Poisson regression models. [c]Frequencies among subjects included in age-adjusted analyses. [d]Numbers of subjects in these analyses are lower than in age-adjusted analyses because of missing observations for some covariates (models adjusted for demographic and lifestyle factors include 49,211 subjects; models additionally adjusted for other pesticides include 40,719 subjects). [e]Estimates adjusted for other pesticides are shown because inclusion of other pesticide variables in the model changed the effect estimate for glyphosate by at least 20%. [f]The estimate for myeloma was not confounded by other pesticides according to our change-in-estimate rule of ≥ 20%; however, the fully adjusted estimate is shown for the purpose of comparison with state-specific estimates (in the text), which were confounded by other pesticides and required adjustment.

on the exposure-day component; therefore, only results for cumulative exposure days are shown further. When using never exposed as the referent, the association between glyphosate use and multiple myeloma was more pronounced, with more than 4-fold increased risk associated with the highest tertile of cumulative exposure days (tertile 1: RR = 2.3; 95% CI, 0.6–8.9; tertile 2: RR = 2.6; 95% CI, 0.6–11.5; tertile 3: RR = 4.4; 95% CI, 1.0–20.2; *p*-value for trend = 0.09). Although the myeloma cases were sparsely distributed in analyses of quartiles and quintiles, the highest increased risks were observed in the highest exposure categories (full set of results not shown: upper quartile vs. never exposed: RR = 6.6; 95% CI, 1.4–30.6; *p*-value for trend across quartiles = 0.01).

Discussion

There was no association between glyphosate exposure and all cancer incidence or most of the specific cancer subtypes we evaluated, including NHL, whether the exposure metric was ever used, cumulative exposure days, or intensity-weighted cumulative exposure days. The most consistent finding in our study was a suggested association between multiple myeloma and glyphosate exposure, based on a small number of cases.

Although our study relied on self-reported exposure information, farmers have been shown to provide reliable information regarding their personal pesticide use (Blair et al. 2002; Blair and Zahm 1993; Duell et al. 2001; Engel et al. 2001; Hoppin et al. 2002). Investigators have used pesticide supplier reports (Blair and Zahm 1993) and self-reported pesticide use information provided earlier (Engel et al. 2001) to assess the validity of retrospectively reported pesticide use data. Among farmers in the AHS, Blair et al. (2002) reported high reliability for reports of ever use of a particular pesticide (ranging from 70 to > 90%). Agreement for duration and frequency of use was lower but generally 50–60% for specific pesticides. Hoppin et al. (2002) have demonstrated that farmers provide plausible data regarding lifetime duration of use, with fewer than 5% reporting implausible values for specific chemicals.

There were rather few cases of NHL for inclusion in this analysis ($n = 92$); nevertheless,

Table 3. Association of glyphosate exposure (cumulative exposure days and intensity-weighted exposure days) with common cancers[a] among AHS applicators.

	Cumulative exposure days[b]				Intensity-weighted exposure days[c]			
Cancer site	Tertile cut points	No.	RR (95% CI)[d]	*p*-Trend	Tertile cut points	No.	RR (95% CI)[d]	*p*-Trend
All cancers	1–20	594	1.0		0.1–79.5	435	1.0	
	21–56	372	1.0 (0.9–1.1)		79.6–337.1	436	0.9 (0.8–1.0)	
	57–2,678	358	1.0 (0.9–1.1)	0.57	337.2–18,241	438	0.9 (0.8–1.1)	0.35
Lung	1–20	40	1.0		0.1–79.5	27	1.0	
	21–56	26	0.9 (0.5–1.5)[e]		79.6–337.1	38	1.1 (0.7–1.9)[e]	
	57–2,678	26	0.7 (0.4–1.2)[e]	0.21	337.2–18,241	27	0.6 (0.3–1.0)[e]	0.02
Oral cavity	1–20	18	1.0		0.1–79.5	11	1.0	
	21–56	10	0.8 (0.4–1.7)		79.6–337.1	14	1.1 (0.5–2.5)	
	57–2,678	10	0.8 (0.4–1.7)	0.66	337.2–18,241	13	1.0 (0.5–2.3)	0.95
Colon	1–20	32	1.0		0.1–79.5	25	1.0	
	21–56	28	1.4 (0.9–2.4)[e]		79.6–337.1	20	0.8 (0.5–1.5)[e]	
	57–2,678	15	0.9 (0.4–1.7)[e]	0.54	337.2–18,241	30	1.4 (0.8–2.5)[e]	0.10
Rectum	1–20	20	1.0		0.1–79.5	16	1.0	
	21–56	17	1.3 (0.7–2.5)		79.6–337.1	18	1.0 (0.5–2.0)	
	57–2,678	14	1.1 (0.6–2.3)	0.70	337.2–18,241	16	0.9 (0.5–1.9)	0.82
Pancreas	0–20	9	1.0		0–79.5	6	1.0	
	21–56	9	1.6 (0.6–4.1)		79.6–337.1	16	2.5 (1.0–6.3)	
	57–2,678	7	1.3 (0.5–3.6)	0.83	337.2–18,241	3	0.5 (0.1–1.9)	0.06
Kidney	1–20	20	1.0		0.1–79.5	20	1.0	
	21–56	8	0.6 (0.3–1.4)		79.6–337.1	7	0.3 (0.1–0.7)	
	57–2,678	9	0.7 (0.3–1.6)	0.34	337.2–18,241	10	0.5 (0.2–1.0)	0.15
Bladder	1–20	23	1.0		0.1–79.5	14	1.0	
	21–56	14	1.0 (0.5–1.9)		79.6–337.1	8	0.5 (0.2–1.3)	
	57–2,678	17	1.2 (0.6–2.2)	0.53	337.2–18,241	13	0.8 (0.3–1.8)	0.88
Prostate	1–20	239	1.0		0.1–79.5	167	1.0	
	21–56	132	0.9 (0.7–1.1)		79.6–337.1	169	1.0 (0.8–1.2)	
	57–2,678	145	1.1 (0.9–1.3)	0.69	337.2–18,241	174	1.1 (0.9–1.3)	0.60
Melanoma	1–20	23	1.0		0.1–79.5	24	1.0	
	21–56	20	1.2 (0.7–2.3)		79.6–337.1	16	0.6 (0.3–1.1)	
	57–2,678	14	0.9 (0.5–1.8)	0.77	337.2–18,241	17	0.7 (0.3–1.2)	0.44
All lymphohematopoietic cancers	1–20	48	1.0		0.1–79.5	38	1.0	
	21–56	38	1.2 (0.8–1.8)		79.6–337.1	40	1.0 (0.6–1.5)	
	57–2,678	36	1.2 (0.8–1.8)	0.69	337.2–18,241	43	1.0 (0.7–1.6)	0.90
NHL	1–20	29	1.0		0.1–79.5	24	1.0	
	21–56	15	0.7 (0.4–1.4)		79.6–337.1	15	0.6 (0.3–1.1)	
	57–2,678	17	0.9 (0.5–1.6)	0.73	337.2–18,241	22	0.8 (0.5–1.4)	0.99
Leukemia	1–20	9	1.0		0.1–79.5	7	1.0	
	21–56	14	1.9 (0.8–4.5)[e]		79.6–337.1	17	1.9 (0.8–4.7)[e]	
	57–2,678	9	1.0 (0.4–2.9)[e]	0.61	337.2–18,241	8	0.7 (0.2–2.1)[e]	0.11
Multiple myeloma	1–20	8	1.0		0–79.5	5	1.0	
	21–56	5	1.1 (0.4–3.5)[e]		79.6–337.1	6	1.2 (0.4–3.8)[e]	
	57–2,678	6	1.9 (0.6–6.3)[e]	0.27	337.2–18,241	8	2.1 (0.6–7.0)[e]	0.17

[a]Cancers for which at least 30 subjects had sufficient information for inclusion in age-adjusted analyses. [b]Numbers of subjects in analyses vary depending on missing observations for cumulative exposure days and some covariates (models adjusted for demographic and lifestyle factors include 36,823 subjects; models additionally adjusted for other pesticides include 30,699 subjects). [c]Numbers of subjects in analyses vary depending on missing observations for intensity-weighted cumulative exposure days and some covariates (models adjusted for demographic and lifestyle factors include 36,509 subjects; models additionally adjusted for other pesticides include 30,613 subjects). [d]Relative rate ratios and 95% CIs from Poisson regression analyses. [e]Estimates adjusted for other pesticides are shown because inclusion of other pesticide variables in the model changed the effect estimate for glyphosate by at least 20%.

the available data provided evidence of no association between glyphosate exposure and NHL incidence. This conclusion was consistent across analyses using the different exposure metrics and in analyses using either never exposed or low exposed as the referent. Furthermore, there was no apparent effect of glyphosate exposure on the risk of NHL in analyses stratified by state of residence or in analyses of highly exposed groups comparing the highest with the lowest quintile of exposure. These findings conflict with recent studies. The first report of an association of glyphosate with NHL was from a case–control study, but the estimate was based on only four exposed cases (Hardell and Eriksson 1999). A pooled analysis of this initial study with a study of hairy cell leukemia showed a relationship between glyphosate exposure and an increased risk of disease [unadjusted analysis: odds ratio (OR) = 3.0; 95% CI, 1.1–8.5] (Hardell et al. 2002). A more extensive study conducted across a large region of Canada found an elevated risk of NHL associated with glyphosate use more frequent than 2 days/year (OR = 2.1; 95% CI, 1.2–3.7) (McDuffie et al. 2001). Similarly, increased NHL risk in men was associated with having ever used glyphosate (OR = 2.1; 95% CI, 1.1–4.0) after adjustment for other commonly used pesticides in a pooled analysis of National Cancer Institute–sponsored case–control studies conducted in Nebraska, Kansas, Iowa, and Minnesota (De Roos et al. 2003b). These previous studies were retrospective in design and thereby potentially susceptible to recall bias of exposure reporting. Our analysis of the AHS cohort had a prospective design, which should largely eliminate the possibiliry of recall bias. Differences in recall bias could account for discrepant study results; however, evaluation of the potential for recall bias in case–control studies of pesticides among farmers has not uncovered evidence that it occurred (Blair and Zahm 1993).

Our finding of a suggested association of multiple myeloma incidence with glyphosate exposure has not been previously reported, although numerous studies have observed increased myeloma risk associated with farming occupation (Boffetta et al. 1989; Brownson et al. 1989; Cantor and Blair 1984; Cerhan et al. 1998; Cuzick and De Stavola 1988; Eriksson and Karlsson 1992; Figgs et al. 1994; Gallagher et al. 1983; La Vecchia et al. 1989; Nandakumar et al. 1986, 1988; Pasqualetti et al. 1990; Pearce et al. 1985; Pottern et al. 1992; Reif et al. 1989; Vagero and Persson 1986). A possible biologic mechanism of how glyphosate might act along the causal pathway of this plasma cell cancer has not been hypothesized, but myeloma has been associated with agents that cause either DNA damage or immunosuppression (De Roos et al. 2003a). The association we observed was with ever use of glyphosate and cumulative exposure days of use (a combination of duration and frequency), but not with intensity of exposure. Estimated intensity of glyphosate exposure was based on general work practices that were not glyphosate specific, including the percentage of time spent mixing and applying pesticides, application method, use of personal protective equipment, and repair of pesticide application equipment (Dosemeci et al. 2002). Information on work practices specific to glyphosate use would clarify whether intensity of exposure contributes to myeloma risk.

The number of myeloma cases in our study was small, and ir is plausible that spurious associations arose by chance; however, several aspects of our results argue against a chance association. The findings were internally consistent, with increased risk observed in both states. Adding to the credibility of the association, rhere was some indication of a dose–response relationship, with risk estimates increasing across categories of increasing exposure and stronger associations observed when using never-exposed subjects as the referent (as opposed to low exposed). Another possible explanation for spurious associations is unadjusted confounding. Our risk estimates were adjusted for some demographic and lifestyle factors and other pesticides. Of the other pesticides included in the fully adjusted model, only diazinon and trifluralin were important confounders of the glyphosate–myeloma association. It is certainly possible that an unknown risk factor for myeloma could have confounded our results; however, any unknown confounder would have to be linked with glyphosate use. Finally, the increased myeloma risk associated with glyphosate use could be due to bias resulting from a selection of subjects in adjusted analyses that differed from subjects included in unadjusted analyses. Table 1 shows that 54,315 subjects were included in age-adjusted models, whereas because of missing data for covariates, only 40,719 subjects were included in fully adjusted analyses. The association of glyphosate with myeloma differed between the two groups, even without adjustment for any covariates, with no association among the full group and a positive association among the more restricted group. Subjects who answered all the questions and were thus included in adjusted analyses differed from those who dropped out of such analyses in that they were more likely to be from Iowa (71.8% in included group vs. 44.6% in dropped group), were younger (average age, 51.5 vs. 57.9 years), and were more highly educated (46.7% educated beyond high school graduate vs. 30.2%); however, the two groups were similar in their use of glyphosate (75.9% vs. 74.5%). The increased risk associated with glyphosate in adjusted analyses may be due to selection bias or could be due to a confounder or effect modifier that is more prevalent among this restricted subgroup and is unaccounted for in our analyses. Further follow-up of the cohort and reevaluation of the association between glyphosate exposure and myeloma incidence after a greater number of cases develop will allow more detailed examination of the potential biases underlying the association.

Certain limitations of our data hinder the inferences we can make regarding glyphosate and its association with specific cancer subtypes. Although the AHS cohort is large, and there were many participants reporting glyphosate use, the small numbers of specific cancers occurring during the follow-up period hindered precise effect estimation. In addition, most applicators were male, precluding our abiliry to assess the association between glyphosate exposure and cancer incidence among women, for both non-sex-specific cancers and sex-specific cancers (e.g., of the breast or ovary). Our analysis provides no information on the timing of pesticide use in relation to disease, limiting the ability to sufficiently explore latency periods or effects resulting from glyphosate exposure at different ages. Despite limitations of our study, certain inferences are possible. This prospective study of cancer incidence provided evidence of no association between glyphosate exposure and most of the cancers we studied, and a suggested association between glyphosate and the risk of multiple myeloma. Future analyses within the AHS will follow up on these findings and will examine associations between glyphosate exposure and incidence of less common cancers.

References

Alavanja MC, Sandler DP, McMaster SB, Zahm SH, McDonnell CJ, Lynch CF, et al. 1996. The Agricultural Health Study. Environ Health Perspect 104:362–369.

Blair A, Tarone R, Sandler D, Lynch CF, Rowland A, Wintersteen W, et al. 2002. Reliability of reporting on lifestyle and agricultural factors by a sample of participants in the Agricultural Health Study from Iowa. Epidemiology 13:94–99.

Blair A, Zahm SH. 1993. Patterns of pesticide use among farmers: implications for epidemiologic research. Epidemiology 4:55–62.

Boffetta P, Stellman SD, Garfinkel L. 1989. A case-control study of multiple myeloma nested in the American Cancer Society prospective study. Int J Cancer 43:554–559.

Bolognesi C, Bonatti S, Degan P, Gallerani E, Peluso M, Rabboni R, et al. Genotoxic activity of glyphosate and its technical formulation Roundup. J Agric Food Chem 45:1957–1962.

Brownson RC, Reif JS, Chang JC, Davis JR. 1989. Cancer risks among Missouri farmers. Cancer 64:2381–2386.

Cantor KP, Blair A. 1984. Farming and mortality from multiple myeloma: a case-control study with the use of death certificates. J Natl Cancer Inst 72:251–255.

Cerhan JR, Cantor KP, Williamson K, Lynch CF, Torner JC, Burmeister LF. 1998. Cancer mortality among Iowa farmers: recent results, time trends, and lifestyle factors (United States). Cancer Causes Control 9:311–319.

Cuzick J, De Stavola B. 1988. Multiple myeloma—a case-control study. Br J Cancer 57:516–520.

Daruich J, Zirulnik F, Gimenez MS. 2001. Effect of the herbicide

glyphosate on enzymatic activity in pregnant rats and their fetuses. Environ Res 85:226–231.

De Roos AJ, Baris D, Weiss NS, Herrinton LJ. 2003a. Epidemiology of multiple myeloma. In: Myeloma: Biology and Management (Malpas JS, Bergsagel DE, Kyle RA, Anderson KC, eds). 3rd ed. Philadelphia:Saunders, 117–158.

De Roos AJ, Zahm SH, Cantor KP, Weisenburger DD, Holmes FF, Burmeister LF, et al. 2003b. Integrative assessment of multiple pesticides as risk factors for non-Hodgkin's lymphoma among men. Occup Environ Med 60:E11. Available: http://oem.bmjjournals.com/cgi/content/full/60/9/e11 [accessed 30 November 2004].

Dosemeci M, Alavanja MC, Rowland AS, Mage D, Zahm SH, Rothman N, et al. 2002. A quantitative approach for estimating exposure to pesticides in the Agricultural Health Study. Ann Occup Hyg 46:245–260.

Duell EJ, Millikan RC, Savitz DA, Schell MJ, Newman B, Tse CJ, et al. 2001. Reproducibility of reported farming activities and pesticide use among breast cancer cases and controls. A comparison of two modes of data collection. Ann Epidemiol 11:178–185.

El Demerdash FM, Yousef MI, Elagamy EI. 2001. Influence of paraquat, glyphosate, and cadmium on the activity of some serum enzymes and protein electrophoretic behavior (in vitro). J Environ Sci Health B 36:29–42.

Engel LS, Seixas NS, Keifer MC, Longstreth WT Jr, Checkoway H. 2001. Validity study of self-reported pesticide exposure among orchardists. J Expo Anal Environ Epidemiol 11:359–368.

Eriksson M, Karlsson M. 1992. Occupational and other environmental factors and multiple myeloma: a population based case-control study. Br J Ind Med 49:95–103.

Figgs LW, Dosemeci M, Blair A. 1994. Risk of multiple myeloma by occupation and industry among men and women: a 24-state death certificate study. J Occup Med 36:1210–1221.

Folmar LC, Sanders HO, Julin AM. 1979. Toxicity of the herbicide glyphosphate and several of its formulations to fish and aquatic invertebrates. Arch Environ Contam Toxicol 8:269–278.

Gallagher RP, Spinelli JJ, Elwood JM, Skippen DH. 1983. Allergies and agricultural exposure as risk factors for multiple myeloma. Br J Cancer 48:853–857.

Garry VF, Burroughs B, Tarone R, Kesner JS. 1999. Herbicides and adjuvants: an evolving view. Toxicol Ind Health 15:159–167.

Grisolia CK. 2002. A comparison between mouse and fish micronucleus test using cyclophosphamide, mitomycin C and various pesticides. Mutat Res 518:145–150.

Hardell L, Eriksson M. 1999. A case-control study of non-Hodgkin lymphoma and exposure to pesticides. Cancer 85:1353–1360.

Hardell L, Eriksson M, Nordstrom M. 2002. Exposure to pesticides as risk factor for non-Hodgkin's lymphoma and hairy cell leukemia: pooled analysis of two Swedish case-control studies. Leuk Lymphoma 43:1043–1049.

Hietanen E, Linnainmaa K, Vainio H. 1983. Effects of phenoxy-herbicides and glyphosate on the hepatic and intestinal biotransformation activities in the rat. Acta Pharmacol Toxicol (Copenh) 53:103–112.

Hoppin JA, Yucel F, Dosemeci M, Sandler DP. 2002. Accuracy of self-reported pesticide use duration information from licensed pesticide applicators in the Agricultural Health Study. J Expo Anal Environ Epidemiol 12:313–318.

Kale PG, Petty BT Jr, Walker S, Ford JB, Dehkordi N, Tarasia S, et al. 1995. Mutagenicity testing of nine herbicides and pesticides currently used in agriculture. Environ Mol Mutagen 25:148–153.

La Vecchia C, Negri E, D'Avanzo B, Franceschi S. 1989. Occupation and lymphoid neoplasms. Br J Cancer 60:385–388.

Li AP, Long TJ. 1988. An evaluation of the genotoxic potential of glyphosate. Fundam Appl Toxicol 10:537–546.

Lioi MB, Scarfi MR, Santoro A, Barbieri R, Zeni O, Di Berardino D, et al. 1998a. Genotoxicity and oxidative stress induced by pesticide exposure in bovine lymphocyte cultures in vitro. Mutat Res 403:13–20.

Lioi MB, Scarfi MR, Santoro A, Barbieri R, Zeni O, Salvemini F, et al. 1998b. Cytogenetic damage and induction of pro-oxidant state in human lymphocytes exposed in vitro to gliphosate, vinclozolin, atrazine, and DPX-E9636. Environ Mol Mutagen 32:39–46.

Martinez TT, Long WC, Hiller R. 1990. Comparison of the toxicology of the herbicide Roundup by oral and pulmonary routes of exposure. Proc West Pharmacol Soc 33:193–197.

McDuffie HH, Pahwa P, McLaughlin JR, Spinelli JJ, Fincham S, Dosman JA, et al. 2001. Non-Hodgkin's lymphoma and specific pesticide exposures in men: cross-Canada study of pesticides and health. Cancer Epidemiol Biomarkers Prev 10:1155–1163.

Mitchell DG, Chapman PM, Long TJ. 1987. Acute toxicity of Roundup and Rodeo herbicides to rainbow trout, chinook, and coho salmon. Bull Environ Contam Toxicol 39:1028–1035.

Moriya M, Dhta T, Watanabe K, Miyazawa T, Kato K, Shirasu Y. 1983. Further mutagenicity studies on pesticides in bacterial reversion assay systems. Mutat Res 116:185–216.

Nandakumar A, Armstrong BK, de Klerk NH. 1986. Multiple myeloma in Western Australia: a case-control study in relation to occupation, father's occupation, socioeconomic status and country of birth. Int J Cancer 37:223–226.

Nandakumar A, English DR, Dougan LE, Armstrong BK. 1988. Incidence and outcome of multiple myeloma in Western Australia, 1960 to 1984. Aust NZ J Med 18:774–779.

National Center for Health Statistics. 1999. National Death Index Homepage. Hyattsville, MD:National Center for Health Statistics. Available: http://www.cdc.gov/nchs/r&d/ndi/ndi.htm [accessed 30 November 2004].

National Institutes of Health. 2004. Agricultural Health Study Homepage. Bethesda, MD:National Institutes of Health. Available: http://www.aghealth.org [accessed 25 September 2004].

Olorunsogo OO, Bababunmi EA, Bassir O. 1979. Effect of glyphosate on rat liver mitochondria in vivo. Bull Environ Contam Toxicol 22:357–364.

Pasqualetti P, Casale R, Collacciani A, Colantonio D. 1990. Work activities and the risk of multiple myeloma. A case-control study. Med Lav 81:308–319.

Pearce NE, Smith AH, Fisher DO. 1985. Malignant lymphoma and multiple myeloma linked with agricultural occupations in a New Zealand Cancer Registry-based study. Am J Epidemiol 121:225–237.

Peluso M, Munnia A, Bolognesi C, Parodi S. 1998. ^{32}P-Postlabeling detection of DNA adducts in mice treated with the herbicide Roundup. Environ Mol Mutagen 31:55–59.

Pottern LM, Heineman EF, Olsen JH, Raffn E, Blair A. 1992. Multiple myeloma among Danish women: employment history and workplace exposures. Cancer Causes Control 3:427–432.

Rank J, Jensen AG, Skov B, Pedersen LH, Jensen K. 1993. Genotoxicity testing of the herbicide Roundup and its active ingredient glyphosate isopropylamine using the mouse bone marrow micronucleus test, Salmonella mutagenicity test, and Allium anaphase-telophase test. Mutat Res 300:29–36.

Reif J, Pearce N, Fraser J. 1989. Cancer risks in New Zealand farmers. Int J Epidemiol 18:768–774.

Steinrucken HC, Amrhein N. 1980. The herbicide glyphosate is a potent inhibitor of 5-enolpyruvyl-shikimic acid-3-phosphate synthase. Biochem Biophys Res Commun 94:1207–1212.

U.S. EPA. 1993. U.S. Environmental Protection Agency Reregistration Eligibility Decision (RED) Glyphosate. EPA-738-R-93-014. Washington, DC:U.S. Environmental Protection Agency.

Vagero D, Persson G. 1986. Occurrence of cancer in socio-economic groups in Sweden. An analysis based on the Swedish Cancer Environment Registry. Scand J Soc Med 14:151–160.

Vigfusson NV, Vyse ER. 1980. The effect of the pesticides, Dexon, Captan and Roundup, on sister-chromatid exchanges in human lymphocytes in vitro. Mutat Res 79:53–57.

Walsh LP, McCormick C, Martin C, Stocco DM. 2000. Roundup inhibits steroidogenesis by disrupting steroidogenic acute regulatory (StAR) protein expression. Environ Health Perspect 108:769–776.

WHO. 1977. International Classification of Diseases: Manual of the International Statistical Classification of Diseases, Injuries, and Causes of Death, Vol 1, 9th revision. Geneva:World Health Organization.

WHO. 1994. International Programme on Chemical Safety. Glyphosate. Environmental Health Criteria 159. Geneva:World Health Organization.

Wildeman AG, Nazar RN. 1982. Significance of plant metabolism in the mutagenicity and toxicity of pesticides. Can J Genet Cytol 24:437–449.

Williams GM, Kroes R, Munro IC. 2000. Safety evaluation and risk assessment of the herbicide Roundup and its active ingredient, glyphosate, for humans. Regul Toxicol Pharmacol 31:117–165.

Yousef MI, Salem MH, Ibrahim HZ, Helmi S, Seehy MA, Bertheussen K. 1995. Toxic effects of carbofuran and glyphosate on semen characteristics in rabbits. J Environ Sci Health B 30:513–534.

DRAFT-

Lymphoma risk and pesticide use in the Agricultural Health Study

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ABBREVIATIONS

Agricultural Health Study (AHS)

Rate ratios (RR)

95% confidence intervals (CI)

Organochlorine insecticides (OC)

Organophosphate insecticides (OP)

United States Environmental Protection Agency (U.S. EPA)

International Agency for Research on Cancer (IARC)

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Running Title: Pesticides and Non-Hodgkin Lymphoma

Abstract: 247 words: 250 word limit for EHP.

Manuscript, references and tables 1-5: 8,162 including title page etc.. [narrative (abstract & main manuscript 3,717, references 1,411, tables 2942] 7000 word limit for EHP.

Comment [a1]: If we have the message and analyses right we have to cut 1,200 words for EHP. We may want to go to another journal.

Comment [AB2]: I suggest go to another journa

ABSTRACT

Background: Farming and eExposure to pesticides haves been linked to non-Hodgkin lymphoma (NHL) in a number of previous studies. **Objective**: To evaluate specific pesticides for associations with NHL and NHL subtypes in a prospective cohort of farmers and commercial pesticide applicatorsregistered pesticide applicators. **Methods**: We examined NHL incidence in a prospective cohort of 57,310 licensed pesticide applicators in Iowa and North Carolina from 1993- 2008. Information on pesticide and other agricultural eExposure, information lifestyle and medical historyhealth histories wasere obtained from a self-administered questionnaires administered at enrollment (1993-1997) and in a telephone follow-up questionnaire administered approximately five years later (1998-2004). Poisson regression modeling was used to evaluate the association between use of specific pesticides and the rate ratios of NHL and NHL subtypes while adjusting for age and other potential confounding variables. **Results**: A statistically significant monotonic increase in the risk of overall NHL with increasing life-time exposure-days for lindane (organochlorine insecticide) was observed and a significant positive non-monotonic trend was observed for butylate (thiocarbamate herbicide), among 50 pesticides evaluated. Significantly increasing risk of specific NHL subtypes with increasing life-time exposure-days of use were observed for lindane, butylate, dicamba, terbufos, alachlor, EPTC, imazethapyr and trifluralin. The total number of different pesticides used was not associated with NHL risk overall, but the number of different triazine/triazone herbicides was significantly associated NHL. Chlorinated and organophosphate insecticide and triazine/triazone herbicides used, was related to risk in specific NHL subtypes. **Conclusions**: A wide variety of chemically-distinct herbicides and insecticides were significantly associated with different NHL subtypes. Most pesticides are associated with only one NHL subtype.

Comment [AB3]: Need to indicate which subtypes were associated with which pesticides.

Comment [AB4]: Mention the chemical class – subtype associations before the specific pesticide associations. Go from the general to the specific.

Comment [AB5]: I am not sure we want to deliver this message. As written it says we believe we found a number of meaningful pesticide – subtype links and that the links were specific. This implies we believe these findings are probably "real." I think the message should be – this is one o the few studies (and the only prospective study I think) that has looked at specific pesticide – subtype associations. Since different subtypes may have different etiologies these findings provide leads for future evaluations.

Keywords: Cohort Study, Farming, Pesticide Exposure, Non-Hodgkin Lymphoma.

INTRODUCTION

Non-Hodgkin lymphomas (NHLs) are a heterogeneous group of over ~~20~~ different B and T-cell neoplasms affecting the immune system/ lymphatic system arising primarily in the lymph nodes (Swerlow et al. 2008; Shankland et al., 2012). M~~Numerous~~ eta-analyses (Blair et al., 1985; Blair et al., 1993; Beane Freeman, 2009) studies relate lymphohaematopoietic cancers with farming (~~Blair A et al., 1993; Blair and~~ Beane Freeman, 2009), with exposure to pesticides being a hypothesized etiologic agent. Since the 1980s a number of studies have been conducted to evaluate possible links between specific pesticides and NHL. A meta-analysis of 13 case-control studies published between1993-2005 observed an overall significant meta-odds ratio between occupational exposure to pesticides and NHL (OR=1.35; 95% CI: 1.2-1.5). When observations were limited to those that had more than 10 years of exposure the risk increased (OR=1.65; 95% CI: 1.08-1.95) (Merhi M, et al., 2007). While the meta-analysis supports the hypothesis that pesticides are associated with NHL, it did not~~they lack sufficient detail about~~ evaluate exposure to specific pesticide exposure and other information on risk factors for hematopoietic cancers to identify specific causes (Merhi M, et al., 2007). In individual studies of NHL have reported links a number of specific pesticides including phenoxy acid herbicides (Dich et al 1997; Hardell L et al., 1981; Hoar SK et al., 1986; Zahm et al, 1990, Miligi et al, 2006, McDuffie et al, 2001Eriksson M et al., 2008; Burns et al., 2011; 8), ~~and~~ chlorinated pesticides (McDuffie et al, 2001, Colt et al., 2006; Spinelli JJ et al 2007, Purdue et al, 2007, Brauner EV, et al., 2012; Quintana et al., 2004; Coco et al., 2004), organophosphates (Waddell et al., 2001; Hohenadel et al., 2011)dicamba (McDuffie et al., 2001; nitro-derivaties (Miligi et al., 2003); and triazole fungicides and urea herbicides (Orsi et al., 2009)~~have been suggested as causes of NHL, -~~but the evidence has been inconsistent. Little evidence of an association between phenoxy acid herbicides and NHL was observed in New Zealand (Pearce NE et al 1987), Washington state (USA) (Woods JS, et al 1987), or Minnesota and Iowa (USA) (Cantor KP et al, 1992) and little evidence for chlorinated pesticides was observed in a European study that measure pesticide metabolites in plasma samples (Cocco P et al, 2008). A variety of other pesticides have also been associated with NHL but the evidence available to date does not conclusively link a specific pesticide to NHL (Alavanja M et al., 2012; Cocco P et al., 2013). In a study from the six Canadian provinces case-control study, the risk of NHL increased with the number of different pesticides used (Hohenadel K et al., 2011).(I think the flow of this first

Comment [AB6]: References are numbered in th reference list, but not in the test.

Comment [AB7]: Is the Beane Freeman article cited here Laura's livestock article? It is the only one in the references.

Comment [a8]: Moved the Merhi study up to mention the general association first and later the pesticide class specific-Done

Comment [a9]: Added reference

Comment [a10]: Added reference

Comment [a11]: Added reference

Comment [a12]: Added Purdue

Comment [a13]: Sentence added in reference to Laura's comment to mention other chemical associations by way of citing a review article.-Done We are >8,100 words, EHP limit 7,000

Comment [a14]: Cindy suggests cutting down the introduction --Done

paragraph can be modified to make it clearer. Start with farming, then list pesticides that have been linked to NHL in some studies. This should cover the different pesticides that have been linked to NHL. Then list your review and Cocco (2013) to indicate that the evidence is not conclusive for any pesticide).

In the Agricultural Health Study (AHS) we had the opportunity to evaluate the risk of NHL overall and by cell type by ~~both the association of~~ lifetime use of individual pesticides obtained from enrollment and follow-up questionnaires ~~and the number of different pesticides used and NHL incidence overall and by cell type~~ in a prospective cohort study of licensed pesticide applicators in Iowa and North Carolina.

~~We evaluated potential confounders including a previous history of malignant disease (Wang et al., 2007), different immunosuppressive states (Simard JF, et al., 2012), and body mass index (BMI) (Patel et al., 2013) and other factors observed to be associated with NHL in the AHS cohort.~~

MATERIALS & METHODS

Study Population

The AHS is a prospective cohort study of 52,394 licensed private pesticide applicators in Iowa and North Carolina and 4,916 licensed commercial applicators from Iowa. The cohort has been described in detail (Alavanja et al., 1996). Briefly, the cohort included individuals seeking licenses for restricted use pesticides from December 1993 through December 1997 (82% of the target population enrolled). The protocol was approved by relevant institutional review boards. We obtained cancer incidence information by regular linkage to cancer registry files in Iowa and North Carolina. In addition, we matched cohort members to state residential mortality registries and the National Death Index to identify vital status, and to address records of the Internal Revenue Service, motor vehicle registration files, and pesticide license registries of state

Comment [a15]: Infor about cancer registries deleted as suggested by Laura

agricultural departments to determine residence in Iowa or North Carolina. The current analysis included all incident primary non-Hodgkin lymphomas (*n*=333) diagnosed from enrollment (1993-1997) through December 31, 2008. We censored follow-up at diagnosis of NHL or any other cancer, date of death, movement out of state, or December 31, 2008, whichever was earlier. Person-years of follow-up summed to 714,770.

Tumor Characteristics

Information on tumor characteristics was obtained from state cancer registries. Cases were classified into 5 groups of cell types according to the Surveillance Epidemiology and END Result (SEER) coding scheme (http://seer.cancer.gov/lymphomarecode) SEER recodes of cell type are listed in appendix 1. The first group (n=117) includes chronic B-cell lymphocytic lymphomas (CLL) /small B-cell lympocytic lymphomas (SLL) [n=101], and mantle-cell lymphomas (MCL) (n=16). The second group includes 94 diffuse large B-cell lymphomas; the third group includes 53 follicular lymphomas. There were 34 'other B-cell lymphomas' consisting of a diverse set of B-cell lymphomas including precursor acute lymphoblastic leukemia/lymphoma (n=4), Waldenstrom macro globulinemia (n=2), lymphoplasmacytic lymphoma (n=2), hairy-cell leukemia (n=6), B-cell non-Hodgkin lymphoma not otherwise specified(n=6), Burkitt lymphoma/leukemia (n=1), and extra-nodal Marginal Zone Lymphomas (MZL)/ MALT type/ Nodal MZL(n=13). The fifth grouping included 35 cases consisting of T-cell lymphomas (n=12) and non-Hodgkin lymphoma of unknown lineage (n=23). The fifth grouping was excluded from cell type-specific analyses because of small numbers of cases with identified cell types. Although multiple myeloma (MM) (n=77) and plasmacytomas (n=6) are

Comment [lbf16]: Did you remove prevalent cancers? Does this mean that you also included second cancers if they were NHL? Eg. If someone had an incident prostate cancer and then was diagnosed with an NHL, do you consider them to be an NHL case? Or, did you censor them at their diagnosis of prostate cancer? I would remove all prevalent cancers (n=1,074) and only include first primary NHL diagnoses, censoring at diagnosis of any cancer.

Comment [a17]: Yes, we removed all prevalent cancers and included only primary NHL cases.- clarification made in sentence.-no other change necessary.

Comment [a18]: Cindy would like the 5 groups to be named. They do not have names so it is may b inappropriate to give them non-standard names. I gave the SEER recode number in the table as a means of identification.

Comment [lbf19]: Since you present them in th appendix, I would suggest taking them out of the te here—it'shard to read with all these numbers. You could also add them to the relevant tables under the specific sub-types.

Comment [a20]: SEER recodes deleted as recommended by Laura.

now classified as a type of non-Hodgkin lymphoma (Morton LM et al., 2007), the pesticide literature prior to 2008 (including the AHS) examined multiple myeloma (and plasmacytomas) separately. (AB - I wonder if the decision not to include myeloma might seem inconsistent with our decision to go with the new definition of NHL. We say we are changing the cancers we characterize as NHL to fit the new definition, but then we promptly say we are not going to follow the new definition for all of the new inclusions, i.e., myeloma will not be included. It is inconsistent and seems gerrymandered. The reason given also does not seem adequate (myeloma has been analyzed separately for pesticides) because there have also been studies that looked a pesticides and chronic lymphocytic leukemia, yet it is included as NHL here. Not sure what to do but the whole thing just seems messy. We need to talk about this on an EC call.) We continue to examine MM separately to facilitate comparisons to the previous literature. We provide supplemental table 7 which shows NHL risk (previous definition, ICD-O-3) and lifetime use of individual pesticides (AB - I think to make clear the possible the impact, or lack of it, of changing the NHL definition, Table 7 needs to include ORs from both definitions of NHL for the same length of follow up. This would make it clear that any difference regarding specific pesticides would be due to differences in disease classification.) A comparison of cell types in the previous (ICD-O-3) and recent Inter Lymph hierarchical classification of NHL is provided in appendix 2.

Comment [a21]: We added the phrase 'prior to 2008' to avoid a large increase in citations which would contribute an additional 90 words or more (approximately)

Comment [lbf22]: You will need to cite these papers in the discussion

Exposure Assessment

Information on lifetime use of 50 pesticides was captured in two self-administered questionnaires (http://aghealth.org/questionnaires.html) completed during cohort enrollment (Phase 1). All 57,310 applicators completed the first enrollment questionnaire, which inquired about ever/never use of the 50 pesticides, as well as duration (years) and frequency (average days/year) of use for a subset of 22 pesticides. In addition, 25,291 (44.1%) of the applicators returned the second (take-home) questionnaire, which inquired about duration and frequency of use for the remaining 28 pesticides.

A follow-up questionnaire, which ascertained pesticide use since enrollment, was administered about five~~5~~ years after enrollment (1998-2003, Phase 2) and completed by 36,342 (63%) of the original participants. For participants who did not complete a Phase 2 questionnaire (20,968 applicators~~, 37%~~), a data-driven multiple imputation procedure based on logistic regression and stratified sampling was employed to impute likely use of specific pesticides in Phase 2 (Heltshe et al.,2012)~~ which used logistic regression and stratified sampling to impute the use of specific pesticides in phase 2.~~

Comment [a23]: Description of imputation procedure shortened considerable per suggestion.- Done

Information on pesticide use obtained from Phase 1 and Phase 2 interviews was used to construct two individual pesticide exposure metrics~~We used 2 exposure metrics to assess cumulative exposure to each pesticide~~: (i) lifetime days of pesticide use, i.e. the product of years of use of a specific pesticide and the number of days used per year; and (ii) intensity-weighted lifetime days of use, i.e. the product of lifetime days of use and a measure of exposure intensity. Intensity of exposure was derived from an algorithm using questionnaire data on mixing status, application method, equipment repair and use of personal protective equipment (Coble et al. 2011).

Comment [a24]: Dropped Dosemeci as suggested Dosemeci is referenced in Coble et al N additional changes made to this section

We analyzed total NHL risk and specific cell type NHL by pesticide classes, individual pesticides use, and by the number of different pesticides used within a chemical/functional class and the total number of different pesticides used in a working lifetime.

Comment [a25]: Analysis requested by Aaron

Statistical Analyses

We used Poisson regression to calculate rate ratios (RR) and 95% confidence intervals (95% CI) for overall NHL and four NHL subtypes in relation to pesticide use. Data were obtained from AHS data release versions P1REL201005.00 (for Phase 1) and P2REL201007.00 (for Phase 2). We evaluated pesticides with 15 or more exposed cases of total NHL, thereby excluding aldicarb, aluminum phosphide, carbon tetrachloride/carbon disulfide, dieldrin, (Might look specifically at dieldrin even though it is below your cutpoint because it has been linked to NHL in the past.) ethylene dibromide, maneb, parathion, 2,4,5-TP, trichlorofon, and ziram (This list is different than that provided in the first draft. Why the change?). For each pesticide analyzed, we categorized exposure into non-exposed and tertiles of exposure based on the distribution of exposed cases. A first set of rate ratios were adjusted for age and a second set of rate ratios were adjusted for age and other statistically significant (α=0.05) predictors of NHL in the AHS. We evaluated several lifestyle and demographic measures and identified the following as potential confounding variables: age at enrollment (<40, 40-49, 50-59, 60-70, ≥70), race (White, Black, other, missing), state (Iowa, North Carolina), family history of lymphoma in first-degree relatives (yes, no, missing), body mass index (BMI <25, 25-<30, ≥30), cigarette smoking history (never, former, current, missing), alcohol consumption per week (none, < once per week, ≥ once

Comment [a26]: Correction suggested by Cindy

Comment [a27]: We analyzed BMI and it was not a confounder. We added to table 1

We examined available pack-years and there was no confounding

per week) and several occupational exposures (i.e., number of livestock, poultry, acres planted, welding, diesel use, number of different pesticides used, and pesticides shown to be associated with NHL in the current analysis)(So all of these factors all significantly associated with risk of NHL here? From Table 1 it looked like most of the other adjustment factors were not significantly associated with NHL.). Tests for trend used the midpoint value of each exposure category, and the Likelihood Ratio tests were used to assess differences between strata (p-interaction). All tests were two-sided and conducted at the α=0.05 level. (I do not quite understand the rationale for the tables. The above indicates ORs were adjusted for several factors. The first set of tables say they are "age adjusted." The supplemental tables have more extensive adjustment. If it is important to adjust for factors other than age, why are these analyses in supplemental tables. If they are not important, why are they done at all. In any case I am not sure you need two tables. Often you see age adjusted and more extensively adjusted ORs in the same table. That would be better because it allows the reader to see if the additional adjusment made any difference in the ORs.)

We also conducted various sensitivity analyses. We analyzed Phase 1 data alone to assess the impact of the additional information collected or imputed from Phase 2. We also explored the effect of lagging exposure data 5 and 15 years since ~~recent these~~ recent exposures may not have had an impact on the development of cancer. Reported results show un-lagged exposure data from Phase 1 and Phase 2 combined for cumulative intensity-weighted and un-weighted days of use. (AB - I think we should start doing some analyses by type of protective equipment used. I know it is supposedly taken into account in the intensity score, but it would be informative if there were differences in OR by different protective approaches. It could be used with number

Comment [AB28]: Probably need to add you chose to show these data because the other analyses had not impact.

of days of pesticide use where it has not been taken into account. It provides information that is useful to farmers and extension agents.)

RESULTS

The risk of NHL increased significantly and in a near monotonic fashion with age in the AHS cohort (Table 1). The age-adjusted risk of NHL is significantly lower in NC compared to IA and among current smokers compared to nonsmokers. Other demographic factors including gender, license type, educational level, alcohol consumption, BMI, and a family history of lymphomas were not significant risk factors of NHL in this cohort. We evaluated whether other occupational factors were associated with NHL. Of those evaluated, the number of livestock on the farm and whether cohort members drove farm equipment with diesel engines significantly increased risk of NHL.

The age-adjusted risk of NHL and NHL subtypes from possible exposure to~~associated with~~ 16 insecticides and herbicides ~~associated with NHL or NHL subtypes or~~ previously associated with NHL are listed in Table 2 (age-adjusted risk of NHL for all other evaluated pesticides in the AHS may be found in supplemental table 1 and fully-adjusted risk of NHL in supplemental table 2). Lindane, an organochlorine insecticide, is the only pesticide showing a monotonic rise in overall NHL risk with increasing life-time days of use (p trend=0.003) and intensity-weighted lifetime days of use (p trend=0.05). Butylate, a thiocarbamate herbicide, showed a significant increasing trend in life-time days of use (p trend=0.004) and intensity-weighted lifetime days of

Comment [lbf29]: I think that you can cut down on reporting the results that are presented in the tables, but I would like to see some more results in the text that aren't in the tables. E.g., what happens when you put both lindane and butylate in the model? What is frequency of use of chemicals, etc.

Comment [a30]: Narrative now mentions that there is no apparent confounding between lindane and butylate. Only pesticides with 15 or more exposed cases are listed in the tables for analysis. Space limits more extensive discussion of frequency of pesticide use in the AHS, although this can be ascertained from use in controls.

Comment [AB31]: The Methods says they were significant risk factors

Comment [a32]: Previous table 2 deleted and discussion of potential confounding variables shortened as suggested by Laura

Comment [t33]: It's not clear why you are showing these 22 pesticides

Comment [AB34]: I think it would help the reader if you presented ever/never results for all pesticides analyzed. This would set the stage for the exposure response analyses. You would largely include only those pesticides with some excess in the ever category in the trend analyses. Now it is not clear why some are listed and others are not. As of now the Results just sort of jump into detailed exposure-response analyses.

Comment [t35]: If there's not a big difference between age and fully adjusted models I would delete fully adjusted

use (p trend=0.04) but the associations were not monotonic. Some other pesticides had individual point estimates that were significant but did not show a significant pattern of increasing risk with increasing exposure. Lindane and butylate did not show confounding with each other when they were put in the same model. The significant increasing trend of NHL risk with exposure to lindane and butylate was also not changed with the adjustment days of all other pesticide use, nor with adjustment for days of use of organophosphate insecticides, carbamate insecticides, other insecticides, triazine/triazone herbicides, other herbicides, fungicides, or fumigants. The results from fully adjusted risk of NHL (i.e., Age [<45,45-49,50-54,55-59,60-64,65-69,≥70], smoking status(current, former, never), number of livestock (0,,<100,100-999,>999), drove diesel tractor (<weekly,≥weekly, state (NC, IA) [data not shown were comparable to the age-adjusted risk]. Also, these unlagged results were comparable (not shown) to 5 year and 15 year lagged exposures, therefore we present RRs for unlagged exposure only.

Comment [lbf36]: I find these lists of RR and 95% CI throughout to be a bit hard to read, plus they take up a lot of words. I think it would be better to provide more information in the text about results that aren't presented in the tables. E.g., for lindane, how many people reported using it in Phase 1 vs. Phase 2 as it was approaching phase out. This will help to set the stage for putting the results in contex later in the discussion.

Comment [a37]: Point estimates deleted to reduce word count as recommended.

Comment [a38]: Need to define the pesticides included in each group appendix 2-done

Comment [AB39]: Supplement Table 2 does show the fully adjusted model, right?

We also analyzed Phase 1 data only to assess the impact of the additional information collected or imputed from Phase 2, although there was an increase in precession including phase 2 estimates, no meaningful change was observed in the risk estimates. ,

Comment [lbf40]: I don't think you mention th in the results.

Comment [lbf41]: How did you choose the 22 pesticides in this table? Why not 28 as in table 2? Regardless, need to explain rationale/criteria for presenting some and not others

The risk of the four major categories of B cell lymphomas by number of days of use of individual pesticide is shown in Table 3. For the CLL/SLL/MCL group of lymphomas, dicamba, a carbamate herbicide (p trend=0.03) and butylate, a thiocarbamate herbicide (p trend=0.04), and

lindane, a chlorinated insecticide, (p trend=0.005) were observed to have a significant increased trend of risk with increasing lifetime-days of use. Metribuzin, a triazone herbicide, (p trend=0.06) had a near significant relationship with this group of lymphomas. Carbaryl, a carbamate insecticide, was observed to have a significant inverse relationship (p trend=0.007).

Comment [a42]: Metribuzin is a triazone herbicide not a triazine herbicide -corrected

A significant increase in the risk of Other B-cell Lymphomas was associated with the number of life-time days of use of six herbicides and one insecticide: alachlor (p trend=0.02); butylate, (p trend=0.0499); dicamba (p trend=0.02); EPTC use (p trend=0.01): imazethapyr (p trend=0.03); trifluralin use (p trend=0.01); and terbufos (p trend=0.01) (Table 3). Risk of other B-cell lymphomas was also associated with a non-significant elevated risk for the low and medium exposure categories and was significantly associated with the highest category of exposure for atrazine use (RR=3.6 [95% CI: 1.2-10.8]; p trend=0.06).

Comment [AB43]: Since insecticides come before the herbicides in the table discuss terbufos before the herbicides here in the text

No pesticide had a significant exposure response pattern with either diffuse large B-cell lymphomas or follicular B-cell lymphomas, although significant point estimates of risk were identified for butylate, terbufos, and methyl bromide.

Comment [AB44]: Glyphosate had a significant trend for diffuse and chlordane and malathion were borderline. EPTC and butylate had borderline trend for follicular

The number of different triazine/triazone herbicides used, adjusted for age and lifetime days of use of triazine/triazone herbicides was associated with a significant increasing trend with total NHL risk (p trend=0.04) (Table 4). No other chemical/functional class showed a significant pattern of NHL risk. The association between the age-adjusted risk of the four NHL B-cell sub-types and the total number of different pesticides by chemical class used is presented in Table 5. For the CLL/SLL/MCL group of lymphomas, the number of different chlorinated insecticides (p

Comment [AB45]: Not sure what is meant here. Triazine triazones adjusted for triazine/triazone?

trend=0.02) and the number of different organophosphate insecticides (p trend= 0.03) showed a significant trend of increase risk with increasing number of insecticides from these chemical/functional classes. Similar trends were observed for the number of different triazine/triazone herbicides (p trend=0.07), other herbicides (p trend=0.06) and fungicides (p trend=0.11) but the trends were not statistically significant.

Comment [a46]: Typo corrected as suggested.

For either diffuse large B-cell lymphomas or follicular B-cell lymphomas, no pesticide class had a significant pattern of increasing risk with number of pesticides used, although a significant decreased risk with increasing number of pesticides used was observed for chlorinated pesticides (p trend=0.05) and other insecticides (p trend= 0.04) with the diffuse large B-cell lymphoma group.

For the other B-cell lymphoma group, the number of different triazine/triazone herbicides (p trend=0.006) and the number of different acetamide herbicides (p trend= 0.009) both were observed to have a significant trend of increasing risk with increasing days of use. Similar trends were observed for the number of different carbamate herbicides (p trend=0.11) and 'other herbicides' (p trend=0.06) but these trends were not statistically significant.

Comment [a47]: These will be adjusted for tota number of exposure days to chemicals in this class.- Done

Comment [lbf48]: Throughout , you need to reference the previous analyses of AHS data and specific chemicals. You reference Mark Purdue's paper in the intro, but no others

Comment [a49]: See changes made throughout to address these points

Comment [lbf50]: *This paper just came out and used the most recent definitions of NHL. Actually supportive of these AHS findings.*
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Lymphoma risk and occupational exposure to pesticides: results of the Epilymph study

DISCUSSION

AB – I think we need to start with the big picture comparisons first. I suggest the order for the discussion should be: (1) Ever/never comparisons for NHL overall, (2) Then move to trends for NHL overall. (3) Then trends for subtypes. (4) Next have a discussion of how the change in

NHL definition might affect comparison of our results with those from the literature. (5) Comparison of these results with literature pesticide by pesticide (or pesticide group). (6) Strengths and limitations. (7) Conclusions.

In this analysis, we observed a significant increase in the risk of overall NHL with two pesticides, lindane an organochlorine insecticide no longer registered for use in the U.S and butylate a thio-carbamate herbicide widely used in the United States and other countries. Our findings for total NHL are inconsistent with a number of other studies which found increased risks with a variety of chlorinated and organophosphate insecticides and triazine and phenoxy acid herbicides (Dich et al 1997; Hardell L et al., 1981; Hoar SK et al., 1986; Zahm et al, 1990). However, we did find significantly increasing risk of specific NHL subtypes with increasing life-time exposure days of individual pesticides use. Butylate and dicamba, carbamate herbicides, and lindane, a chlorinated insecticide, were observed to have a significant increasing risk of the CLL/SLL/ MCL lymphomas sub-types with increasing lifetime-days of use. (This first paragraph just sort of jumps into the subtype/specific pesticide links. I think a smoother opening paragraph would be to comment on ever/never for specific pesticides, then exposure trends by specific pesticide, and finally exposure trends by NHL subtypes. This summary of the findings should then be followed by a discussion of the effects, or lack of them, from the change in the definition of NHL. Then the findings from this analysis can be compared to the previous literature.)

Comment [lbf51]: What was percentage of use in P1 vs P2? If people aren't still using, but we stil have excess then we need to explore this further. D we see stronger effects in earlier time periods? Do we expect this to not be aproblem since lindane is n longer on the market? Or, is this going to be a persistent problem? We also need to say something about when lindane was taken off the market.

Comment [AB52]: There is a bit of an inconsistency here. Says there is an excess for lindane, but these findings differ from earlier work that saw excesses for a variety of chlorinated insecticides. Lindane is a chlorinated insecticide.

Comment [lbf53]: This sounds like all the other studies are positive, which isn't actually true. I thin that you need to have a more in-depth discussion of specific pesticides and findings.

Comment [AB54]: I do not think we can make this statement of differences with past studies without immediately including a discussion of the difference in disease definition and whether or not this might account for the differences or similarities with past research. Probably need to start the discussion with comparison of results of analyses fc the two different definitions to orient the reader regarding what changes occurred simply because of the change in definition. Then this should be followed with a discussion of findings from an ever/never comparison. Then you go to trends

Other B-cell lymphomas are a varied group including 8 different cell types of lymphomas. Excess risks of other B-cell lymphomas were observed for several widely-used pesticides including: the organophosphorous insecticide terbufos, for alachlor, an acetanilide-herbicide, imazethapyr, an imidazoline-herbicides, and trifluralin, a dinitroaniline-herbicide, and for

butylate, dicamba, and, EPTC which all belong to the family of carbamate herbicides. The triazine herbicides atrazine and cyanazine had specific point estimates that were elevated but the trends of risk were neither significant nor monotonic. ~~Metribuzin, a triazone herbicide, had too few other B-cell lymphomas to evaluate.~~ The wide array of functional groups and chemical classes that are associated with an increased risk of Other B-cell lymphomas does not suggest a single known mechanism of action. Multiple pathways seem to be involved.

Comment [AB55]: I am not sure you want to tal about pathways. This assumes that the links observed here are real. Perhaps the wide array of function groups and chemical classes is just noise. You might try to dissect the individual histologies i this "Other B-cell" to see if any one stands out with particular pesticide.

In a Swedish case-control study a significant excess risk of NHL was associated with the phenoxy herbicide MCPA and glyphosate (Ericksson et al., 2008). 2,4-D and 2,4,5-T (2,4,5-trichlorophenoxyacetic acid) have been banned from Sweden and could not be evaluated (Eriksson M et al.,2008). In our study we could not evaluate MCPA but found no excess risk of NHL or its subtypes with the use of glyphospate, 2,4-D or 2,4,5-T.

Comment [AB56]: Check to make sure 2,4-D was banned during the time of pesticide use by people in Eriksson's study. My impression is that it just was not used much in Scandinavia, but was not banned until later.

In a population-based case-control study conducted in six Canadian provinces increased risk to NHL was associated with a positive family history of cancer both with and without pesticide exposure [OR=1.72 (95% CI 1.21-2.45) and OR=1.43 (95% CI: 1.12-1.83), respectively] (McDuffie HH, et.al, 2009). In this same case-control study six pesticides/pesticide analytes also showed a significant association with NHL [beta-hexachlorocyclohexane, *p, p'*- dichloro-diphenyl-dichloroethylene (DDE), hexachlorobenzene, mirex, oxychlordane and trans-nonachlor] (Spinelli et al., 2007). The strongest association was found for oxychlordane, a metabolite of the pesticide chlordane (highest vs. lowest quartile OR=2.68, 95% CI 1.69-4.2). These finding were not confirmed in a recent analysis of plasma samples from 174 NHL cases and 203 controls from France, Germany and Spain. The risk of NHL did not increase with

Comment [AB57]: Not sure we need this sentence. Certainly should not lead with it because family history was not evaluate our NHL study.

plasma levels of hexachlorobenzene, beta-hexachlorobenzene or DDE (Cocco P et al., 2008). In our study NHL was associated with lindane but no excess risk was observed for chlordane and no excess risk was observed among those with a family history of lymphoma. ~~The other chemicals evaluated in the Canadian six province study were not evaluated in the AHS cohort.~~

New evidence linking NHL with chlorinated pesticide use (Brauner EV, et al., 2012) and a study linking the number of different pesticides used with NHL (Hohenadel K et al., 2011) are somewhat supported by our findings in the AHS cohort. While the number of different pesticides used overall was not associated with NHL risk in the AHS, a significant increase in the CLL/SLL/MCL sub-group of NHL was observed with the number of different chlorinated pesticides used and the number of different organophosphate chemicals used. A similar pattern of increase risk was observed in the other B-cell lymphoma subgroup of NHL with an increasing number of triazine/triazone pesticides used.

Comment [lbf58]: Expand to discuss what these actually show—similar to ours? Not similar to ours

Comment [a59]: Modified sentence in response to comment

Comment [AB60]: I have a hard time following the discussion. I wonder if it might not be clearing the link to previous literature is done pesticide by pesticide. Then you could indicate what is found here and follow that with findings for that pesticide in the literature. This means previous studies could be cited numerous times, but it would be easier to see the relationship between our findings and those from other studies for individual pesticides

A strength of this investigation is that a relatively large population of licensed pesticide applicators provided reliable information regarding their pesticide application history (Blair et al. 2002; Coble et al. 2011, should cite Jane's paper on reliability also). In the AHS, a priori derived algorithm scores that incorporated several exposure determinants were found to be able to ~~used to~~ predict urinary pesticide levels (Thomas et al., Coble 2011). Few? studies of pesticide use with a prospective design have been large enough or had sufficiently detailed exposure information, to evaluate the potential link between NHL, NHL subtypes and specific pesticide exposures (Are there any other prospective studies that could look at specific pesticides?). Also, because occupational pesticide users are seldom exposed to a single agent, we controlled for the total pesticide exposure days and total pesticide exposure days by chemical/functional class and found

no meaningful change in the associations. Additionally, potential confounding of pesticides by other occupational exposures was reported to be minimal in the AHS (Coble et al., 2002) and adjustment for various agricultural exposures did not fundamentally change calculated RR for NHL from various pesticide exposures. – (Mention ability to control of possible non-occupational confounders, use of incidence rather than mortality)

Comment [AB61]: I have a real problem with this approach and the interpretation of the findings from it. Is total pesticide exposure days associated with NHL? If not, then it clearly does not control from individual pesticides because some individual pesticides are associated with NHL. This would work if most pesticides were associated with NHL, but most are not Thus, this total pesticide scale is s water down that it cannot control for anything. Thi said, I doubt that there is confounding among the pesticides, but we cannot us this approach as evidence for no confounding. The most straightforward, and usual approach, is to adjust the RR for one pesticide by each individual pesticide thought to be a potential confounder.

Although this is a large prospective study, there are limitations~~limitations should be acknowledged~~. Cell-type information in the AHS was obtained from the cancer registry database and did not involve pathologic re-review of diagnostic slides. Other limitations including a small number of exposed cases for certain chemical of interest.

Comment [AB62]: I do not think I would list this. These are data that are used to establish cancer patterns by the NCI. I think the reliability/validity o the diagnosis from tumor registries is well accepted

Need to add a paragraph of exposure assessment. Discuss the information on our exposure scale in relation to the monitoring work. Discuss the likely magnitude of misclassification and its likely impact on the estimates of RR. Might also want to say something about multiple exposures. Cannot look only at a single exposure. This is an issue raised by critics. Just as well address it here.

AB – This next paragraph seems part of the conclusions. I would try to merge it with the conclusions paragraph.

In our study no pesticide had a significant exposure response pattern with either diffuse large B-cell lymphoma or follicular B-cell lymphoma, although significant relative~~point estimates of~~ risks were identified for butylate (a carbamate herbicide), terbufos (an organophosphate insecticide), and methyl bromide (an organic halide)(Not clear what you are trying to say here – No exposure-response pattern, but significant RRs.). Previously, NHL subtypes with t (14;18) translocations were associated with the chlorinated insecticides dieldrin, lindane, and toxaphene

Comment [AB63]: But there were borderline trends for these subtypes.

and the triazine herbicide atrazine (chiu BCH et al., 2006 and Chiu BCH and Blair A 2009). We were unable to evaluate translocations in this analysis. Although it is possible that t (14;18) translocations are an initiating event of a causative cascade leading to an NHL subtype, follicular lymphoma (FL), much more work needs to be done to establish this etiologic pathway. (Not sure mentioning t(14;18) is worthwhile here. This study sheds no light on this issue. This point might be combined in a paragraph that discusses future research, but it does not fit by itself)—

Conclusion:

(I do not think you should start the conclusion with comments about subtypes. Start with NHL overall. In summary, our results suggest that there is subtype specificity in associations between NHL and pesticides exposures. The varying etiology of NHL sub-types may have masked real associations between pesticides and NHL in previous studies where NHL sub-type information was not available (Not sure how varying etiology by subtype would mask associations with NHL overall. If each study had all the subtypes then either the subtype links power through to overall NHL or they do not. The reverse is true. Looking only at NHL overall would hide associations with specific subtypes.). Although the epidemiological evidence for associations between specific pesticides and specific cell types is growing (probably should cite the other papers that have information on specific pesticides and subtypes), the observation that pesticides of different chemical and functional classes and different known toxicological properties are associated with the same cell type (Is it know that different pesticides are associated with the same cell type?) indicates that relatively little is known about the biological/toxicological mechanisms by which these compounds may be contributing to this disease. Cautious interpretation of these results is advised since the number of exposed-cases for

each subgroup of NHL in the AHS is still relatively small. (Overall I think the conclusion is too strong. It seems to say that the links between specific pesticides and certain NHL subtypes observed in this study are real and this is why we do not understand the mechanisms for pesticides causing cancer. The findings here are interesting, but they are leads to be confirmed. I do not think they are strong enough to be making statements about what this says about mechanisms. I think the tone should be – few studies have been able to look at specific pesticides and NHL subtypes. What we found is interesting. Need to see if other studies will have similar findings. I may be in a minority about this, but I would like to have a discussion about this on an EC call.)

Acknowledgements

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Comment [AB64]: This affiliation does not cover ally coauthors. Don't we usually put some comment of appreciation to the participants in the AHS in the acknowledgements?

Comment [a65]: Get correct contract numbers here.

The authors have no conflicts of interest in connection with this manuscript.

References:

1. Agopian J, Navarro JM, Gac AC, Lecluse Y, Briand M, Grenot P, Gauduchon P, Ruminy P, Lebally P, Nadel B, and Roulland S. Agricultural pesticide exposure and the molecular connection to lymphomagenesis. *J Exp Med.* 2009; 206 (7):1473-1483

2. Alavanja MCR, Sandler DP, McMaster SB, Zahm SH, McDonnell CJ, Lynch CF, Pennybacker M, Rothman N, Dosemeci M, Bond AE, Blair A. The Agricultural Health Study. Environ Health Perspect 1996; 104:362-369.

3. Alavanja MCR, Sandler DP, McMaster SB, Zahm SH, McDonnell CJ, Lynch CF, Pennybacker M, Rothman N, Dosemeci M, Bond AE, Blair A. The Agricultural Health Study. Environ Health Perspect 1996; 104:362-369.

4. Alavanja M, Bonner M. Occupational pesticide exposure and cancer risk. A review. J. Toxicol Environ Health B Critic Review. 2012; 1594):238-263.

5. Beane Freeman L E, DeRoos AJ, Koutros S, Blair A, Ward MH, Alavanja MCR, Hoppin JA. Poultry and livestock exposure and cancer risk among farmers in the agricultural health study. *Cancer Causes Control* 2012; 23:663-670.

Blair A, Malker H, Cantor KP, Burmeister L, Wikland K. Cancer among farmers: a review. Scand Work Environ Health 1985;11:397-407.

Blair A, Zahm SH, Pearce NE, Heineman EF, Fraumeni JF Jr. Clues to cancer etiology from studies of farmers. Scand J Work Environ Health 1992;7:532-540.

6. Blair A, Dosemeci M, Heineman EF. Cancer and other causes of death among male and female farmers from twenty-three states. *Am J Ind Med.* 1993; 23:729-742.

7. Blair A. Tarone R, Sandler D, Lynch CF, Rowland A, Winterstein W, et al., 2002. Reliability of reporting on life-style and agricultural factors by a sample of participants in the Agricultural Health Study from Iowa. Epidemiology 2002;13(1):94-99.

8. Boers D, Portengen L, Turner WE, Bas Bueno-de-Mesquita H, Heedrick D, Vermeulen R. Plasma dioxin levels and cause-specific mortality in an occupational cohort of workers exposed to chlorphenoxy herbicides, chlorphenols, and contaminants. *Occup Environ Med.* 2012;69;113-118.

9. Brauner EV, Sorensen MA, Gaudreau E, LeBlanc A, Erikson KT, Tjonneland A, Overvard K, Raaschou-Nielsen O. A prospective study of organochlorines in adipose tissue and risk of non-Hodgkin lymphoma. *Environ Health Perspect.* 2012; 120(1): 105-111.

10. Cattillo JJ, Dalia S. Cigarette smoking is associated with a small increase in the incidence of non Hodhkin lymphoma: a meta analysis of 24 observation studies. *Leukemia & Lymphoma* 2012(10), 1911-1919.

11. Cantor KP, Blair A, Everett G, Gibson R, Burmeister LF, Brown LM. Pesticides and other agricultural risk factors for non-Hodgkin's lymphoma among men in Iowa and Minnesota. *Can Re*. 1992;52:2447-2452.

12. Chiu BCH, Dave BJ, Blair A, Gapstur SM, Zahm SH, and Weisenberger DD. Agricultural pesticide use and risk of t(14;18)-defined subtypes of non-Hodgkin lymphoma. *Blood* . 2006; 108 (4):1363-1369.

13. Chiu BCH, Blair A. Pesticides, chromosomal aberrations, and non-Hodgkin's lymphoma. *J Agromedicine*. 2009; 14 (2):250-255.

14. Coble J, Hoppin JA, Engel L, Elci OC, Dosemeci M, Lynch CF, et al. 2002. Prevalence of exposure to solvents, metals, grain dust, and other hazards among farmers in the Agricultural Health Study. J Exp Anal Environ Epidemiol 12(6):418-426.

15. Coble J, Thomas KW, Hines CJ, Hoppin JA, Dosemeci M, Curwin B, Lubin JH, Beane Freeman L, Blair A, Sandler DP, Alavanja MCR. An updated algorithm for estimation of pesticide exposure intensity in the Agricultural Health Study. Int J Environ Res Public Health. 2011;8(12):4608-4622.

16. Cocco P, Brennan P, Ibba A, de Sanjose Llongueras S, Maynadie M, Nieters A, Becker N, Ennas MG, Tocco MG, Boffetta P. Plasma polychlorobiphenyl and organochlorine pesticide level and risk of major lymphoma subtypes. *Occup Environ Med* 2008;65:132-140.

17. Cocco P, Satta G, Dubois S, Pilli C, Pillieri M, Zucca M, Mannetje AM, becker N, Benavente Y, de Sanjose' S, Foretova L, Staines A, Maynadie M, Nieters A, brennan P, Milligi L, Ennas MG, Boffetta P. Occupational Envir Med 2013; 70(2):91-98.

Colt JS, Davis S, Severson RK, Lynch CF, Cozen W, Camann D, Engels EA, Blair A, Hartge P. Resideential insecticide use and risk of non-Hodgkin's lymphoma. Cancer Epidemiol Biomarkers Prevent 2006;15:251-257.

18. Dich J, Zahm SH, Hanberg A, Adami HO. Pesticides and cancer etiology from studies of farmers [review]. *Cancer Causes Control* 1997;8:420-443.

19. Eriksson M, Hardell L, Carlberg M, and Akerman M. Pesticide exposure as risk factors for non-Hodkin lymphoma including histopathological subgroup analysis. *Int J Cancer*. 2008;123 (7):1657-1663.

20. Fuscoe J C. Simultaneous quantification of t(14;18) and HPRT exon 2/3 deletions in human lymphocytes. *Methods Mol Biol* . 2005; 291: 171-178.

21. Hardell L, Eriksson M, Lenner P, Lundgren E. Malignant lymphoma and exposure to chemicals, especially. Organic solvents, chlorophenols and phenoxy acids: a case-control study. *Br J Cancer* 1981;43:169-176.

22. Helthshe SL, Lubin JH, Koutros S, Coble JB, Ji B-T, Alavanja MCR, Blair A, Sandler DP, Hines CJ, Thomas KW, barker J, Andreotti G, Hoppin JA, Bean Freeman LE. Using multiple imputation to assign pesticide use for non-respondents in the follow-up questionnaire in the Agricultural Health Study. J. Exp Sci Environ Epidemiol 2012:22(4):409-416.

23. http://seer.cancer.gov/lymphomarecode

24. Hoar SK, Blair A, Holme FF, Boysean CD, Robel RJ, Hoover R, Fraumeni JF Jr. Agricultural herbicide use and risk of lymphoma and soft-tissue sarcoma. *JAMA*. 1986;256(9): 1141-1147.

25. Hohenadel K, Harris SA, McLaughlin JR, Spinelli JJ, Pahwa P, Dosman JA, Demers PA, Blair A. Exposure to multiple pesticides and risk of non-Hodgkin Lymphoma in men from six Canadian provinces. *Int J Environ Res Public Health*. 2011, 8, 2320-2330.

26. McDuffie HH, Pahwa P, Karunanayake CP, Spinelli JJ, Dosman JA. Clustering of cancer among families of cases with Hodgkin Lymphoma (HL), multiple myeloma (MM), soft tissue sarcoma (STS) and control subjects. BMC Cancer. 2009; 9: 1-9.

27. Merhi M, Raynal H, Cahuzac E, Vinson F, Cravedi JP, and Gamet-Payrastre L. Occupational exposure to pesticides and risk of hematopoietic cancers: meta-analysis of case-control studies. *Cancer Causes Control.* 2007; 18:1209-1226.

Add Miligi et al. 2003. Cited but not listed.

28. Morton LM, Turner JJ, Cerhan JR, Linet MS, Treseler PA, Clarke CA, Jack A, Cozen W, Maynadie' M, Spinelli JJ, Constantini AS, Scarpa A, Zheng T, Weisenburger DD. Blood 20007;110(2):695-708.

Orsi L, Delabre L, Monnereau A, Delval P, Berthou C, Fraux P, Marit G, Soubeyran P, Huguet F, Milpied N, Leporrier M, Hernon D, Troussard X, Clavel J. Occupational exposure to pesticides and lymphoid neoplasms among men: results of a French case-control study. Occup Environ Med 2009;66:291-298.

29. Pahwa M, Harris SA, Hohenadel K, McLaughlin JR, Spinelli JJ, Pahwa P, Dosman JA and Blair. Pesticides use, immunologic conditions, and risk of non-Hodgkin Lymphoma in Canadian men in six provinces. *Int J Cancer*. 2012; doi: 10.1002/ijc.27522. [Epub ahead of print].

30. Patel AV, Diver WR, Teras LR, Birmann BM, Gapstur SM. Body mass index height and risk of lymphoid neoplams in a large United States cohort. *Leukemia & Lymphoma*, 2013; DOI:10.3109/10428194.2012.742523.

31. Pearce NE, Sheppard RA, Smith AH, Teague CA. Non-Hodgkin's lymphoma and farming: an expanded case-control study. *Int J Cancer* 1987;39:155-161.

32. Percy C, Fritz A, Ries L. Conversion of neoplasms by topography and morphology from the International Classification of Disease for Oncology, second edition, to International Classification of Diseases for Oncology, 3rd ed. Cancer Statistics branch, DCCPS, SEER Program, National Cancer Institute; 2001.

33. Purdue MP, Hoppin JA, Blair A, Dosemeci M, Alavanja MCR. Occupational exposure to organochlorine insecticides and cancer incidence in the Agricultural Health Study. *Int J Cancer*. 2007;120(3):642-649.

34. SAS Institute, Cary, North Carolina {complete reference}

35. Schroeder JC, Olshan AF, Baric A, Dent GA, Weinberg CR, Yount B, Cerhan JR, Lynch CF, Schuman LM, Tolbert PE, Rothman N, Cantor KP, and Blair A. Agricultural risk factors for t(14;18) subtypes of non-Hodgkin's lymphoma. *Epidemiology*. 2001;12:701-709.

36. Shankland KR, Armitage JO, Hancock BW. Non-Hodgkin Lymphoma. *Lancet*. 2012; 380 (9844),848-857.

37. Simard JF, Baecklund F, Chang ET, Baecklund E, Hjalgrim H, Adami OH, Smedby KE. Lifestyle factors, autoimmunne disease and family history in prognosis of non-hodgkin lymphoma overall and subtypes. *Int J Cancer*. 2012 Nov 12 DOI: 10.1002/ijc.27944. {Epub ahead of print}

38. Spinelli JJ, Ng CH, Weber JP, Connors JM, Gascoyne RD, Lai AS, Brooks-Wilson AR, Le ND, Berry BR, Gallagher RP. Organochlorines and risk of non-Hodgkin lymphoma. *Int J Cancer*. 2007; 121(12): 2767-2775.

39. Svec MA, Ward MH, Dosemeci M, Checkoway H, DeRoos AJ. Risk of lymphatic or haematopoietic cancer mortality with occupational exposure to animals or the public. *Occup Environ Med* 2005;62:726-735.

40. Swerdlow SH, Campo E , Harris N, et al (2008) WHO Classification of Tumours of haematopoietic and Lymphoid Tissue. Oxford Uni Pr. ISBN 978-92-832-2431-0.

41. Thomas KW, Dosemeci M, Coble JB, Hoppin JA, Sheldon LS, Chapa G, et al. 2010. Assessment of a pesticide exposure intensity algorithm in the Agricultural Health Study. J Expo Sci Environ Epidemiol 20(6):559-569.

Waddell BL, Zahm SH, Baris D, Weisenburger DD, Holmes F, Burmeister LF, Cantor KP, Blair A. Agricultural use of organophosphate pesticides and the risk of non-Hodgkin's lymphoma among male farmers (United States). Cancer Causes Control 2001;12:509-517.

42. Woods JS, Polissar L, Severson RK, Heuser LS, Kulander BG. Soft tissue sarcoma and non-Hodgkin's lymphoma in relation to phenoxyherbicide and chlorinated phenol exposure in western Washington. *J Natl Cancer Institute* 1987;78:899-910.

43. Zahm SH, Weisenburger DD, Babbitt PA, Saal RC, Vaught JB, Cantor KP, Blair A. A case-control study of non-Hodgkin's lymphoma and the herbicide 2,4-dichlorophenoxyacetic acid (2,4-D) in eastern Nebraska. *Epidemiol*. 1990;1(5):349-356.

Table 1. Baseline characteristics of AHS study participants in the NHL incidence analysis from 1993 through 2008				
	All NHL cases	Cohort Person-years.	RR[1]	95% CI
Age at Enrollment				
<45	51	368,766.80	1.0 (ref)	
45-49	34	88,648.48	2.8	1.8-4.3
50-54	51	75,781.37	4.9	3.3-7.2
55-59	59	67,981.37	6.3	4.3-9.1
60-64	46	53,346.73	6.2	4.2-9.3
65-69	46	34,532.71	9.6	6.5-14.4
≥70	46	25,713.12	12.9	8.7-19.3
Gender				
Male	328 (ref)	695,190.90	1.0 (ref)	
Female	5	19,579.34	0.5	0.2-1.3
State				
IA	213 (ref)	461,697.24	1.0 (ref)	
NC	120	253,072.27	0.8	0.6-0.97
License type				
Private	318	652,562.25	1.0 (ref)	
Commercial	15	62,207.89	0.9	0.5-1.5
Education				
<12 yrs.	57	61,656.39	1.0 (ref)	
HS/GED	143	326,344.92	0.8	0.6-1.1
>12 yrs.	121	297,437.85	1.0	0.7-1.4
Smoking Status				

Never	165	371,929.66	1.0 (ref)	
Former	127	203,445.28	0.93	0.7-1.2
Current	29	116,254.87	0.6	0.4-0.9
Body Mass Index (BMI)				
<25	58		1.0 (ref)	
25-<30	138		1.1	0.8-1.5
≥30	61		0.94	0.7-1.4
Alcohol consumption per week				
None	128	212,928.70	1.0 (ref)	
<once a week	89	217,015.35	1.0	0.8-1.4
≥once a week	89	240,745.51	1.0	0.8-1.4
First degree relative with lymphoma				
No	291	639,748.82	1 (ref)	
Yes	7	12,606.85	1.1	0.5-2.4

[1] All variables except age are age adjusted (<45,45-49,50-54,55-59,60-64,65-69,≥70)

[2] Numbers do not sum to totals (333 cases, 714,770 person-years) due to missing data.

Table 2. Pesticide exposure (Lifetime Days [LD] & intensity weighted Lifetime Days [IWLD]) and the age-adjusted risk of NHL incidence (1993 through 2008)

Insecticides				
Pesticide (chemical-functional class) [median days of lifetime exposure for each category]	NHL Cases	RR[1] (95%) by Total Days of Exposure	NHL Cases	RR[1] (95% CI) Intensity-weighted days of exposure
Carbaryl (carbamate-insecticide)				
None	81	1.0 (ref)	81	1.0 (ref)
Low [8.75]	31	0.9 (0.5-1.5)	27	0.9 (0.5-1.5)
Medium [56]	23	0.7 (0.4-1.1)	26	0.8 (0.5-1.4)
High [124.5]	25	0.9 (0.6-1.5)	26	0.8 (0.5-1.3)
		P trend=0.86		P trend=0.47
Malathion (organophosphorous-insecticide)				
None	55	1.0 (ref)	55	1.0 (ref)
Low [8.75]	46	1.0 (0.7-1.5)	37	1.0 (0.7-1.6)
Medium [42.75]	28	0.7 (0.4-1.2)	38	0.8 (0.5-1.3)
High [103.75]	36	1.0 (0.7-1.6)	35	0.91 (0.6-1.4)
		P trend=0.74		P trend=0.71
Terbufos (organophosphorous-insecticide)				
None	157	1.0 (ref)	157	1.0 (ref)
Low [24.5]	58	1.4 (1.1-1.9)	43	1.3 (0.92-1.8)
Medium [56]	38	2.0 (1.4-2.8)	43	2.0 (1.4-2.8)
High [116]	34	1.2 (0.8-1.7)	42	1.2 (0.9-1.8)

		P trend=0.23		P trend=0.19
Chlorinated Insecticide				
Chlordane (Chlorinated Insecticide)				
None	223	1.0 (ref)	223	1.0 (ref)
Low [8.75]	23	0.9 (0.6-1.4)	13	1.1 (0.7-2.0)
Medium [20]	6	1.7 (0.8-3.8)	13	0.9 (0.5-1.6)
High [38.75]	9	0.8 (0.4-1.6)	12	0.9 (0.5-1.6)
		P trend=0.89		P trend=0.77
DDT (Chlorinated Insecticide)				
None	194	1.0 (ref)	194	1.0 (ref)
Low [8.75]	20	0.8 (0.5-1.3)	19	0.9 (0.6-1.5)
Medium [56]	18	0.9 (0.6-1.6)	18	0.8 (0.5-1.4)
High [116]	17	1.5 (0.9-2.5)	18	1.4 (0.8-2.2)
		P trend=0.14		P trend=0.28
Lindane (Chlorinated Insecticide)				
None	209	1.0 (ref)	209	1.0 (ref)
Low [17.75]	11	1.0(0.5-2.0)	10	1.1(0.6-2.0)
Medium [56]	10	1.2(0.6-2.3)	11	1.4(0.7-2.6)
High [116]	10	2.7(1.4-5.1)	9	1.9(0.95-3.7)
		P trend=0.003		P trend=0.04
Herbicides				
Alachlor (acetamide-herbicide)				
None	138	1.0 (ref)	138	1.0 (ref)

Comment [ibf66]: I like this heading—suggest using them throughout the tables and then deleting the chemical class in parentheses

Low [24.5]	65	1.0 (0.7-1.3)	53	1.0 (0.7-1.3)
Medium [116]	49	0.9(0.6-1.2)	50	0.9 (0.6-1.2)
High [224.75]	43	1.3(0.9-1.9)	51	1.2 (0.9-1.7)
		P trend=0.12		P trend=0.19
Atrazine (triazine-herbicide)				
None	85	1.0 (ref)	85	1.0 (ref)
Low [38.75]	88	1.2(0.8-1.7)	79	1.1(0.8-1.6)
Medium [114.5]	72	1.3(0.96-1.9)	78	1.4(1.0-2.0)
High [224.75]	77	1.2(0.9-1.6)	78	1.2(0.8-1.6)
		P trend=0.56		P trend=0.68
Butylate (thiocarbamate-herbicide)				
None	107	1.0 (ref)	107	1.0 (ref)
Low [24.5]	22	1.0(0.6-1.5)	16	0.9(0.5-1.5)
Medium [56]	18	2.8(1.7-4.7)	16	2.1(1.2-3.5)
High [56]	7	1.1(0.5-2.4)	15	1.5(0.9-2.6)
		P trend=0.004		P trend=0.04
Dicamba (benzoic-herbicide)				
None	121	1.0 (ref)	121	1.0 (ref)
Low [20]	66	1.3(0.94-1.8)	56	1.2(0.9-1.8)
Medium [56]	52	1.5(1.1-2.1)	54	1.5(1.1-2.1)
High [128.5]	47	1.2(0.9-1.7)	55	1.3(0.9-1.8)
		P trend=0.38	P trend=0.23	
2,4-D (phenoxy-herbicide)				

None	71	1.0 (ref)	71	1.0 (ref)
Low [46.75]	83	1.0(0.7-1.4)	82	1.0(0.7-1.4)
Medium [133.35]	83	1.2(0.8-1.6)	83	1.1(0.8-1.6)
High [371.75]	82	1.0(0.7-1.4)	81	1.0(0.7-1.4)
		P trend=0.96		P trend=0.94
EPTC (thiocarbamate-herbicide)				
None	229	1.0 (ref)	229	1.0 (ref)
Low [8.75]	28	1.3(0.9-2.0)	20	1.3(0.8-2.1)
Medium [50.75]	14	1.0(0.6-1.7)	20	1.2(0.7-1.8)
High [108.5]	18	1.3(0.8-2.0)	19	1.1(0.7-1.8)
		P trend=0.35		P trend=0.54
Glyphosate (phosphinic acid-herbicide)				
None	70	1.0 (ref)	70	1.0 (ref)
Low [20]	89	0.8(0.6-1.2)	83	0.9(0.6-1.3)
Medium [65.75]	78	0.8(0.6-1.2)	84	0.8(0.5-1.1)
High [173.25]	83	1.0(0.7-1.4)	82	1.0(0.7-1.3)
		P trend=0.58		P trend=0.81
Imazethapyr (imidazolinone-herbicide)				
None	181	1.0 (ref)	181	1.0 (ref)
Low [8.75]	39	0.9(0.6-1.3)	36	1.0(0.7-1.4)
Medium [28.75]	34	0.9(0.6-1.4)	37	0.9(0.6-1.3)
High [56]	35	1.2(0.8-1.7)	35	1.2(0.8-1.7)
		P trend=0.54		P trend=0.55
Metribuzin				

(triazine-herbicide)				
None	94	1.0 (ref)	94	1.0 (ref)
Low [8.75]	28	1.0 (0.7-1.7)	21	1.2(0.7-2.0)
Medium [50.75]	15	0.9(0.5-1.6)	23	1.1(0.7-1.7)
High [56]	20	1.7(1.0-2.7)	19	1.3(0.8-2.2)
		P trend=0.06		P trend=0.28
Trifluralin **(dinitroaniline-herbicide)**				
None	140	1.0 (ref)	140	1.0 (ref)
Low [25]	51	1.0 (0.7-1.4)	50	1.0(0.7-1.4)
Medium [108.5]	58	1.1(0.8-1.5)	52	1.1(0.8-1.5)
High [224.75]	43	1.0(0.7-1.3)	48	0.9(0.7-1.3)
		P trend=0.81		P trend=0.65

[1]Age adjusted (<45,45-49,50-54,55-59,60-64,65-69,≥70)

[2] Numbers do not sum to total number of NHL cases (n=333) due to missing data.

Table 3. Pesticides exposure (Lifetime-days and the age-adjusted risk of NHL by cell type (1993-2008).

	CLL, SLL, MCL		Diffuse Large B-cell		Follicular B-cell		Other B-cell types	
Insecticides, fungicide and fumigant								
	RR[1] (95% CI)	n	RR[1] (95% CI)	n	RR[1] (95% CI)	n	RR[1] (95% CI)	N
Carbaryl								
None	1.0 (ref)	32	1.0 (ref)	23	1.0 (ref)	9	1.0 (ref)	9
Low	1.1(0.5-2.2)	15	0.7(0.3-1.5)	10	1.1(0.3-4.0)	5	Xxx	6
Medium	1.0(0.2-4.2)	2	1.3(0.6-3.0)	8	1.8(0.6-5.9)	4	Xxx	0
High	0.4(0.2-0.8)	8	1.5(0.7-3.5)	8	1.3(0.4-4.1)	4	xxx-	1
	P trend=0.007		P trend=0.19		P trend=0.66		P trend=xxx	
Malathion								
None	1.0 (ref)	21	1.0 (ref)	16	1.0 (ref)	5	1.0 (ref)	6
Low	0.94(0.5-1.8)	17	0.8(0.4-1.7)	16	1.0(0.3-3.6)	6	xxx-	8
Medium	0.8(0.4-1.7)	11	0.9(0.4-2.1)	8	1.2(0.3-4.3)	5	-xxx	0
High	0.8(0.4-1.7)	11	1.7(0.8-3.8)	11	1.5(0.4-4.9)	5	-xxx	3
	P trend=0.52		P trend=0.07		P trend=0.48		P trend=xxx	
Terbufos								
None	1.0 (ref)	53	1.0 (ref)	47	1.0 (ref)	26	1.0 (ref)	10
Low	1.8(1.0-3.1)	17	0.9(0.4-1.7)	12	2.5(1.1-5.4)	8	2.3 (0.8-6.6)	6
Medium	2.2(1.3-3.6)	21	2.2(1.2-4.2)	12	1.8(0.7-4.3)	7	3.1(1.1-9.2)	5
High	1.4(0.8-2.6)	13	1.1(0.5-2.3)	10	0.7(0.3-1.8)	6	4.1(1.4-11.9)	5
	P trend=0.16		P trend=0.34		P trend=0.54		P trend=0.01	
Chlorinated pesticides								
Chlordane								
None	1.0 (ref)	74	1.0 (ref)	68	1.0 (ref)	35	1.0 (ref)	21

Comment [lbf67]: Insert the codes here and the you can remove them from the text

Comment [lbf68]: Would suggest using the headings as suggest in Table 2 to orient people to chemical class

Low	1.4 (0.7-2.7)	10	0.8 (0.4-2.0)	6	1.6 (0.4-6.9)	2	Xxx	1
Medium	2.8 (0.9-9.0)	3	1.8 (0.6-5.1)	4	0.8 (0.2-3.4)	2	Xxx	2
High	0.8 (0.3-2.7)	3	1.0 (0.2-4.1)	2	0.7 (0.1-5.1)	1	Xxx	0
	P trend=0.56		P trend=0.09		P trend=0.92		P trend=xxx	
DDT								
None	1.0 (ref)	62	1.0 (ref)	53	1.0 (ref)	36	1.0 (ref)	22
Low	0.91 (0.4-2.0)	8	1.1 (0.5-2.6)	7	1.1 (0.4-3.4)	4	0.4 (0.1-1.9)	2
Medium	1.1 (0.5-2.4)	8	2.3 (1.0-5.4)	7	0.3 (0.1-2.6)	1	1.4 (0.3-6.2)	2
High	2.3 (1.0-5.3)	7	1.2 (0.5-2.9)	6	0.7 (0.1-5.0)	1	0.9 (0.1-6.7)	1
	P trend=0.45		P trend=0.31		P trend=0.72		P trend=0.77	
Lindane								
None	1.0 (ref)	41	1.0 (ref)	39	1.0 (ref)	14	1.0 (ref)	14
Low	1.6(0.7-3.6)	8	0.7(0.2-3.0)	9	2.7(0.8-9.4)	3	Xxx	1
Medium	1.1(0.3-4.8)	3	1.1(0.3-3.7)	6	3.6(0.8-15.9)	2	Xxx	0
High	3.8(1.5-9.6)	5	1.3(0.2-9.7)	5	2.4(0.5-10.4)	2	Xxx	0
	P trend=0.005		P trend=0.25		P trend=0.25		P trend=xxx	
Herbicides								
Alachlor (acetanilide)								
None	1.0 (ref)	53	1.0 (ref)	42	1.0 (ref)	22	1.0 (ref)	9
Low	0.9(0.6-1.5)	23	0.9(0.5-1.6)	13	1.3(0.6-2.6)	10	1.6 (0.6-4.4)	7
Medium	0.8(0.5-1.4)	18	0.7(0.4-1.3)	14	0.8(0.3-1.6)	9	2.1 (0.8-5.3)	10
High	1.1(0.6-2.1)	14	0.8(0.4-1.6)	10	1.1(0.4-2.7)	6	4.0 (1.2-13.0)	4
	P =0.67		P trend=0.52		P trend=0.99		P trend=0.02	
Atrazine (triazine)								
None	1.0 (ref)	34	1.0 (ref)	26	1.0 (ref)	12	1.0 (ref)	5

Low	1.0 (0.6-1.7)	29	1.1(0.6-2.0)	21	1.7(0.7-3.9)	17	2.4 (0.9-6.8)	13
Medium	1.2 (0.7-2.0)	25	1.1(0.6-2.2)	23	1.3(0.5-3.4)	10	1.7(0.5-5.9)	6
High	1.0 (0.6-1.7)	26	0.9(0.5-1.7)	19	1.4(0.6-3.4)	13	3.6 (1.2-10.8)	9
	P trend=0.90		P trend=0.62		P trend=0.83		P trend=0.06	
Butylate (thio-carbamate-)								
None	1.0 (ref)	40	1.0 (ref)	33	1.0 (ref)	14	1.0 (ref)	8
Low	0.8(0.4-1.9)	7	1.1(0.4-3.0)	4	0.8(0.2-2.9)	3	3.0 (0.8-11.3)	3
Medium	3.5(1.6-7.6)	8	1.2(0.4-3.5)	4	6.3(2.1-19.3)	4	4.0(1.2-13.7)	4
High	1.3(0.4-4.3)	3	0.8(0.2-2.5)	3	1.0(0.1-7.9)	1	2.4 (0.3-19.7)	1
	P trend=0.04		P trend=0.69		P trend=0.07		P trend=0.0499	
2,4-D (Chlorinated Phenoxy)								
None	1.0 (ref)	25	1.0 (ref)	23	1.0 (ref)	9	1.0 (ref)	5
Low	0.90(0.5-1.5)	31	0.9(0.5-1.7)	23	1.8(0.8-4.4)	14	1.9 (0.6-6.2)	10
Medium	1.2(0.7-2.0)	29	1.0(0.6-1.9)	21	1.0(0.4-2.4)	14	1.7 (0.5-5.6)	9
High	1.3(0.7-2.2)	29	0.7(0.4-1.3)	21	1.4(0.6-3.4)	12	2.2 (0.7-7.2)	9
	P trend=0.20		P trend=0.23		P trend=0.84		P trend=0.35	
Dicamba (benzoic acid)								
None	1.0 (ref)	39	1.0 (ref)	40	1.0 (ref)	22	1.0 (ref)	6
Low	1.5 (0.9-2.6)	23	1.1 (0.6-2.1)	12	1.5(0.7-3.4)	9	3.2 (1.0-9.9)	8
Medium	1.5 (0.9-3.4)	20	1.1 (0.6-2.1)	13	1.8(0.90-4.0)	10	5.2(1.6-16.6)	7
High	2.0 (1.1-3.4)	20	0.7 (0.4-1.4)	11	0.7(0.3-1.5)	8	5.1(1.6-16.1)	7
	P trend=0.03		P trend=0.26		P trend=0.32		P trend=0.02	

EPTC (thio-carbamate)								
None	1.0 (ref)	86	1.0 (ref)	62	1.0 (ref)	40	1.0 (ref)	19
Low	1,2(0.6-2.3)	9	1.2(0.6-2.7)	7	xxx	3	2.1 (0.7-6.0)	4
Medium	1.2(0.6-2.5)	8	1.7(0.7-4.2)	5	xxx	0	2.1 (0.6-7.1)	3
High	1.4(0.6-3.4)	5	0.8(0.3-2.3)	4	xxx	1	4.9 (1.4-16.7)	3
	P trend= 0.41		P trend=0.98		P trend=0.10		P trend=0.01	
Glyphosate (isopropyl-amine)								
None	1.0 (ref)	25	1.0 (ref)	19	1.0 (ref)	13	1.0 (ref)	10
Low	0.6(0.4-1.1)	32	1.3(0.7-2.6)	23	0.7(0.3-1.7)	15	0.4 (0.1-1.2)	9
Medium	1.1(0.6-1.9)	29	1.1(0.5-2.1)	23	0.6(0.2-1.4)	11	0.6 (0.2-1.6)	7
High	1.1(0.6-1.8)	29	0.7(0.4-1.3)	22	0.7(0.3-1.8)	12	0.6 (0.2-1.8)	7
	P trend=0.21		P trend=0.05		P trend=0.66		P trend=0.98	
Imazethapyr (imid-azolinone)								
None	1.0 (ref)	68	1.0 (ref)	57	1.0 (ref)	29	1.0 (ref)	12
Low	1.0(0.6-1.8)	16	0.7(0.3-1.4)	10	0.7(0.3-1.7)	6	1.6 (0.6-3.8)	8
Medium	0.8(0.4-1.6)	11	0.6(0.3-1.4)	6	1.1(0.3-3.5)	6	5.2 (1.6-16.6)	4
High	1.2(0.6-2.2)	12	0.5(0.2-1.2)	5	1.0(0.4-2.8)	5	3.2 (1.0-10.0)	4
	P trend=0.71		P trend=0.16		P trend=0.90		P trend=0.03	
Metribuzin (Triazone)								
None	1.0 (ref)	30	1.0 (ref)	35	1.0 (ref)	13	1.0 (ref)	9
Low	1.5(0.7-2.9)	11	0.5(0.2-1.4)	5	1.4(0.5-3.9)	5	1.0 (0.2-4.9)	3

Medium	2.1(1.1-4.0)	13	0.5(0.1-2.0)	3	0.8(0.2-2.9)	3	2.8 (0.9-8.9)	5
High	1.8(0.6-5.2)	4	0.4(0.1-1.6)	2	1.3(0.2-9.8)	1	-	0
	P trend=0.06		P trend=0.13		P trend=0.88		P trend=0.60	
Trifluralin (dinitro-aniline)								
None	1.0 (ref)	45	1.0 (ref)	43	1.0 (ref)	25	1.0 (ref)	10
Low	1.1(0.7-1.9)	23	0.9(0.5-1.7)	14	0.9(0.4-1.9)	8	1.2 (0.4-3.2)	7
Medium	1.6(0.9-2.6)	21	0.8(0.4-1.7)	11	0.8(0.4-1.8)	8	2.7 (1.0-7.0)	7
High	1.1(0.6-1.9)	15	0.6(0.3-1.2)	11	0.8(0.3-1.9)	7	3.3 (1.2-9.1)	6
	P trend= 0.81		P trend=0.13		P trend=0.62		P trend=0.01	

[1] Age adjusted (<45,45-49,50-54,55-59,60-64,65-69,≥70)
[2] Numbers do not sum to NHL subtype totals due to missing data.

Table 4: The number of different pesticides in a pesticide class used and the risk of NHL (95% CI)

Number pesticides in a pesticide class	All NHL Cases[1]	Cohort Person-Years	RR[2]	95% CI
All pesticide				
0-4	36	46,624	1.0 (ref)	
5-8	58	62,304	1.2	(0.8-1.9)
9-11	50	56,373	1.2	(0.8-2.0)
12-16	65	93,714	0.9	(0.5-1.4)
17-20	48	57,874	1.1	(0.7-1.8)
>20	75	71,281	1.1	(0.7-1.8)
			P trend=0.53	
Chlorinated Insecticides				
0	111	344,026	1.0 (ref)	
1	63	131,439	1.1	(0.6-1.9)
2	42	77,989	1.1	(0.6-2.0)
≥3	89	122,276	0.9	(0.5-1.7)
			P trend=0.45	
Organophosphate insecticides				
0	38	90,621	1.0 (ref)	
1	59	128,694	1.2	(0.7-1.8)
2	69	146,183	1.3	(0.8-2.0)
3	56	133,273	1.1	(0.6-1.8)
≥4	107	208,634	1.2	(0.7-2.1)
			P trend=0.59	
Carbamate insecticide				
0	104	231,849	1 (ref)	
1	126	294,727	0.7	(0.5-1.0)
≥2	89	163,706	0.9	(0.6-1.4)
			P trend=0.64	
Other insecticides				
0	251	532,835	1.0 (ref)	
>1	43	112,489	1.1	(0.6-1.8)
			P trend=0.36	
Triazine herbicides				
0	67	161,040	1.0	
1	92	187,057	1.2	(0.6-2.4)
2	78	185,777	1.0	(0.5-2.1)
3	92	173,920	1.4	(0.7-3.0)
			P trend=0.04	
Acetamide herbicides				
0	90	206,537	1.0	
1	115	236,407	1.6	(0.8-3.4)
2	102	219,200	1.7	(0.7-3.7)

			P trend=0.10	
Carbamate herbicides				
0	193	414,729	1.0 (ref)	
1	79	179,871	0.8	(0.5-1.2)
2	40	84,589	0.8	0.8 (0.4-1.4)
			P trend=0.80	
Other herbicides				
0	13	25,880	1.0 (ref)	
1-2	67	131,595	1.1	(0.5-2.7)
3-4	76	162,359	1.0	(0.4-2.4)
5-6	78	185,337	1.0	(0.4-2.5)
≥7	97	205,915	1.1	(0.4-2.6)
			P trend=0.19	
Fungicides				
0	203	442,307	1.0 (ref)	
1	73	152,882	1.1	(0.8-1.5)
≥2	52	110,590	1.5	(0.99-2.3)
			P trend=0.31	
Fumigants				
0	240	538,867	1.0 (ref)	
1	73	123,473	1.4	(0.9-2.1)
≥2	15	42,165	0.9	(0.4-1.9)
			P trend=0.24	

[1] Numbers do not sum to totals (333 cases, 714,770 person-years) due to missing data
[2] NHL risks are age adjusted (<45,45-49,50-54,55-59,60-64,65-69,≥70)and adjusted for lifetime days of use of pesticides in the specific pesticide class

Table 5. Number of different pesticides used by pesticide type (in the NHL incidence analysis from 1993 through 2008) for B cell sub-types.[1,2]

	CLL, SLL, PLL, MCL		Diffuse Large B-cell		Follicular B-cell		Other B-cell types	
	RR [1] (95% CI)	n	RR[1] (95% CI)	n	RR[1] (95% CI)	n	RR[1] (95% CI)	n
Insecticides								
Carbamate insecticides[3]								
0	1.0 (ref)	34	1.0(ref)	33	1.0(ref)	12	1.0 (ref)	13
1	0.8 (0.5-1.3)	45	0.7(0.4-1.2)	36	1.5(0.8-3.0)	26	0.3 (0.1-0.8)	7
2-3	1.1 (0.7-1.7)	32	0.7(0.4-1.2)	20	1.2(0.5-2.7)	12	1.2 (0.5-2.5)	13
	P trend= 0.82		P trend=0.21		P trend=0.63		P trend= 0.75	
Chlorinated insecticides[4]								
None	1.0 (ref)	8	1.0(ref)	16	1.0(ref)	3	1.0 (ref0	6
1	1.6 (0.7-3.8)	17	0.9 (04-1.7)	18	4.1(1.2-14.1)	15	0.9 (0.3-2.7)	7
2	2.2 (0.95-5.0)	19	0.6(0.3-1.3)	10	2.5(0.6-9.6)	7	0.5 (0.1-1.9)	3
3	2.4 (1.2-5.2)	41	0.5(0.3-1.0)	17	1.7(0.5-6.5)	9	0.8 (0.3-2.3)	10
	P trend=0.02		P trend=0.05		P trend=0.73		P trend= 0.48	
Organophosphate Insecticides[5]								
0	1.0 (ref)	13	1.0 (ref)	14	1.0(ref)	5	1.0	5
1	0.93(0.4-2.0)	15	1.2(0.6-2.4)	21	1.3(0.4-3.9)	8	0.8 (0.2-2.8)	5
2	1.4 (0.7-2.7)	25	1.0(0.5-2.0)	20	1.7(0.6-4.7)	12	1.3 (0.4-4.0)	9
3	1.3 (0.6-2.5)	20	0.8(0.4-1.7)	14	1.4(0.5-4.1)	9	0.5 (0.1-2.1)	3
≥4	1.7 (0.92-3.2)	42	0.8(0.4-1.6)	23	1.6(0.6-4.4)	17	1.3 (0.5-3.7)	12

Comment [lbf69]: Interesting results

	P trend =0.03		P trend= 0.28		P trend=0.38		P trend=0.67	
Other Insecticides[6]								
0	1.0 (ref)	86	1.0 (ref)	71	1.0(ref)	35	1.0 (ref)	22
1	0.94 (0.6-1.6)	19	0.5(0.2-1.0)	9	1.3(0.6-2.4)	12	1.1 (0.5-2.8)	6
	P trend=0.78		P trend= .04		P trend=0.49	6	P trend=0.82	
Herbicides								
Acetamide Herbicide[7]								
0	1.0 (ref)	37	1.0(ref)	32	1.0(ref)	14	1.0	6
1	0.97 (0.6-1.5)	35	1.0(0.6-1.6)	32	1.3(0.7-2.6)	19	1.4 (0.5-4.0)	8
2	1.2 (0.8-2.0)	39	0.6(0.4-1.1)	18	1.2(0.6-2.4)	15	3.9 (1.2-8.2)	16
	P trend=0.35		P trend=0.16		P trend=0.72		P trend= 0.009	
Carbamate Herbicide[8]								
0	1.0 (ref)	67	1.0(ref)	58	1.0(ref)	27	1.0	16
1	0.98 (0.6-1.5)	27	0.7(0.4-1.2)	17	1.3(0.7-2.5)	16	1.5 (0.7-3.4)	10
2	1.5 (0.9-2.5)	17	0.9(0.4-1.7)	9	0.6(0.2-1.8)	3	2.2 (0.9-5.7)	6
	P trend=0.29		P trend=0.33		P trend=0.71		P trend=0.11	
Other herbicides[9]								
0	1.0 (ref)	6	1.0(ref)	6	1.0(ref)	1	1.0	2
1-2	1.2(0.5-2.8)	25	1.0(0.4-2.5)	22	3.2(0.5-27.0)	13	0.6 (0.1-3.1)	4
2-4	0.9 (0.4-2.2)	20	1.4(0.6-3.4)	33	2.5(0.3-19.2)	10	0.94(0.2-4.6)	7
5-6	1.2 (0.5-2.8)	26	0.7(0.3-1.7)	16	4.0(0.5-29.8)	17	1.2(0.3-5.7)	9
≥7	1.7 (0.7-4.1)	38	0.7(0.3-1.7)	16	2.5(0.3-19.3)	11	1.7(0.4-7.6)	12
	P trend=0.06		P trend=0.08		P trend=0.84		P trend= 0.06	
Triazine/Triazone herbicides[10]								
0	1.0	29	1.0 (ref)	22	1.0(ref)	6	1.0 (ref)	4
1	0.8 (0.5-1.4)	24	1.5(0.9-2.6)	34	3.2(1.3-8.0)	20	2.0 (0.6-6.6)	8

Comment [lbf70]: Interesting results

2	1.0(0.6-1.7)	27	0.8(0.4-1.5)	17	2.1(0.8-6.7)	13	2.5 (0.8-8.3)	9
3	1.5 (0.91-2.5)	35	1.1(0.6-2.0)	20	2.3(0.9-6.1)	13	4.2 (1.4-13.1)	13
	P trend=0.07		P trend=0.64		P trend=0.30		P trend=.006	
Fungicides and Fumigants								
Fungicides[11]								
0	1.0 (ref)	4	1.0 (ref)	6	1.0(ref)	3	1.0	2
1	1.3 (0.4-3.6)	29	0.7(0.3-1.8)	28	1.1(0.3-3.6)	23	1.2 (0.3-5.6)	14
2	1.7 (0.6-4.6)	81	0.8(0.3-1.8)	58	0.6(0.2-2.1)	26	0.8 (0.2-3.4)	18
	P trend=0.11		P trend=0.75		P trend=0.10		P trend=0.29	
Fumigants[12]								
0	1.0 (ref)	43	1.0 (ref)	30	1.0(ref)	25	1.0	9
1	1.0 (0.6-1.9)	13	2.0(1.1-3.7)	17	0.6(0.2-1.7)	4	2.8 (1.0-7.4)	7
≥2	0.95(0.6-1.4)	58	1.1(0.7-1.8)	45	0.7(0.4-1.2)	22	1.5(0.7-3.3)	18
	P trend=0.81		P trend=0.75		Ptrend=0.20		P trend=0.43	

[1]Age adjusted (<45,45-49,50-54,55-59,60-64,65-69,≥70 [2] Numbers do not sum to NHL subtype totals due to missing data [3]Carbamate insecticides: carbofuran, aldicarb, carbaryl [4]Chlorinated insecticides: aldrin, chlordane, dieldrin, DDT, heptachlor, lindane, toxaphene [5]Organophosphate insecticides: Chlorpyrifos, coumaphos, diazinon, dichlorvos, fonofos, malathion, parathion, phorate, terbufos, [6]Other insecticides: permethrin [7]Acetamide: metolachlor, alachlor [8]Carbamate herbicide: Butylate: EPTC [9]Other herbicides: Glyphosate, imazethapyr, herbicide oil, paraquat, chlorimuron ethyl, dicamba, pendimethalin, trifluralin, 2,4-D, 2,4,5-T, 2,4-TP[10]Triazine herbicides: Atrazine, cyanazine, metribuzin [11]Fungicides: Benomyl, chlorthalonil, captan, maneb/macozeb, metalaxyl, ziram [12]Fumigants: methyl bromide, aluminum phosphate, ethylene dibromide, carbon tetra chloride/carbon disulfide

Supplemental Table 1 Other pesticide exposures (lifetime days [LD] and intensity weighted total days) and age-adjusted risk of NHL incidence (1993 through 2008).

Pesticide (chemical-functional class) [median days of lifetime exposure for each category]	NHL Cases	RR (95%) by Lifetime- Days of Exposure	NHL Cases	RR (95% CI) Intensity weighted Lifetime-Days of exposure
Benomyl (carbamate-fungicide)				
None	134	1.0 (ref)	134	1.0 (ref)
Low [0.5]	6	5.6 (2.4-12.6)	6	4.1(1.8-9.3)
Medium [12.25]	5	1.0 (0.4-2.6)	5	1.0 (0.4-2.6)
High [108.5]	5	0.8 (0.3-1.9)	5	0.8 (0.3-1.9)
		P for trend=0.50		P for trend=0.57
Captan (dicarboximide-fungicide)				
None	258	1.0 (ref)	258	1.0 (ref)
Low [4]	8	0.6 (0.3-1.3)	8	0.7 (0.4-1.5)
Medium [12.25]	8	1.6 (0.6-4.1)	7	1.2 (0.5-2.9)
High [124]	7	0.6 (0.3-1.5)	7	0.5 (0.2-1.3)
		P for trend=0.33		P for trend=0.20
Carbofuran (carbamate-insecticide)				
None	199	1.0 (ref)	199	1.0 (ref)
Low [8.75]	35	1.1 (0.8-1.6)	29	1.2 (0.8-1.8)
Medium [38.75]	25	1.0 (0.7-1.6)	29	0.9 (0.6-1.3)
High [56]	28	1.0 (0.7-1.5)	28	1.1 (0.8-1.7)

Comment [lbf71]: I think that you need to put number of days for each pesticide. Low/Med/High is not the same for each pesticide under study and this leaves the impression that they are.

Comment [a72]: Lifetime days added as suggested.

		P trend=0.81		P trend=0.74
Chlorpyrifos (organophosphate-insecticide)				
None	189	1.0 (ref)	189	1.0 (ref)
Low [14.75]	44	1.1 (0.7-1.5)	40	1.1 (0.8-1.5)
Medium [38.75]	45	1.3(0.9-1.8)	41	1.0 (0.7-1.5)
High [116]	43	0.9 (0.7-1.3)	39	1.1 (0.8-1.5)
		P trend=0.57		P trend=0.67
Chlorthalonil (thalonitrile-fungicide)				
None	301	1.0 (ref)	301	1.0 (ref)
Low [8]	7	1.3 (0.6-2.7)	7	1.1 (0.5-2.4)
Medium [54.25]	6	0.6 (0.2-1.6)	6	0.6 (0.2-1.5)
High [79]	6	0.6 (0.2-1.2)	6	0.7 (0.3-1.5)
		P for trend=0.12		P for trend=0.23
Coumaphos (0rganophosphate-insecticide)				
None	258	1.0(ref)	258	1.0 (ref)
Low [8.75]	12	1.2 (0.7-2.2)	10	1.6 (0.8-2.9)
Medium [38.75]	10	1.4 (0.8-2.7)	11	1.2 (0.6-2.1)
High [63.75]	8	1.2 (0.6-2.4)	9	1.2 (0.6-2.3)
		P for trend=0.41		P for trend=0.55
DDVP (dimethyl phosphate-insecticide)				
None	261	1.0 (ref)	261	1.0 (ref)

Low [8.75]	10	1.2 (0.6-2.2)	10	1.2 (0.7-2.3)
Medium [108.5]	11	1.1 (0.6-2.0)	9	0.8 (0.4-1.6)
High [457.25]	7	0.7 (0.3-1.5)	9	1.0 (0.5-1.9)
		P for trend=0.42		P for trend=0.95
Diazinon (organophosphosphorous-insecticide)				
None	113	1.0 (ref)	113	1.0 (ref)
Low [8.75]	19	1.2 (0.7-2.0)	14	1.3 (0.7-2.2)
Medium [30]	10	0.7 (0.3-1.7)	15	0.9 (0.5-1.7)
High [56]	13	1.1 (0.6-2.1)	13	1.1 (0.6-1.9)
		P trend=0.73		P trend=0.92
Fonofos (phosphonothioate-insecticide)				
None	220	1.0 (ref)	220	1.0 (ref)
Low [20]	28	1.3 (0.9-1.9)	23	1.2 (0.8-1.9)
Medium [50.75]	19	1.2 (0.8-2.0)	23	1.4 (0.93-2.2)
High [108.5]	22	1.1 (0.7-1.7)	22	1.0 (0.6-1.5)
		P for trend=0.67		P for trend=0.98
Metalaxyl (analine methyl ester-fungicide)				
None	126	1.0 (ref)	126	1.0 (ref)
Low [3.5]	10	1.2 (0.6-2.2)	10	1.8 (0.95-3.4)
Medium [24.5]	11	0.9 (0.5-1.7)	11	0.7 (0.4-1.4)
High [50]	9	0.8 (0.4-1.5)	9	0.8 (0.4-1.5)

		P for trend=0.43		P for trend=028
Methyl bromide (methyl halide-fumigant)				
None	268	1.0 (ref)	268	1.0 (ref)
Low [8]	25	1.9 (1.2-2.8)	17	1.9 (1.2-3.1)
Medium [15.5]	9	0.9 (0.4-1.7)	16	1.3 (0.8-2.1)
High [28]	16	0.6 (0.3-0.9)	16	0.5 (0.3-0.9)
		P for trend=0.03		P for trend=0.02
Permethrin Animals (pyrethroid-insecticide)				
None	263	1.0 (ref)	263	1.0 (ref)
Low [8.75]	15	1.3 (0.8-2.3)	10	1.3 (0.7-2.5)
Medium [24]	5	0.8 (0.3-2.5)	10	0.8 (0.4-1.7)
High [56]	9	0.6 (0.3-1.2)	9	0.8 (0.4-1.5)
		P trend= 0.18		P trend=0.43
Permethrin Crops (pyrethroid-insecticide)				
None	249	1.0 (ref)	249	1.0 (ref)
Low [8.75]]	17	1.0 (0.6-1.7)	12	1.1 (0.5-2.2)
Medium [24.5]	9	1.1 (0.5-2.3)	12	1.2 (0.7-2.2)
High [59]	10	0.7 (0.4-1.4)	11	0.6 (0.3-1.1)
		P for trend=0.36		P for trend=0.15
Phorate (organophosphate-insecticide)				
None	102	1.0 (ref)	102	1.0 (ref)
Low [20]	20	1. (0.6-1.6)	17	0.9(0.5-1.5)

Comment [lbf73]: Do you show permethrin on crops anywhere?

Medium [24.5]	20	2.2 (1.4-3.5)	17	1.9 (1.1-3.1)
High [56]	10	0.7 (0.4-1.3)	16	1.0(0.6-1.7)
		P for trend=0.80		P for trend=0.67
Herbicide exposures				
	Life-time days of Exposure		Intensity weighted days of exposure[a]	
	NHL Cases	RR (95%)	NHL Cases	RR (95% CI)
Chlorimuron-ethyl (benzoic acid ester-herbicide)				
None	105	1.0 (ref)	105	1.0 (ref)
Low [8.75]	28	1.2(0.9-1.8)	18	1.1(0.6-1.9)
Medium [24.5]	18	1.9(1.2-3.2)	18	1.5(0.9-2.5)
High [24.5]	7	0.7(0.3-1.5)	17	1.1(0.7-1.9)
		P for trend=0.83		P for trend=0.60
Cyanazine (triazine-herbicide)				
None	162	1.0 (ref)	162	1.0 (ref)
Low [20]	58	1.4(0.9-1.9)	45	1.3(0.8-1.7)
Medium [56]	43	1.2(0.8-1.7)	45	1.4(1.0-1.9)
High [116]	35	1.1(0.8-1.6)	44	1.1(0.8-1.5)
		P for trend=0.81		P for trend=0.67
Herbicide Oil (Petroleum oils-herbicide)				
None	120	1.0 (ref)	120	1.0 (ref)
Low [20]	14	1.0(0.6-1.9)	13	1.3(0.7-2.3)
Medium [56]	13	1.8(1.0-1.1)	12	1.1(0.6-1.9)

High [173.25]	10	1.0(0.5-2.0)	12	1.3(0.7-2.4)
		P for trend=0.84		P for trend=0.36
Metolachlor (acetamide-herbicide)				
None	145	1.0 (ref)	145	1.0 (ref)
Low [20]	50	1.2(0.9-1.7)	49	1.2(0.8-1.6)
Medium [56]	54	1.3(0.94-1.5)	49	1.4(1.0-2.0)
High [116]	44	1.1(0.8-1.5)	48	1.1(0.8-1.5)
		P for trend=0.67		P for trend=0.28
Paraquat				
None	127	1.0 (ref)	127	1.0 (ref)
Low [7]	10	1.5(0.8-2.8)	10	1.9(1.0-3.7)
Medium [24.5]	10	0.8(0.4-1.5)	9	0.5(0.3-1.1)
High [116]	8	1.0(0.5-2.0)	9	1.5(0.8-3.0)
		P for trend= 0.88		P for trend=0.26
Pendimethalin				
None	96	1.0 (ref)	96	1.0 (ref)
Low [8.75]	32	1.1(0.7-1.6)	25	1.1(0.6-1.8)
Medium [24.5]	23	1.2(0.7-2.0)	26	1.0(0.7-1.6)
High [56]	20	1.0(0.6-1.6)	24	1.2(0.7-1.8)
		P for trend=0.87		P for trend=0.52
2,4,5 T (phenoxyacetic acid)				
None	71	1.0 (ref)	71	1.0 (ref)
Low [8.75]	30	1.7(1.1-2.5)	17	1.6(0.9-2.8)
Medium [8.75]	4	1.2(0.4-3.3)	16	1.9(1.1-3.2)
High [20]	15	1.2(0.7-2.2)	16	1.0(0.6-1.7)

		P for trend=0.52		P for trend=0.51

[1]Age adjusted (<45,45-49,50-54,55-59,60-64,65-69,≥70)

Supplemental Table 2. Pesticide exposures (total days and intensity weight total days) fully adjusted risks of NHL incidence (1993 through 2008).

	NHL Cases	RR (95%) by Total Days of Exposure	NHL Cases	RR (95% CI) Intensity weighted days of exposure
Benomyl				
none	134	1.0 (ref)	134	1.0 (ref)
Low	6	6.1(2.7-13.8)	6	4.6 (2.0-10.6)
medium	5	1.0(0.4-2.6)	5	1.4 (0.6-3.5)
High	5	1.0(0.4-2.6)	5	1.1 (0.4-2.8)
		P trend (full)=0.98		P trend (full)=0.94
Captan				
none	258	1.0 (ref)	258	1.0 (ref)
Low	8	0.6(0.3-1.2)	8	0.7 (0.3-1.4)
medium	8	1.7(0.7-4.3)	7	1.2 (0.5-2.0)
High	7	0.7(0.3-1.6)	7	0.6 (0.2-1.4)
		P trend (full)=0.45		P trend (full)=0.28
Carbaryl				
none	81	1.0(ref)	81	1.0 (ref)
Low	31	0.96(0.6-1.6)	27	0.91 (0.6-1.5)
medium	23	0.8(0.5-1.4)	26	0.99 (0.6-1.6)
High	25	1.3(0.8-2.2)	26	1.1 (0.7-1.9)
		P trend (full)=0.26		P trend (full)=0.54
Carbofuran				
none	199	1.0 (ref)	199	1.0 (ref)
Low	35	1.0(0.7-1.5)	29	1.1(0.8-1.6)
medium	25	0.97(0.6-1.5)	29	0.8(0.5-1.2)
High	28	0.96(0.6-1.4)	28	1.1(0.7-1.6)

		P trend (full)=0.83		P trend (full)=0.95
Chlorthalonil				
none	301	1.0 (ref)	301	1.0 (ref)
Low	7	1.4(0.7-3.0)	7	1.2 (0.6-2.6)
Medium	6	0.7(0.3-1.8)	6	0.6 (0.2-1.9)
High	6	0.6 (0.3-1.4)	6	0.7 (0.3-1.6)
		P trend (full)=0.21		P trend (full)=0.37
Chlorpyrifos				
None	189	1.0 (ref)	189	1.0 (ref)
Low	44	1.0(0.7-1.5)	40	1.0 (0.7-1.5)
Medium	45	1.2(0.9-1.7)	41	0.94 (0.7-1.3)
High	43	0.8(0.6-1.2)	39	1.0 (0.7-1.4)
		P trend (full)=0.31		P trend (full)=0.99
Coumaphos				
none	258	1.0 (ref)	258	1.0 (ref)
Low	12	1.1(0.6-2.0)	10	1.4 (0.8-2.7)
medium	10	1.3 (0.7-2.5)	11	1.1 (0.6-2.0)
High	8	1.1(0.5-2.2)	9	1.1 (0.6-2.1)
		P trend (full)=0.62		P trend (full)=0.75
Diazinon				
None	113	1.0 (ref)	113	1.0 (ref)
Low	19	1.3(0.8-2.1)	14	1.3 (0.7-2.2)
medium	10	0.8(0.3-1.8)	15	0.9 (0.5-1.7)
High	13	1.3(0.7-2.5)	13	1.3 (0.7-2.3)
		P trend (full)=0.41		P trend (full)=0.50

DDVP				
none	261	1.0 (ref)	261	1.0 (ref)
Low	10	1.0 (0.5-1.9)	10	1.1 (0.6-2.1)
medium	11	0.92 (0.5-1.7)	9	0.7 (0.4-1.4)
High	7	0.6 (0.3-1.3)	9	0.9 (0.4-1.7)
		P trend (full)=0.22		P trend (full)=0.61
Fonofos				
None	220	1.0 (ref)	220	1.0 (ref)
Low	28	1.2(0.8-1.7)	23	1.1(0.7-1.7)
medium	19	1.1(0.7-1.7)	23	1.2(0.8-1.9)
High	22	0.9 (0.6-1.5)	22	0.9(0.5-1.3)
		P trend (full)=0.76		P trend (full)=0.51
Lindane				
None	122	1.0 (ref)	122	1.0 (ref)
Low	11	0.9(0.5-1.8)	10	1.0(0.5-1.8)
medium	10	1.0(0.5-2.0)	11	1.2(0.6-2.3)
High	10	2.3(1.2-4.5)	9	1.7(0.9-3.3)
		P trend (full)=0.01		P trend (full)=0.12
Malathion				
none	55	1.0 (ref)	55	1.0 (ref)
Low	46	0.9(0.6-1.3)	37	0.9 (0.6-1.4)
medium	28	0.7(0.4-1.1)	38	0.8 (0.5-1.1)
High	36	1.0(0.7-1.5)	35	0.9 (0.6-1.4)
		P trend (full)=0.68		P trend (full)=0.91
Metalaxyl				
none	126	1.0 (ref)	126	1.0 (ref)
Low	10	1.2(0.6-2.4)	10	1.7 (0.9-3.4)

medium	11	1.1(0.6-2.2)	11	0.9 (0.4-1.7)
High	9	1.1(0.5-2.3)	9	1.0 (0.5-2.2)
		P trend (full)=0.89		P trend (full)=0.93
Methyl bromide				
none	268	1.0 (ref)	268	1.0 (ref)
Low	25	2.2 (1.4-3.4)	17	2.3 (1.4-3.8)
medium	9	1.1 (0.5-2.1)	16	1.5 (0.9-2.6)
High	16	0.7 (0.4-1.2)	16	0.7 (0.4-1.1)
		P trend (full)=0.13		P trend (full)=0.07
Permethrin Animals				
None	263	1.0 (ref)	263	1.0 (ref)
Low	15	1.1(0.7-1.9)	10	1.1(0.6-2.1)
medium	5	0.7(0.2-2.1)	10	0.7(0.3-1.4)
High	9	0.5(0.3-1.0)	9	0.6(0.3-1.2)
		P trend (full)=0.055		P trend (full)=0.15
Permethrin Crops				
None	249	1.0 (ref)	249	1.0 (ref)
Low	17	0.9(0.5-1.6)	12	1.0(0.5-2.0)
medium	9	1.1(0.5-2.2)	12	1.2(0.7-2.2)
High	10	0.8(0.4-1.5)	11	0.6(0.3-1.2)
		P trend (full)=0.44		P trend (full)=0.18
Phorate				
none	102	1.0 (ref)	102	1.0 (ref)
Low	20	0.8(0.5-1.3)	17	0.7 (0.4-1.2)
medium	20	1.7(1.0-2.8)	17	1.5 (0.9-2.5)
High	10	0.6(0.3-1.0)	16	0.8 (0.5-1.4)
		P trend (full)=0.26		P trend (full)=0.70

Terbufos				
None	157	1.0 (ref)	157	1.0 (ref)
Low	58	1.3(0.9-1.8)	43	1.2(0.8-1.7)
medium	38	1.7(1.2-2.5)	43	1.7(1.2-2.4)
High	34	1.0(0.7-1.5)	42	1.1(0.8-1.6)
		P trend (full)=0.78		P trend (full)=0.65
Herbicide exposures				
	Life-time days of Exposure		Intensity weighted days of exposure*	
	NHL Cases	RR (95%)	NHL Cases	RR (95% CI)
Alachlor				
None	138	1.0 (ref)	138	1.0 (ref)
Low	65	0.9 (0.7-1.2)	53	0.9(0.7-1.2)
medium	49	0.8((0.6-1.1)	50	0.8 (0.6-1.1)
High	43	1.2((0.9-1.8)	51	1.2 (0.8-1.6)
		P trend (full)=0.20		P trend (full)=0.27
Atrazine				
None	85	1.0 (ref)	85	1.0 (ref)
Low	88	1.1(0.8-1.5)	79	1.0(0.7-1.4)
medium	72	1.2 (0.8-1.6)	78	1.2(0.9-1.7)
High	77	1.0 (0.7-1.4)	78	0.98(0.7-1.4)
		P trend (full)= 0.72		P trend (full)=0.73
Butylate				
None	107	1.0 (ref)	107	1.0 (ref)
Low	22	0.9(0.5-1.4)	16	0.8 (0.5-1.3)
medium	18	2.4(1.4-4.0)	16	1.8 (1.0-3.0)
High	7	1.0(0.4-2.1)	15	1.3 (0.8-2.3)

		P trend (full)=0.03		P trend (full)=0.14
Chlorimuron-ethyl				
None	105	1.0 (ref)	105	1.0 (ref)
Low	28	1.1 (0.7-1.7)	18	1.0 (0.6-1.7)
medium	18	1.7 (1.0-2.9)	18	1.3(0.8-2.2)
High	7	0.7 (0.3-1.5)	17	1.1(0.6-1.8)
		P trend (full)=0.69		P trend (full)=0.68
Cyanazine				
None	162	1.0 (ref)	162	1.0 (ref)
Low	58	1.3(0.94-1.8)	45	1.2(0.8-1.7)
medium	43	1.1(0.8-1.6)	45	1.3(0.9-1.8)
High	35	1.0(0.7-1.4)	44	1.0(0.7-1.4)
		P trend (full)=0.65		P trend (full)=0.76
Dicamba				
None	121	1.0 (ref)	121	1.0 (ref)
Low	66	1.2 (0.8-1.7)	24	1.1(0.7-1.6)
medium	52	1.3 (0.9-1.9)	54	1.3(0.9-1.9)
High	47	1.1 (0.7-1.6)	55	1.1(0.8-1.6)
		P trend (full)=0.99		P trend (full)=0.76
2,4-D				
None	71	1.0 (ref)	71	1.0 (ref)
Low	83	0.9(0.6-1.3)	82	0.9 (0.6-1.2)
medium	83	1.0(0.7-1.4)	83	0.97 (0.7-1.4)
High	82	0.8(0.6-1.2)	81	0.9 (0.6-1.2)
		P trend (full)=0.35		P trend (full)=0.46
EPTC				
None	229	1.0 (ref)	229	1.0 (ref)

Low	28	1.2(0.8-1.8)	20	1.2 (0.8-2.0)
medium	14	0.9(0.7-1.9)	20	1.1 (0.7-1.7)
High	18	1.2(0.7-1.9)	19	1.0 (0.6-1.7)
		P trend (full)=0.56		P trend (full)=0.85
Glyphosate				
None	70	1.0 (ref)	70	1.0 (ref)
Low	89	0.8(0.6-1.2)	83	0.91 (0.6-1.3)
medium	78	0.8(0.6-1.2)	84	0.8 (0.5-1.1)
High	83	1.0(0.7-1.4)	82	0.97 (0.7-1.4)
		P trend (full)=0.63		P trend (full)=0.69
Herbicide Oil				
None	120	1.0 (ref)	120	1.0 (ref)
Low	14	1.0(0.6-1.7)	13	1.2 (0.6-2.1)
medium	13	1.7(0.93-2.9)	12	1.0 (0.5-1.8)
High	10	0.9((0.5-1.8)	12	1.2 (0.7-2.2)
		P for trend (full)=0.88		P for trend (full)=0.56
Imazethapyr				
None	181	1.0 (ref)	181	1.0 (ref)
Low	39	0.8(0.5-1.2)	36	0.8 (0.6-1.2)
medium	34	0.8(0.5-1.2)	37	0.7 (0.5-1.1)
High	35	1.0(0.7-1.5)	35	0.99 (0.7-1.5)
		P trend (full)=0.90		P trend (full)=0.92
Metolachlor				
None	145	1.0 (ref)	145	1.0 (ref)
Low	50	1.2 (0.8-1.6)	49	1.1(0.8-1.5)
medium	54	1.2 (0.8-1.7)	49	1.3(0.9-1.9)
High	44	1.0 (0.7-1.4)	48	0.98(0.7-1.4)

		P trend (full)=0.90		P trend (full)=0.81
Metribuzin				
None	94	1.0 (ref)	94	1.0 (ref)
Low	28	1.0(0.6-1.5)	21	1.0 (0.6-1.7)
medium	15	0.8(0.4-1.3)	23	0.91 (0.6-1.5)
High	20	1.4(0.8-2.3)	19	1.1 (0.7-1.9)
		P trend (full)=0.29		P trend (full)=0.66
Paraquat				
None	127	1.0 (ref)	127	1.0 (ref)
Low	10	1.6(0.8-3.0)	10	2.0 (1.0-3.7)
medium	10	0.9(0.5-1.7)	9	0.6 (0.3-1.3)
High	8	1.2(0.6-2.5)	9	1.9 (0.9-3.9)
		P trend (full)=0.72		P trend (full)=0.08
Pendimethalin				
None	96	1.0 (ref)	96	1.0 (ref)
Low	32	1.0(0.6-1.5)	25	0.9 (0.5-1.6)
medium	23	1.0(0.6-1.8)	26	0.9 (0.6-1.4)
High	20	1.0(0.6-1.5)	24	1.1 (0.7-1.8)
		P trend (full)=0.72		P trend (full)=0.60
Trifluralin				
None	140	1.0 (ref)	140	1.0 (ref)
Low	51	0.9(0.7-1.3)	50	0.9 (0.6-1.2)
medium	58	1.0(0.7-1.3)	52	1.0 (0.7-1.4)
High	43	0.8(0.6-1.2)	48	0.8 (0.6-1.1)
		P trend (full)=0.41		P trend (full)=0.30
2,4,5 T				
None	71	1.0 (ref)	71	1.0 (ref)

Low	30	1.6(1.0-2.4)	17	1.6 (0.9-2.6)
medium	4	1.1(0.4-3.0)	16	1.7 (1.0-2.9)
High	15	1.1(0.7-2.0)	16	1.0 (0.6-1.7)
		P trend (full)=0.78		P trend (full)=0.23

[1]Age adjusted (<45,45-49,50-54,55-59,60-64,65-69,≥70), smoking status(current, former, never), number of livestock (0,<100,100-999,>999), drove diesel tractor(<weekly,≥weekly), state (NC, IA)

Supplemental Table 1A. Chlorinated Insecticide exposure (in total days and intensity weighted days) and NHL age-adjusted relative risk(1993 through 2008).				
	Total exposure days		Intensity weight exposure days	
	NHL cases	RR (95% CI)[1]	NHL cases	RR (95% CI)
Aldrin (Chlorinated Insecticide)				
None	232	1.0 (ref)	232	1.0 (ref)
Low [8.75]	14	0.8 (0.5-1.6)	12	0.9(0.5-1.6)
Medium [56]	14	0.8(0.5-1.4)	12	0.8(0.4-1.4)
High [116]	7	1.6(0.7-3.4)	11	1.0(0.6-1.9)
		P trend=0.70		P trend=0.86
Aldrin				
None	232	1.0 (ref)	232	1.0 (ref)
Low	14	0.8 (0.5-1.4)	12	0.9 (0.5-1.6)
medium	14	1.6 (0.8-3.4)	12	1.0 (0.6-1.9)
high	7	0.9 (0.7-1.2)	11	0.9 (0.7-1.2)
		P for trend=0.42		P for trend=0.95
		P for trend (full)=0.34		P for trend (full)=0.60
Heptachlor (Chlorinated Insecticide)				
None	240	1.0 (ref)	240	1.0 (ref)
Low [8.75]	11	2.1 (1.3-3.6)	10	2.8 (1.5-5.3)
Medium [24.5]	15	0.9 (0.3-2.1)	10	1.0 (0.5-1.9)
High [24.5]	5	1.0 (0.7-1.3)	10	1.0 (0.7-1.30
		P trend=0.26		P trend=0.42

Heptachlor				
None	240	1.0 (ref)	240	1.0 (ref)
Low	11	0.9 (0.5-1.6)	11	0.9 (0.5-1.7)
medium	15	2.1 (1.3-3.6)	10	2.8 (1.5-5.3)
high	5	0.9 (0.4-2.1)	10	1.0 (0.5-1.9)
		P for trend=0.11		P for trend=0.41
		P for trend (full)=0.19		P for trend (full)=0.16
2,4,5 TP				
None	276	1.0 (ref)	276	1.0 (ref)
Low	8	1.8 (0.9-3.7)	4	1.6 (0.6-4.3)
medium	0	0.6 (0.2-1.9)	4	1.4 (0.5-3.8)
high	3	0.9 (0.6-1.2)	3	0.8 (0.2-2.4)
		P for trend=0.40		P for trend=0.75
		P for trend (full)=0.27		P for trend (full)=0.74
Toxaphene (Chlorinated Insecticide)				
None	250	1 .0 (ref)	250	1.0 (ref)
Low [8.75]	10	3.4(1.4-8.3)	7	0.8(0.4-1.6)
Medium [20]	5	0.6(0.3-1.3)	8	0.7(0.3-1.6)
High [50.75]	6	1.0(0.7-1.3)	6	1.0(0.7-1.3)
	P trend=0.66		P trend=0.83	
Toxaphene				
None	250	1.0 (ref)	250	1.0 (ref)
Low	10	3.4 (1.4-8.3)	7	1.6 (0.8-3.5)
medium	5	0.6 (0.3-1.3)	8	0.8 (0.4-1.6)
high	6	1.0 (0.7-1.3)	6	0.7 (0.3-1.6)

	P for trend=0.33		P for trend=0.31
	P for trend (full)= 0.12		P for trend (full)=0.69

[1]Age adjusted (<45,45-49,50-54,55-59,60-64,65-69,≥70)

Supplemental Table 2A. Chlorinated Insecticide exposure (in total days and intensity weighted days) and NHL fully adjusted relative risk (1993 through 2008).

	Life-time exposure days		Intensity weight exposure days	
	NHL cases	RR (95% CI)[1]	NHL cases	RR (95% CI)
Aldrin				
None	232	1.0 (ref)	232	1.0 (ref)
Low	14	0.7 (0.4-1.3)	12	0.8 (0.5-1.5)
medium	14	0.7 (0.4-1.2)	12	0.7 (0.4-1.3)
high	7	1.4 (0.7)	11	0.9 (0.5-1.7)
		P for trend (full)=0.34		P for trend (full)=0.60
Chlordane				
None	223	1.0 (ref)	223	1.0 (ref)
Low	23	1.0 (0.6-1.6)	13	1.2 (0.7-2.2)
medium	6	1.8 (0.8-4.2)	13	0.9 (0.5-1.7)
high	9	0.4 (0.4-1.7)	12	1.0 (0.6-1.8)
		P for trend (full)=0.63		P for trend (full)=0.90
DDT				
None	194	1.0 (ref)	194	1.0 (ref)
Low	20	0.8 (0.5-1.3)	19	0.9 (0.6-1.5)

medium	18	1.0 (0.6-1.6)	18	0.9 (0.5-1.4)
high	17	1.5 (0.9-2.5)	18	1.4 (0.9-2.4)
		P for trend (full)=0.48		P for trend (full)=0.61
Heptachlor				
None	240	1.0 (ref)	240	1.0 (ref)
Low	11	0.8 (0.4-1.5)	11	0.8 (0.5-1.6)
medium	15	1.9 (1.1-3.3)	10	2.4 (1.3-4.7)
high	5	0.8 (0.3-1.9)	10	0.9 (0.5-1.8)
		P for trend (full)=0.19		P for trend (full)=0.16
Lindane				
None	122	1.0 (ref)	122	1.0 (ref)
Low	11	0.9 (0.5-1.8)	10	1.0(0.5-1.8)
medium	10	1.0 (0.5-2.0)	11	1.2(0.6-2.3)
high	10	2.4 (1.2-4.5)	9	1.7(0.9-3.3)
		P for trend (full)=0.01		P for trend (full)=0.12
Toxaphene				
None	250	1.0 (ref)	250	1.0 (ref)
Low	10	0.91 (0.5-1.7)	7	1.6 (0.7-3.3)
medium	5	3.4 (1.4-8.3)	8	0.8 (0.4-1.6)
high	6	0.6 (0.3-1.3)	6	0.7 (0.3-1.7)
		P for trend (full)= 0.12		P for trend (full)=0.69

Supplemental Table 3. Herbicide exposures (Life-time days) and age-adjusted NHL risk by cell type (1993 through 2008).

Pesticide (chemical class)	CLL, SLL, PLL, MCL		Diffuse Large B-cell		Follicular B-cell		Other B-cell types	
	RR (95% CI)	n	RR (95% CI)	n	RR (95% CI)	n	RR (95% CI)	n
Alachlor (acetanilide)								
None	1.0 (ref)	53	1.0 (ref)	43	1.0 (ref)	22	1.0 (ref)	9
low	0.9(0.6-1.5)	23	0.9(0.5-1.6)	13	1.3(0.6-2.6)	10	1.6 (0.6-4.4)	7
medium	0.8(0.5-1.4)	18	0.7(0.4-1.3)	14	0.8(0.3-1.6)	9	2.1 (0.8-5.3)	10
high	1.1(0.6-2.1)	14	0.8(0.4-1.6)	10	1.1(0.4-2.7)	6	4.0 (1.2-13.0)	4
	LD P =0.67		LD P trend=0.52		LD P trend=0.99		LD P trend=0.02	
	IWLD P=0.49		IWLD P trend=0.092		IWLD P trend=0.97		IWLD P trend= 0.20	
Atrazine (triazine)								
None	1.0 (ref)	34	1.0 (ref)	26	1.0 (ref)	12	1.0 (ref)	5
low	1.0 (0.6-1.7)	29	1.1(0.6-2.0)	21	1.7(0.7-3.9)	17	2.4 (0.9-6.8)	13
medium	1.2 (0.7-2.0)	25	1.1(0.6-2.2)	23	1.3(0.5-3.4)	10	1.7(0.5-5.9)	6
high	1.0 (0.6-1.7)	26	0.9(0.5-1.7)	19	1.4(0.6-3.4)	13	3.6 (1.2-10.8)	9
	LD P trend=0.90		LD P trend=0.62		LD P trend=0.83		LD P trend=0.06	
	IWLD P trend=0.75		IWLD P trend=0.87		IWLD P trend=0.76		IWLD P trend=0.22	

Butylate (thio-carbamate-)								
None	1.0 (ref)	40	1.0 (ref)	33	1.0 (ref)	14	1.0 (ref)	8
low	0.8(0.4-1.9)	7	1.1(0.4-3.0)	4	0.8(0.2-2.9)	3	3.0 (0.8-11.3)	3
medium	3.5(1.6-7.6)	8	1.2(0.4-3.5)	4	6.3(2.1-19.3)	4	4.0(1.2-13.7)	4
high	1.3(0.4-4.3)	3	0.8(0.2-2.5)	3	1.0(0.1-7.9)	1	2.4 (0.3-19.7)	1
	LD P trend=0.04		LD P trend=0.69		LD P trend=0.07		LD P trend=0.05	
	IWLD P trend=0.19		IWLD P trend=0.89		IWLD P trend=0.12		IWLD P trend=0.13	
Chlorimuron-ethyl (Sulfonylurea)								
None	1.0 (ref)	38	1.0 (ref)	29	1.0 (ref)	14	1.0 (ref)	14
low	1.3(0.7-2.6)	11	1.4(0.7-3.0)	9	0.9(0.3-3.1)	3	-	1
medium	2.9(1.4-6.6)	9	1.2(0.4-4.0)	3	2.8(0.9-8.7)	4	-	1
high	0.3(0.1-2.5)	1	1.4(0.5-3.9)	4	0.7(0.9-5.1)	1	-	0
	LD P for trend=0.91		LD P trend=0.21		LD P trend=0.56		LD P for trend=xx	
	IWLD P trend=0.56		IWLD P trend=0.92		IWLD P trend=0.62		IWLD P trend=	
Cyanazine (triazine)								
None	1.0 (ref)	65	1.0 (ref)	46	1.0 (ref)	24	1.0 (ref)	10
low	1.2 (0.7-2.2)	15	1.4 (0.8-2.4)	16	1.9(0.9-3.8)	12	3.7(1.4-9.7)	7
medium	0.9 (0.5-1.6)	16	0.8 (0.4-1.8)	8	1.7(0.8-3.6)	9	2.9 (1.5-7.5)	8
high	1.1(0.6-2.0)	14	1.0 (0.5-2.1)	8	0.8(0.3-2.2)	4	2.6(0.9-7.5)	5
	LD P trend=0.93		LD P trend=0.93		LD P trend=0.87		LD P trend=0.17	

	IWLD P trend=0.35		IWLD P trend=0.47		IWLD P trend=0.68		IWLD P trend=0.15	
2,4-D (Chlorinated Phenoxy)								
None	1.0 (ref)	25	1.0 (ref)	23	1.0 (ref)	9	1.0 (ref)	5
low	0.90(0.5-1.5)	31	0.9(0.5-1.7)	23	1.8(0.8-4.4)	14	1.9 (0.6-6.2)	10
medium	1.2(0.7-2.0)	29	1.0(0.6-1.9)	21	1.0(0.4-2.4)	14	1.7 (0.5-5.6)	9
high	1.3(0.7-2.2)	29	0.7(0.4-1.3)	21	1.4(0.6-3.4)	12	2.2 (0.7-7.2)	9
	LD P trend=0.20		LD P trend=0.23		LD P trend=0.84		LD P trend=0.35	
	IWLD P trend=0.83		IWLD P trend=0.41		IWLD P trend=0.22		IWLD P trend=0.75	
Dicamba (benzoic acid)								
None	1.0 (ref)	39	1.0 (ref)	40	1.0 (ref)	22	1.0 (ref)	6
low	1.5 (0.9-2.6)	23	1.1 (0.6-2.1)	12	1.5(0.7-3.4)	9	3.2 (1.0-9.9)	8
medium	1.5 (0.9-3.4)	20	1.1 (0.6-2.1)	13	1.8(0.90-4.0)	10	5.2(1.6-16.6)	7
high	2.0 (1.1-3.4)	20	0.7 (0.4-1.4)	11	0.7(0.3-1.5)	8	5.1(1.6-16.1)	7
	LD P trend=0.03		LD P trend=0.26		LD P trend=0.32		LD P trend=0.02	
	IWLD P trend=0.04		IWLD P trend=0.35		IWLD P trend=0.22		IWLD P trend=0.02	
EPTC (thio-carbamate)								
None	1.0 (ref)	86	1.0 (ref)	62	1.0 (ref)	40	1.0 (ref)	19
low	1.2(0.6-2.3)	9	1.2(0.6-2.7)	7	-	3	2.1 (0.7-6.0)	4
medium	1.2(0.6-2.5)	8	1.7(0.7-4.2)	5	-	0	2.1 (0.6-7.1)	3
high	1.4(0.6-3.4)	5	0.8(0.3-2.3)	4	-	1	4.9 (1.4-16.7)	3
	LD P trend= 0.41		LD P trend=0.98		LD P trend=0.10		LD P trend=0.01	
	IWLD P trend=0.43		IWLD P trend=0.59		IWLD P trend=0.14		IWLD P trend=0.15	

Glyphosate (isopropyl-amine)								
None	1.0 (ref)	25	1.0 (ref)	19	1.0 (ref)	13	1.0 (ref)	10
low	0.6(0.4-1.1)	32	1.3(0.7-2.6)	23	0.7(0.3-1.7)	15	0.4 (0.1-1.2)	9
medium	1.1(0.6-1.9)	29	1.1(0.5-2.1)	23	0.6(0.2-1.4)	11	0.6 (0.2-1.6)	7
high	1.1(0.6-1.8)	29	0.7(0.4-1.3)	22	0.7(0.3-1.8)	12	0.6 (0.2-1.8)	7
	LD P trend=0.21		LD P trend=0.05		LD P trend=0.66		LD P trend=0.98	
	IWLD P trend=0.18		IWLD P trend=0.19		IWLD P trend=0.83		IWLD P trend=0.75	
Herbicide Oil (petroleum oil)								
None	1.0 (ref)	42	1.0 (ref)	35	1.0 (ref)	17	1.0 (ref)	14
low	1.8(0.8-4.3)	7	1.0(0.4-2.5)	6	1.4(0.3-5.9)	2	-	1
medium	2.6(1.0-6.7)	5	2.8(0.7-11.9)	2	1.1(0.1-8.4)	1	-	1
high	1.0(0.4-2.6)	5	1.4(0.4-4.5)	3	0.5(0.1-3.6)	1	0	0
	LD P trend=0.76		LD P trend=0.55		LD P trend=0.46		LD P trend=xxx	
	IWLD P trend=0.88		IWLD P trend=0.16		IWLD P trend=0.40		IWLD P trend=xxx	
Imazethapyr (imid-azolinone)								
None	1.0 (ref)	68	1.0 (ref)	57	1.0 (ref)	29	1.0 (ref)	12
low	1.0(0.6-1.8)	16	0.7(0.3-1.4)	10	0.7(0.3-1.7)	6	1.6 (0.6-3.8)	8
medium	0.8(0.4-1.6)	11	0.6(0.3-1.4)	6	1.1(0.3-3.5)	6	5.2 (1.6-16.6)	4
high	1.2(0.6-2.2)	12	0.5(0.2-1.2)	3	1.0(0.4-2.8)	5	3.2 (1.0-10.0)	4
	LD P trend=0.71		Ld P trend=0.16		LD P trend=0.90		LD P trend=0.03	
	IWLD P trend=0.95		IWLD P trend=0.34		IWLD P trend=0.83		IWLD P trend=0.03	

Metolachlor (chlor-acetanilide)								
None	1.0 (ref)	52	1.0 (ref)	48	1.0 (ref)	20	1.0 (ref)	10
low	1.2(0.7-2.0)	23	0.9(0.4-2.1)	11	1.4(0.6-3.2)	9	2.7 (1.0-7.0)	9
medium	1.7(0.95-3.2)	17	1.3(0.7-2.4)	12	1.4(0.6-3.7)	9	2.1 (0.6-7.7)	4
high	1.3(0.8-2.3)	18	0.4(0.2-0.9)	9	1.5(0.7-3.6)	8	2.6 (0.9-7.2)	6
	LD P trend=0.19		LD P trend=0.07		LD P trend=0.43		LD P trend=0.19	
	IWLD P trend=0.20		IWLD P trend=0.23		IWLD P trend=0.33		IWLD P trend=0.64	
Metribuzin (Triazinone)								
None	1.0 (ref)	30	1.0 (ref)	35	1.0 (ref)	13	1.0 (ref)	9
low	1.5(0.7-2.9)	11	0.5(0.2-1.4)	5	1.4(0.5-3.9)	5	1.0 (0.2-4.9)	3
medium	2.1(1.1-4.0)	13	0.5(0.1-2.0)	3	0.8(0.2-2.9)	3	2.8 (0.9-8.9)	5
high	1.8(0.6-5.2)	4	0.4(0.1-1.6)	2	1.3(0.2-9.8)	1	-	0
	LD P trend=0.06		LD P trend=0.13		LD P trend=0.88		LD P trend=0.60	
	IWLD P trend=0.03		IWLD P trend=0.21		IWLD P trend=0.10		IWLD P trend=0.43	
Paraquat (bi-pyridylium)								
None	1.0 (ref)	48	1.0 (ref)	37	1.0 (ref)	15	1.0 (ref)	14
low	1.0(0.4-2.4)	5	2.4(0.9-6.7)	4	2.9(0.7-12.7)	2	-	1
medium	1.0(0.2-4.0)	2	0.7-0.2-2.3)	3	1.2(0.3-5.3)	2	-	1
high	1.0(0.3-3.2)	3	0.8(0.2-3.4)	2	1.0(0.1-7.6)	1	-	0
	Ld P trend=0.99		LD P trend=0.23		LD P trend=0.94		LD P trend=xxx	
	IWLD P trend=0.44		IWLD P trend=0.78		IWLD P trend=0.75		IWLD P trend=xxx	

Pendi-methalin (dinitro-aniline)								
None	1.0 (ref)	38	1.0 (ref)	28	1.0 (ref)	11	1.0 (ref)	8
low	1.2(0.6-2.2)	12	1.0(0.4-2.2)	9	1.4(0.5-4.2)	6	1.8 (0.5-6.2)	5
medium	1.2(0.6-2.7)	8	0.92(0.3-2.6)	6	1.5(0.4-5.4)	4	2.3 (0.6-8.9)	4
high	0.8(0.3-1.9)	6	0.8(0.3-2.1)	5	1.4(0.5-4.5)	4	1.8 (0.5-6.9)	3
	LD P trend=0.66		LD P trend=0.66		LD P trend=0.57		LD P trend=0.42	
	IWLD P trend=0.44		IWLD P trend= 0.88		IWLD P trend=0.49		IWLD P trend=0.70	
Trifluralin (dinitro-aniline)								
None	1.0 (ref)	45	1.0 (ref)	43	1.0 (ref)	25	1.0 (ref)	10
low	1.1(0.7-1.9)	23	0.9(0.5-1.7)	14	0.9(0.4-1.9)	8	1.2 (0.4-3.2)	7
medium	1.6(0.9-2.6)	21	0.8(0.4-1.7)	11	0.8(0.4-1.8)	8	2.7 (1.0-7.0)	7
high	1.1(0.6-1.9)	15	0.6(0.3-1.2)	11	0.8(0.3-1.9)	7	3.3 (1.2-9.1)	6
	LD P trend= 0.08		LD P trend=0.13		LD P trend=0.62		LD P trend=0.01	
	IWLD P trend=0.80		IWLD P trend=0.11		IWLD P trend=0.65		IWLD P trend=0.08	
2,4,5 T								
None	1.0 (ref)	37	1.0 (ref)	33	1.0 (ref)	14	1.0 (ref)	12
low	2.1(1.1-3.9)	14	1.3(0.6-3.0)	7	4.6(1.3-16.1)	3	-	3
medium	2.4(0.7-7.00	3	0.9(0.2-3.7)	2	2.1(0.6-7.2)	3	-	0
high	1.1(0.4-2.8)	5	1.3(0.4-4.3)	3	1.1(0.2-4.8)	2	-	1
	LD P trend= 0.33		LD P trend=0.71		LD P trend=0.73		LD P trend=xxx	
	IWLD P trend=0.83		IWLD P trend=0.90		IWLD P trend=0.80		IWLD P trend=0.97	

[1] Age adjusted (<45,45-49,50-54,55-59,60-64,65-69,≥70)

[2] Numbers do not sum to NHL subtype totals due to missing data

Supplemental Table 4. Insecticides, fungicide and fumigant exposure (life-time days) and age-adjusted risk of NHL by cell type (1993 through 2008).

	CLL, SLL, PLL, MCL		Diffuse Large B-cell		Follicular B-cell		Other B-cell types	
	RR (95% CI)	n	RR (95% CI)	n	RR (95% CI)	n	RR (95% CI)	n
Aldicarb								
None	1.0 (ref)	51	1.0 (ref)	40	1.0 (ref)	19	1.0 (ref)	15
low	1.9(0.3-13.4)	1	1.7(0.4-7.2)	2	6.1(0.8-45.7)	1	-	1
medium	0.95(0.1-6.9))	1	4.8(1.2-19.8)	2	1.2(0.2-9.4)	2	-	1
high	-	0	0.5(0.1-4.1)	1	-	0	-	0
	LD P trend=0.15		LD P trend=0.72		LD P trend=0.63		LD P trend=xxx	
	IWLD P trend=0.14		IWLD P trend=0.89		IWLD P trend=0.64		IWLD P trend=xxx	
Carbaryl								
None	1.0 (ref)	32	1.0 (ref)	23	1.0 (ref)	9	1.0 (ref)	9
low	1.1(0.5-2.2)	15	0.7(0.3-1.5)	10	1.1(0.3-4.0)	5	xxx-	6
medium	1.0(0.2-4.2)	2	1.3(0.6-3.0)	8	1.8(0.6-5.9)	4	xxx-	0
high	0.4(0.2-0.8)	8	1.5(0.7-3.5)	8	1.3(0.4-4.1)	4	xxx-	1
	LD P trend=0.007		LD P trend=0.19		LD P trend=0.66		LD P trend=xxx	
	IWLD P trend=0.02		IWLD P trend=0.27		IWLD P trend=0.81		IWLD P trend=xxx	
Carbofuran								
None	1.0 (ref)	67	1.0 (ref)	58	1.0 (ref)	33	1.0 (ref)	19
low	1.4(0.8-2.5)	15	0.9(0.4-1.9)	8	0.96(0.4-2.5)	5	1.0 (0.4-2.7)	5

Comment [lbf74]: It looks like in the main tables you have restricted presenting results when there aren't 5 cases in a cell. You should use the same rules in the supplemtnal tables

medium	1.2(0.6-2.4)	10	0.9(0.4-1.8)	9	1.6(0.7-3.9)	6	1.4(0.2-10.7)	1
high	1.3(0.7-2.4)	12	1.1(0.5-2.9)	5	0.6(0.2-2.0)	3	0.94(0.2-4.1)	2
	LD P trend=0.36		LD P trend=0.81		LD P trend=0.79		LD P trend=0.99	
	IWLD P trend=0.79		IWLD P trend=0.71		IWLD P trend=0.72		IWLD P trend=xxx	
Chlorpyrifos								
None	1.0 (ref)	69	1.0 (ref)	55	1.0 (ref)	26	1.0 (ref)	18
low	0.9(0.5-1.7)	15	1.2(0.6-2.1)	13	1.4(0.7-3.1)	10	0.9(0.3-2.6)	5
medium	1.1(0.7-2.0)	16	1.0(0.5-1.7)	15	1.2(0.5-2.9)	7	4.2(1.7-10.6)	6
high	1.0(0.5-1.7)	14	0.9(0.6-4.0)	7	1.4(0.6-3.4)	6	0.8(0.3-2.3)	4
	LD P trend=0.99		LD P trend=0.66		LD P trend=0.56		LD P trend=0.97	
	IWLD P trend=0.88		IWLD P trend=0.67		IWLD P trend=0.22		IWLD P trend=	
Chlorthalonil								
None	1.0 (ref)	107	1.0 (ref)	84	1.0 (ref)	45	1.0 (ref)	32
low	0.9(0.3-2.9)	3	1.6(0.4-6.6)	2	3.1(0.7-12.6)	2	-	1
medium	0.7(0.2-2.7)	2	1.4(0.3-5.6)	2	1.2(0.3-4.8)	2	-	0
high	0.7(0.2-2.7)	2	0.2(0.1-1.4)	1	0.6(0.1-4.4)	1	-	0
	LD P trend=0.46		LD P trend=0.11		LD P trend=0.61		LD P trend=xxx	
	IWLD P trend=0.96		IWLD P trend=0.17		IWLD P trend=0.41		IWLD P trend=xxx	
Coumaphos								
None	1.0 (ref)	92	1.0 (ref)	72	1.0 (ref)	42	1.0 (ref)	22
low	1.1(0.4-3.1)	4	0.7(0.2-2.3)	3	1.9(0.6-6.0)	3	xxx-	4
medium	2.0(0.8-4.9)	5	2.1(0.5-8.5)	2	0.5(0.1-4.0)	1	xxx-	0

high	1.3(0.4-4.0)	3	1.5(0.4-5.9)	2	2.2(0.3-16.3)	1	-	1
	LD P trend=0.36		LD P trend=0.47		LD P trend=0.43		LD P trend=xxx	
	IWLD P trend=0.53		IWLD P trend=0.74		IWLD P trend=0.82		IWLD P trend=xxx	
Diazinon								
None	1.0 (ref)	40	1.0 (ref)	33	1.0 (ref)	13	1.0 (ref)	12
low	1.5(0.7-3.1)	9	1.2(0.4-3.1)	5	1.6(0.4-5.5)	3	xxx-	2
medium	1.2(0.4-3.6)	5	0.9(0.3-2.8)	4	1.6(0.4-7.4)	3	xxx-	1
high	1.2(0.5-3.0)	5	1.2(0.4-3.8)	3	2.0(0.4-10.0)	2	xxx-	0
	LD P trend=0.72		LD P trend=0.84		LD P trend=0.35		LD P trend=xxx	
	IWLD P trend=0.60		IWLD P trend=0.84		IWLD P trend=0.53		IWLD P trend=xxx	
DDVP								
None	1.0 (ref)	95	1.0 (ref)	74	1.0 (ref)	43	1.0 (ref)	24
low	1.3(0.5-3.5)	4	4.1(1.0-16.9)	2	0.7(0.2-3.1)	2	xxx-	1
medium	1.4(0.6-3.4)	5	0.5(0.1-1.9)	2	2.2(0.3-16.1)	1	xxx-	2
high	0.3(0.1-2.1)	3	0.3(0.1-2.2)	1	0.5(0.1-3.9)	1	-xxx	0
	LD P trend=0.46		LD P trend=0.25		LD P trend=0.54		LD P trend=xxx	
	IWLD P trend=0.85		IWLD P trend=0.54		IWLD P trend=0.53		IWLD P trend=xxx	
Fonofos								
None	1.0 (ref)	79	1.0 (ref)	61	1.0 (ref)	40	1.0 (ref)	17
low	1.6(.8-2.9)	12	1.5(0.8-3.1)	9	-	5	2.2(0.8-5.9)	5
medium	1.2(0.5-2.9)	5	1.0(0.4-2.3)	6	-	0	2.0(0.6-6.7)	3
high	0.9(0.5-2.0)	8	1.3(0.5-3.2)	5	-	2	2.3(0.3-17.0)	1
	LD P trend=0.88		LD P trend=0.62		LD P trend=0.20		LD P trend=0.19	

	IWLD P trend=0.94		IWLD P trend=0.77		IWLD P trend=0.18		IWLD P trend=xxx	
Lindane								
None	1.0 (ref)	41	1.0 (ref)	39	1.0 (ref)	14	1.0 (ref)	14
low	1.6(0.7-3.6)	8	0.7(0.2-3.0)	9	2.7(0.8-9.4)	3	xxx-	1
medium	1.1(0.3-4.8)	3	1.1(0.3-3.7)	6	3.6(0.8-15.9)	2	xxx-	0
high	3.8(1.5-9.6)	5	1.3(0.2-9.7)	5	2.4(0.5-10.4)	2	xxx-	0
	LD P trend=0.005		LD P trend=0.25		LD P trend=0.25		LD P trend=xxx	
	IWLD P trend=0.04		IWLD P trend=0.29		IWLD P trend=0.18		IWLD P trend=xxx	
Malathion								
None	1.0 (ref)	21	1.0 (ref)	16	1.0 (ref)	5	1.0 (ref)	6
low	0.94(0.5-1.8)	17	0.8(0.4-1.7)	16	1.0(0.3-3.6)	6	-xxx	8
medium	0.8(0.4-1.7)	11	0.9(0.4-2.1)	8	1.2(0.3-4.3)	5	-xxx	0
high	0.8(0.4-1.7)	11	1.7(0.8-3.8)	11	1.5(0.4-4.9)	5	-xxx	3
	LD P trend=0.52		LD P trend=0.07		LD P trend=0.48		LD P trend=xxx	
	IWLD P trend=0.24		IWLD P trend=0.33		IWLD P trend=0.56		IWLD P trend=xxx	
Maneb								
None	1.0 (ref)	52	1.0 (ref)	37	1.0 (ref)	19	1.0 (ref)	16
low	2.9(0.9-9.4)	3	2.6(0.6-10.9)	2	2.6(0.4-19.8)	1	-xxx	0
medium	1.6(0.4-6.6)	2	1.3(0.4-4.2)	3	1.1(0.1-8.0)	1	-xxx	0
high	0.3(0.1-2.4)	1	3.5(0.5-25.4)	1	-	0	-xxx	0
	LD P trend=0.43		LD P trend=0.19		LD P trend=0.55		LD P trend=xxx	
	IWLD P trend=0.49		IWLD P trend=0.17		IWLD P trend=0.66		IWLD P trend=xxx	

Metalaxyl								
None	1.0 (ref)	46	1.0 (ref)	34	1.0 (ref)	18	1.0 (ref)	
Low	3.9(1.7-9.3)	6	1.1(0.3-3.6)	4	0.8(0.2-3.4)	2	-xxx	
medium	1.3(0.3-5.4)	2	1.4(0.5-3.9)	5	2.1(0.5-9.2)	2	-xxx	
high	0.4(0.1-1.2)	3	0.9(0.2-4.0)	2	0.9(0.1-6.4)	1	-xxx	
	LD P trend=0.08		LD P trend=0.92		LD P trend=0.81		LD P trend=xxx	
	IWLD P trend=0.04		IWLD P trend=0.85		IWLD P trend=0.83		IWLD P trend=xxx	
Methylbromide								
None	1.0 (ref)	101	1.0 (ref)	65	1.0 (ref)	45	1.0 (ref)	14
low	0.8(0.3-2.1)	4	4.8(2.5-9.3)	10	1.4(0.3-5.8)	2	-xxx	1
medium	0.7(0.3-1.6)	5	1.3(0.6-3.1)	6	1.2(0.4-4.0)	3	-xxx	1
high	0.4(0.1-1.3)	3	1.2(0.5-2.6)	7	-	0	-xxx	0
	LD P trend=0.09		LD P trend=0.71		LD P trend=0.08		LD P trend=xxx	
	IWLD P trend=0.02		IWLD P trend=0.57		IWLD P trend=0.09		IWLD P trend=xxx	
Permethrin animals								
None	1.0 (ref)	95	1.0 (ref)	78	1.0 (ref)	38	1.0 (ref)	25
low	1.3(0.5-3.3)	5	0.2(0.1-1.3)	1	2.8(1.1-7.0)	5	-xxx	1
medium	0.9(0.2-3.7)	3	0.5(0.1-3.4)	1	2.9(0.7-12.0)	2	-xxx	2
high	0.8(0.3-2.5)	3	-	0	0.8(0.2-3.5)	2	-xxx	0
	LD P trend=0.75		LD P trend=0.19		LD P trend=0.93		LD P trend=0.87	
	IWLD P trend=0.70		IWLD P trend=0.29		IWLD P trend=0.73		IWLD P trend=xxx	
Permethrin crops								

None	1.0 (ref)	86	1.0 (ref)	72	1.0 (ref)	39	1.0 (ref)	23
low	1.9(0.6-5.4)	6	0.6(0.1-2.2)	3	1.1(0.3-3.5)	3	-xxx	4
medium	0.8(0.4-1.9)	6	2.7(0.7-10.6)	2	1.5(0.4-6.4)	2	-xxx	0
high	1.2(0.4-4.0)	4	0.4(0.1-1.8)	2	0.5(0.1-3.9)	2	-xxx	0
	LD P trend=0.76		LD P trend=0.28		LD P trend=0.57		LD P trend=0.37	
	IWLD P trend=0.70		IWLD P trend=0.33		IWLD P trend=0.45		IWLD P trend=xxx	
Phorate								
None	1.0 (ref)	36	1.0 (ref)	29	1.0 (ref)	15	1.0 (ref)	10
low	1.4(0.7-3.0)	9	1.0(0.4-2.6)	5	0.6(0.1-2.7)	2	1.4 (0.4-4.6)	4
medium	1.4(0.6-3.2)	6	2.0(0.9-4.7)	7	2.9(0.96-8.7)	4	1.5 (0.2-11.6)	1
high	0.94(0.4-2.4)	5	0.7(0.2-2.4)	3	-	0	1.4 (0.2-11.2)	1
	LD P trend=0.90		LD P trend=0.92		LD P trend=0.82		LD P trend=XXX	
	IWLD P trend=0.53		IWLD P trend=0.98		IWLD P trend=0.33		IWLD P trend=xxx	
Terbufos								
None	1.0 (ref)	53	1.0 (ref)	47	1.0 (ref)	26	1.0 (ref)	10
low	1.8(1.0-3.1)	17	0.9(0.4-1.7)	12	2.5(1.1-5.4)	8	2.3 (0.8-6.6)	6
medium	2.2(1.3-3.6)	21	2.2(1.2-4.2)	12	1.8(0.7-4.3)	7	3.1(1.1-9.2)	5
high	1.4(0.8-2.6)	13	1.1(0.5-2.3)	10	0.7(0.3-1.8)	6	4.1(1.4-11.9)	5
	LD P trend=0.16		LD P trend=0.34		LD P trend=0.54		LD P trend=0.01	
	IWLD P trend=0.14		IWLD P trend=0.40		IWLD P trend=0.18		IWLD P trend=xxx	

[1]Age adjusted (<45,45-49,50-54,55-59,60-64,65-69,≥70)

Supplemental Table 5. Estimated individual and joint effects of pesticide combinations and age-adjusted risk of NHL		
Individual and joint pesticide exposures	**Exposed cases**	**Poisson Regression RR (95% CI)[1]**
Chlordane and DDT		
--Neither	174	1.0 (reference)
--Chlordane only	19	0.6 (0.4-1.0)
--DDT only	49	0.8(0.6-1.2)
--Both	56	0.9 (0.7-1.3)
Chlordane and Lindane		
--Neither	200	1.0 (reference)
--Chlordane only	47	0.8(0.6-1.2)
--Lindane only	23	1.0(0.6-1.5)
--both	28	1.0(0.7-1.6)
Lindane and dicamba		
--Neither	113	1.0 (reference)
--Lindane only	15	1.0 (0.6-1.7)
--dicamba only	120	1.3 (0.98-1.6)
--both	32	1.2 (0.8-1.8)
Atrazine and Chlordane		
--Neither	58	1.0 (reference)
--atrazine only	162	1.3(0.97-1.8)
--Chlordane only	19	1.0(0.6-1.7)
--Both	57	1.1(0.8-1.6)
2,4,5 t and Lindane		
--Neither	190	1.0 (reference)
--2,4,5-t only	57	1.1(0.9-1.6)

Comment [a75]: Need to delete No really interesting findings, no space Timing of pesticides not possible

--Lindane only	27	1.1(0.7-1.6)
--Both	25	1.2 (0.8-1.8)
Atrazine and Lindane		
--Neither	73	1.0 (reference)
--Atrazine only	173	1.1 (0.9-1.5)
--Lindane only	4	0.5 (0.2-1.3)
--both	47	1.3 (0.9-1.9)
Atrazine and Dicamba		
--Neither	61	1.0 (reference)
--Atrazine only	72	1.0 (0.7-1.4)
--Dicamba only	17	1.0 (0.6-1.7)
--both	140	1.3 (0.97-1.8)
Atrazine and Carbofuran		
--Neither	68	1.0 (reference)
--Atrazine only	132	1.1 (0.9-1.5)
--Carbofuran only	9	0.9 (0.4-1.8)
--Both	81	1.2 (0.9-1.6)
Atrazine and Diazinon		
--Neither	58	1.0 (reference)
--atrazine only	163	1.2 (0.9-1.7)
--Diazinon only	20	0.9 (0.5-1.5)
--Both	59	1.1 (0.8-1.6)
Atrazine and alachlor		
--Neither	65	1.0 (reference)
--atrazine only	73	1.1 (0.8-1.5)

--alachlor only	16	0.8 (0.5-1.4)
--Both	146	1.1 (0.8-1.5)
2,4, 5 t and dicamba		
--Neither	94	1.0 (reference)
--2,4,5-t only	32	1.3 (0.9-1.9)
--dicamba only	107	1.4 (1.0-1.8)
--Both	45	1.3 (0.9-1.8)
2,4-D and Chlordane		
--Neither	55	1.0 (reference)
--2,4-D only	164	1.1(0.8-1.5)
--Chlordane only	7	0.7(0.3-1.5)
--Both	70	1.0 (0.7-1.5)
Glyphosate and atrazine		
--Neither	30	1.0 (reference)
--Glyphosate only	60	0.96(0.6-1.5)
--atrazine only	63	1.4(0.9-2.1)
--Both	171	1.1(0.7-1.6)
Glyphosate and 2,4-D		
--Neither	32	1.0 (reference)
--Glyphosate only	44	1.1(0.7-1.7)
--2,4-D only	61	1.4(0.9-2.1)
--Both	188	1.1(0.7-1.5)
Glyphosate and Chlordane		
--Neither	72	1.0 (reference)
--Glyphosate only	147	0.9 (0.7-1.2)

--chlordane only	13	1.0 (0.5-1.7)
--Both	64	0.8 (0.6-1.1)
2,4-D and Lindane		
---Neither	60	1.0 (reference)
---only 2,4-D	180	1.1(0.8-1.4)
---only lindane	3	0.6(0.2-1.8)
---both	48	1.2(0.8-1.7)
2,4-D and atrazine		
---Neither	41	1.0 (reference)
---only 2,4-D	49	1.0(0.7-1.5)
---only atrazine	35	1.2(0.8-1.9)
---both	199	1.2(0.8-1.7)
2,4-D and dicamba		
---Neither	51	1.0 (reference)
---only 2,4-D	81	0.9(0.6-1.3)
---only dicamba	13	1.2(0.7-2.2)
---both	144	1.2(0.9-1.7)
2,4-D and cyanazine		
---Neither	58	1.0 (reference)
---only 2,4-D	104	0.9(0.6-1.2)
---only cyanazine	11	0.9(0.5-1.7)
---both	130	1.2(0.9-1.6)
2,4-D and terbufos		
---Neither	48	1.0 (reference)
---only 2,4-D	113	1.0(0.7-1.5)

---only terbufos	16	1.7(0.97-3.0)
---both	115	1.5(1.0-2.0)
Cyanazine and atrazine		
---Neither	72	1.0 (reference)
---only cyanazine	11	1.3(0.7-2.4)
---only atrazine	90	1.0(0.8-1.4)
---both	130	1.3(0.97-1.7)

[1]Age adjusted (<45,45-49,50-54,55-59,60-64,65-69,≥70)

Appendix 1.
Frequency of NHL in Agricultural Health Study applying New (InterLymp hierarchial classification of lymphoid neoplasms) and Older Definitions (ICD-O-3)

Lymphoma category and type (ICD-O-3 codes)[1]	**Number NHL cases, new definition (InterLymph hierarchical classification)**[1]	**Number cases NHL, older definition (ICD-O-3)**[2]	**SEER Recode**[1]
CLL/SLL/PLL/MCL (Mature NHL, B-cell)			
Small lymphocytic lymphoma (9670)	27	27	08
Chronic lymphocytic leukemia/small lymphocytic lymphoma (9823)	74	0	08
Mantle -cell lymphoma (9673)	16	16	10
Diffuse Large B-cell Lymphoma (Mature NHL, B-cell)			
DLBCL (9680)	94	94	13
Follicular Lymphoma (Mature NHL, B-cell)			
Follicular lymphoma (9690, 9691,9695,9698)	53	53	21
Other B-cell Types			
Precursor acute lymphoblastic leukemia/lymphoma (9835(B), 9836)	4	0	07
Waldenstrom macroglobulinemia (9761)	2	0	12
Lymphoplasmacytic lymphoma (9671)	2	2	11
Hairy-cell leukemia (9940)	6	0	22
NHL, NOS (9591(B), 9675(B))	6	6	26
Burkitt lymphoma/leukemia (9687)	1	1	17
Extranodal marginal zone lymphoma (MZL), Malt type & Nodal MZL (9699)	13	13	19, 20
Plasma cell neoplasms			
Plasmacytoma (9734, 9731)	6	0	23
Multiple myeloma (9732)	77	0	24
Other NHL Types			
Precursor acute lymphoblastic leukemia/lymphoma (9835(T), 9837)	1	0	27
Mycosis fungoides (9700)	6	6	28
Peripheral T-cell lymphoma, NOS (9702)	2	2	30
Anaplastic large cell lymphoma, T or null cell (9714)	2	2	33
Enteropathy type T-cell lymphoma (9717)	1	1	35
Primary cutaneous anaplastic large cell lymphoma (9718)	1	1	37
T-cell lymph, nasal-type/aggressive NK leukemia (9719)	1	1	39
NHL, NOS (9591(T))	1	1	42
Lymphoid leukemia, NOS (9820(U))	1	0	
Precursor acute lymphoblastic leukemia/lymphoma (9727(U), 9835(U))	3	1	43
NHL, NOS (9591(U), 9675(U))	6	6	45
Lymphoid neoplasm, NOS (9590(U))	10	10	47
Total	416	243	

Lineage: B=B-cell, T=T-cell, U=Unknown
[1] http://seer.cancer.gov/lymphomarecode based on Morton LM et al. Blood, 2007;110:695-708.
[2] Percy C. et al., Lyon, France: IARC Press: 2001.

Comment [CL76]: This was originally coded as 9713, which is an ICD-O-2 code, which becomes 9719 in ICD-O-3. Since we are presenting ICD-O-codes in this table, I have changed this code to 9719

Comment [CL77]: Since IA and NC cancer registries are not yet using 2008 WHO codes, the reference for this table should be the Morton LM et al publication noted here. This reference should also be noted in the text. Reference to the 2010 blood paper should not be noted in regard to the NHL classification used in this paper.

Appendix 2. Pesticide Classification by Chemical/Functional Class	
Chemical/functional class	**Pesticide**
Acetamide herbicide	Metolachlor, alachlor
Carbamate herbicde	Butylate, EPTC
Other herbicides	Chloromuron ethyl, 2,4-D, dicamba, glyphosate, herbicide oil, imazethapyr Paraquat, pendimethalin, 2,4,5-T, 2,4,5TP, trifluralin
Triazine/triazinone herbicides	Atrazine, cyanazine, metribuzin
Carbamate insecticides	Carbofuran, aldicarb, carbaryl
Chlorinated insecticides	Aldrin, chlordane, DDT, dieldrin, heptachlor, lindane, toxaphine
Organophosphate insecticides	Chlorpyrifos, coumaphos, diazinon, dichlorvos, fonofos, malathion, parathion, phorate, terbufos
Other insecticides	Permethrin (crops & animals), trichlorfon
Fungicides	Benomyl, chlorthalonil, captan, maneb/mancozeb, methylaxyl, ziram
Fumigants	Methyl bromide, aluminum phosphate, ethylene dibromide, carbon tetra chloride/carbondisulfide

Supplemental table 7: Pesticide exposures (total days and intensity weight total days) age- adjusted risks of NHL incidence (1993 through 2008)[old nhl definition; n=243].

	NHL Cases	RR[1] (95%) by Total Days of Exposure	NHL Cases	RR[1] (95% CI) Intensity-weighted days of exposure
Insecticides, Fungicides and Fumigants				
		P trend=		
Carbaryl (carbamate-insecticide)				
None	56	1.0 (ref)	56	1.0 (ref)
Low	19	0.8 (0.5-1.3)	19	0.9(0.6-1.6)
Medium	20	0.9(0.5-1.5)	20	0.7(0.4-1.2)
High	18	1.1(0.6-1.8)	18	1.2(0.7-2.0)
		P trend=0.64		P trend=0.42
Carbofuran (carbamate-insecticide)				
None	140	1.0 (ref)	140	1.0 (ref)

Low	26	1.2(0.8-1.8)	22	1.0(0.7-1.7)
Medium	18	1.1 (0.7-1.7)	21	1.0 (0.6-1.6)
High	21	1.1(0.7-1.7)	21	1.3(0.8-2.0)
		P trend=0.70		P trend=0.37
Chlorpyrifos (organophosphate-insecticide)				
None	134	1.0 (ref)	134	1.0 (ref)
Low	33	1.2(0.8-1.8)	30	1.2(0.8-1.8)
Medium	33	1.2(0.8-1.8)	30	0.9 (0.6-1.3)
High	32	0.9(0.6-1.3)	29	1.2 (0.8-1.7)
		P trend=0.50		P trend=0.56
Coumaphos				
None	186	1.0(ref)	186	1.0 (ref)
Low	9	1.3(0.7-2.5)	7	1.6(0.7-3.3)
Medium	7	1.1(0.5-2.3)	8	1.1(0.5-2.2)
High	5	1.4(0.6-3.4)	6	1.2(0.5-2.7)
		P trend=0.45		P trend=0.65
Diazinon (organophosphosphorous-insecticide)				
None	80	1.0 (ref)	80	1.0 (ref)
Low	12	1.0(0.6-1.9)	10	1.0(0.5-2.0)
Medium	8	0.9(0.4-1.9)	10	1.1(0.6-2.1)
High	9	1.2(0.6-2.4)	9	1.1(0.5-2.1)
		P trend=0.66		P trend=0.82
DDVP				
None	190	1.0(ref)	190	1.0 (ref)
Low	6	1.0(0.4-2.1)	6	1.1 (0.5-2.5)
Medium	6	0.9(0.4-2.0)	6	0.6(0.3-1.3)

High	5	0.6(0.3-1.6)	5	1.0(0.4-2.4)
		P trend=0.30		P trend=0.99
Fonofos				
None	163	1.0(ref)	163	1.0 (ref)
Low	18	1.1(0.7-1.8)	15	1.3(0.8-2.2)
Medium	13	1.1(0.6-2.0)	15	1.3(0.8-2.2)
Low	13	0.9(0.5-1.5)	14	0.7(0.4-1.2)
		P trend=0.		P trend=0 19
Malathion (organophosphorous-insecticide)				
None	39	1.0 (ref)	39	1.0 (ref)
Low	32	1.0(0.6-1.6)	26	1.1(0.7-1 8)
Medium	23	0.8(0 5-1.3)	27	0.7(0.4-1.2)
High	23	1.0 (0.6-1.7)	25	1 0(0.6-1.7)
		P trend=0.70		P trend=0.79
Metalaxyl				
None	91	1.0 (ref)	91	1.0 (ref)
Low	12	1.0 (0.5-1.8)	7	0.8(0.4-1.7)
Medium	3	0.7 (0.2-2 1)	7	1.1(0.5-2.4)
High	5	0.8 (0.3-2.0)	6	0.8(0 3-1.7)
		P trend=0.56		P trend=0.62
Methylbromide				
None	189	1.0 (ref)	189	1 0 (ref)
Low	16	2.7(1.6-4.5)	15	2.6 (1.6-4.5)
Medium	13	1.3(0.7-2.2)	13	1.5(0.8-2.6)
High	13	0.7(0.4-1.2)	13	0.6(0.4-1.1)
		P trend=0.24		P trend=0.07
Permethrin Animals				

(pyrethroid-insecticide)				
None	189	1.0 (ref)	189	1.0 (ref)
Low	9	1.1(0.6-2.2)	7	1.3(0.6-2.8)
Medium	5	0.9(0.4-2.1)	7	0.7(0.3-1.6)
High	6	0.7(0.3-1.5)	6	0.7(0.3-1.7)
		P trend= 0.27		P trend=0.04
Phorate (organophosphate-insecticide)				
None	72	1.0 (ref)	72	1.0 (ref)
low	15	1.0(0.6-1.8)	12	1.3(0.7-2.5)
medium	15	2.3(1.3-4.1)	12	1.2(0.7-2.3)
high	5	0.5(0.2-1.2)	11	0.9(0.5-1.6)
		P for trend=0.53		P for trend=00.86.
Terbufos (organophosphorous-insecticide)				
None	114	1.0 (ref)	114	1.0 (ref)
Low	40	1.4(0.94-1.9)	31-	1.3(0.9-1.9)
Medium	26	1.9(1.2-2.8)	31	1.7(1.2-2.6)
High	26	1.2(0.8-1.9)	30	1.3(0.9-2.0)
		P trend=0.24		P trend=0.16
Chlorinated insecticides				
Aldrin				
None	86	1.0 (ref)	86	1.0 (ref)
Low	9	0.8(0.4-1.6)	9	1.0(0.5-1.9)
Medium	8	0.7(0.4-1.5)	7	0.7(0.3-1.5)
High	6	2.4(1.0-5.4)	7	1.3(0.6-2.9)
		P trend=0.21		P trend=0.86
Chlordane				

None	78	1.0 (ref)	78	1.0 (ref)
Low	10	1.2(0.7-2.0)	10	1.5(0.8-2.9)
Medium	8	1.3(0.7-2.4)	9	1.0(0.4-2.3)
High	10	1.0(0.9-1.1)	9	1.1(0.6-2.1)
		P trend=0.89		P trend=0.77
DDT				
None	71	1.0 (ref)	71	1.0 (ref)
Low	14	0.9(0.5-1.7)	13	1.1(0.6-2.2)
Medium	12	1.4(0.7-2.6)	12	1.0(0.5-1.8)
High	11	1.1(0.6-2.2)	12	1.3(0.7-2.4)
		P trend=0.61		P trend=0.47
Dieldrin				
None	101	1.0 (ref)	101	1.0 (ref)
Low	3	0.9(0.3-2.9)	3	1.9(0.6-5.9)
Medium	3	2.9(0.9-9.2)	2	1.3(0.3-5.2)
High	1	1.1(0.1-7.7)	2	0.9(0.2-3.8)
		P trend=0.47		P trend=0.97
Heptachlor				
None	88	1.0 (ref)	88	1.0 (ref)
Low	8	0.9(0.7-2.6)	7	1.2(0.6-2.4)
Medium	8	**1.4(0.7-2.6)**	**8**	**1.7(0.7-3.8)**
High	5	1.1(0.6-2.2)	6	1.4(0.6-3.3)
		P trend=0.26		P trend=0.42
Lindane				
None	86	1.0 (ref)	86	1.0 (ref)
Low	7	1.0(0.5-2.1)	7	1.1(0.5-2.3)
Medium	8	1.2(0.6-2.4)	7	1.0(0.5-2.2)
High	6	3.7(1.6-8.4)	6	2.8(1.2-6.4)

		P trend=0.0.01		P trend=0.04
Toxaphene				
None	90	1.0 (ref)	90	1.0 (ref)
Low	8	1.2(0.6-2.5)	6	1.6(0.7-3.5)
Medium	4	4.4(1.6-12.1	7	1.3(0.6-3.0)
High	6	0.9(0.4-2.0)	5	0.9(0.4-2.3)
		P trend=0.66		P trend=0.83
Herbicides				
Alachlor (acetamide-herbicide)				
None	96	1.0 (ref)	96	1.0 (ref)
Low	39	1.1(0.8-1.6)	38	1.1(0.7-1.6)
Medium	45	0.9(0.6-1.2)	40	0.8 (0.6-1.2)
High	31	1.4(0.9-2.0)	36	1.4(0.96-2.1)
		P trend=0.22		P trend=0.09
Atrazine (triazine-herbicide)				
None	59	1.0 (ref)	59	1.0 (ref)
Low	64	1.1(0.8-1.6)	58	1.1(0.8-1.6)
Medium	56	1.3(0.9-1.9)	59	1.2(0.9-1.8)
High	55	1.2(0.8-1.7)	57	1.3(0.9-1.8)
		P trend=0.52		P trend=0.27
Butylate (thiocarbamate-herbicide)				
None	75	1.0 (ref)	75	1.0 (ref)
Low	14	0.9 (0.5-1.6)	12	0.9(0.5-1.6)
Medium	15	3.4(1.9-5.9)	11	2.7(1.4-5.0)
High	5	1.1(0.4-2.7)	11	1.6(0.9-3.0)

		P trend=0.005		P trend=0.049
Chlorimuron-ethyl (benzoic acid ester-herbicide)				
None	75	1.0 (ref)	75	1.0 (ref)
low	20	1.1(0.7-1.9)	13	1.1(0.6-2.0)
medium	11	1.5(0.8-2.9)	12	1.3(0.7-2.4))
high	6	0.7(0.3-1.7)	12	1.0(0.5-1.9)
		P for trend=0.73		P for trend=0.94
Cyanazine (triazine-herbicide)				
None	114	1.0 (ref)	114	1.0 (ref)
Low	41	1.4(0.95-1.9))	33	1.2(0.8-1.7)
Medium	32	1.3(0.9-1.9)	32	1.3(0.9-1.9)
High	25	1.1(0.7-1.6)	32	1.2(0.8-1.8)
		P for trend=0.0.89		P for trend=0.34
Dicamba (benzoic-herbicide)				
None	92	1.0 (ref)	92	1.0 (ref)
Low	39	1.5(1.0-2.2)	38	1.2(0.8-1.8)
Medium	38	1.2(0.8-1.8)	39	1.4(0.9-2.0)
High	38	1.0(0.7-1.5)	37	1.0(0.7-1.5)
		P trend=0.64		P trend=0.95
2,4-D (phenoxy-herbicide)				
None	53	1.0 (ref)	53	1.0 (ref)
Low	60	0.9(0.6-1.3)	59	0.9(0.6-1.4)
Medium	59	1.0(0.7-1.5)	60	1.0(0.7-1.4)
High	59	0.9(0.6-1.3)	58	0.9(0.6-1.3)

		P trend=0.61		P trend=0.69
EPTC (thiocarbamate-herbicide)				
None	164	1.0 (ref)	164	1.0 (ref)
Low	21	1.3(0.9-2.1)	15	1.4(0.8-2.4)
Medium	9	1.1(0.6-2.2)	12	1.1(0.6-2.0)
High	10	0.8(0.4-1.5)	13	0.8(0.5-1.5)
		P trend=0.39		P trend=0.61
Glyphosate (phosphinic acid-herbicide)				
None	48	1.0 (ref)	48	1.0 (ref)
Low	72	1.0(0.7-1.4)	61	1.1(0.7-1.6)
Medium	51	0.7(0.5-1.0)	61	0.7(0.5-1.0)
High	60	1.0(0.7-1.4)	60	0.9(0.6-1.4)
		P trend=0.79		P trend=0.0.99
Herbicide Oil				
None	84	1.0 (ref)	84	1.0 (ref)
Low	9	1.0(0.5-1.9)	9	1.2(0.6-2.4)
Medium	10	1.8(0.95-3.6)	10	1.1(0.6-2.1)
High	8	1.1(0.6-2.6)	8	1.5(0.7-3.1)
		P trend=0.62		P trend=0.29
Imazethapyr (imidazolinone-herbicide)				
None	132	1.0 (ref)	132	1.0 (ref)
Low	30	0.9(0.6-1.3)	25	1.0(0.6-1.5)
Medium	20	0.8(0.5-1.2)	25	0.8(0.5-1.3)
High	24	0.9(0.6-1.4)	24	0.8(0.5-1.2)
		P trend=0.50		P trend=0.64

Metolachlor				
None	101	1.0 (ref)	101	1.0(ref)
Low	36	1.2(0.8-1.8)	35	1.1(0.8-1.7)
Medium	36	1.3(0.9-1.9)	36	1.4(0.9-2.0)
High	34	1.1(0.7-1.6)	34	1.1(0.8-1.6)
		P trend=0.73		P trend=0.71
Metribuzin (triazine-herbicide)				
None	70	1.0 (ref)	70	1.0 (ref)
Low	15	0.8 (0.5-1.5)	14	0.9(0.5-1.6)
Medium	20	1.2(0.7-2.0)	14	1.1(0.6-2.0)
High	6	1.1 (0.5-2.5)	13	1.2(0.6-2.1)
		P trend=0.0.59		P trend=0.55
Paraquat				
None	88	1.0 (ref)	88	1.0(ref)
Low	8	2.1(1.0-4.3)	8	4.8(2.3-9.9)
Medium	8	0.8(0.4-1.7)	7	0.7(0.3-1.5)
High	6	1.0(0.4-2.3)	7	0.9(0.4-2.0)
		P trend=0.91		P trend=0.73
Pendimethalin				
None	63	1.0 (ref)	63	1.0(ref)
Low	22	1.3(0.8-2.0)	19	1.5(0.9-2.5)
Medium	17	1.3(0.8-2.3)	19	1.0(0.6-1.7)
High	17	1.1(0.6-1.9)	18	1.3(0.8-2.2)
		P trend=0.68		Ptrend=0.43
Permethrin (Crop)				
None	179	1.0 (ref)	179	1.0 (ref)
Low	12	1.0(0.6-1.9)	9	1.4(0.7-2.7)

Medium	6	2.2(1.0-5.1)	9	1.2(0.6-2.4)
High	8	0.6(0.3-1.2)	8	0.6(0.3-1.2)
		P trend=0.18		P trend=0.15
Trifluralin (dinitroaniline-herbicide)				
None	104	1.0 (ref)	104	1.0 (ref)
Low	39	1.0 (0.7-1.5)	37	1.0(0.7-1.4)
Medium	40	1.0(0.7-1.4)	36	1.0(0.7-1.4)
High	29	0.8(0.6-1.3)	34	0.9(0.6-1.3)
		P trend=0.0.36		P trend=0.44
2,4,5 T (phenoxyacetic acid)				
None	73	1.0 (ref)	73	1.0 (ref)
low	22	1.9(1.2-3.1)	13	2.0(1.1-3.6)
medium	3	1.3(0.4-4.3)	12	1.8(0.99-3.4)
high	12	1.5(0.8-4.3)	12	1.4(0.7-2.5)
		P for trend=0.0.27		P for trend=0.94

Carbofuran								
None	1.0(ref)	67	1.0(ref)	58	1.0(ref)	33	1.0(ref)	19
Low	1.4 (0.8-2.5)	15	0.9 (0.4-1.9)	8	0.96(0.4-2.5)	5	1.0(04-2.7)	5
Medium	1.2 (0.6-2.4)	10	0.9 (0.4-1.8)	9	1.6(0.7-3.9)	6	1.4(0.2-10.7)	1
High	1.3 (0.7-2.4)	12	1.1 (0.5-2.9)	5	0.6(0.2-2.0)	3	0.94(0.2-4.1)	2
	P trend=0.36		P trend=0.81		P trend=0.79		P trend=0.99	
Chlorpyrifos								
None	1.0 (ref)	69	1.0 (ref)	55	1.0 (ref)	26	1.0 (ref)	18
Low	0.9(0.5-1.7)	15	1.2(0.6-2.1)	13	1.4(0.7-3.1)	10	0.9(0.3-2.6)	5
Medium	1.1(0.7-2.0)	16	1.0(0.5-1.7)	15	1.2(0.5-2.9)	7	4.2(1.7-10.6)	6
High	1.0(0.5-1.7)	14	0.9(0.6-4.0)	7	1.4(0.6-3.4)	6	0.8(0.3-2.3)	4
	P trend=0.99		P trend=0.66		P trend=0.56		P trend=0.97	
Diazinon								
None	1.0 (ref)	40	1.0 (ref)	33	1.0 (ref)	13	1.0 (ref)	12
Low	1.5(0.7-3.1)	9	1.2(0.4-3.1)	5	1.6(0.4-5.5)	3	xxx	2
Medium	1.2(0.4-3.6)	5	0.9(0.3-2.8)	4	1.6(0.4-7.4)	3	xxx-	1
High	1.2(0.5-3.0)	5	1.2(0.4-3.8)	3	2.0(0.4-10.0)	2	xxx	0
	P trend=0.72		P trend=0.84		P trend=0.35		P trend=xxx	
Permethrin animals								
None	1.0 (ref)	95	1.0 (ref)	78	1.0 (ref)	38	1.0 (ref)	25
Low	1.3(0.5-3.3)	5	Xxx	1	2.8(1.1-7.0)	5	xxx-	1
Medium	0.9(0.2-3.7)	3	xxx	1	2.9(0.7-12.0)	2	-xxx	2
High	0.8(0.3-2.5)	3	-xxx	0	0.8(0.2-3.5)	2	-xxx	0
	P trend=0.75		P trend=xxx		P trend=0.93		P trend=xxx	
Cyanazine								

(triazine)								
None	1.0 (ref)	65	1.0 (ref)	46	1.0 (ref)	24	1.0 (ref)	10
Low	1.2 (0.7-2.2)	15	1.4 (0.8-2.4)	16	1.9(0.9-3.8)	12	3.7(1.4-9.7)	7
Medium	0.9 (0.5-1.6)	16	0.8 (0.4-1.8)	8	1.7(0.8-3.6)	9	2.9 (1.5-7.5)	8
High	1.1(0.6-2.0)	14	1.0 (0.5-2.1)	8	0.8(0.3-2.2)	4	2.6(0.9-7.5)	5
	P trend=0.93		P trend=0.93		P trend=0.87		P trend=0.17	

20. Dosemeci M,
Alavanja MCR, Mage D, Rothman N, Rowland A, Sandler D, Blair A. A quantitative approach for estimating exposure to pesticides in the Agricultural Health Study. The Annals of occupational Hygiene 2002; 46:245-260.

42. Turner JJ, Morton LM, Linet MS, Clarke CA, Kadin ME, Vajdic CM, Monnereau A, Maynadie M, Chiu B C,H, Marcos-Gragera R, Constantini AS, Cerhan JR, Weisenberger DD. InterLymph hierarchical classification of lymphoid neoplasms for epidemiologic research based on the WHO classification (2008): update and future directions. Blood, 18 November 2010;116(20):e90-e98.

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ORIGINAL ARTICLE

Using multiple imputation to assign pesticide use for non-responders in the follow-up questionnaire in the Agricultural Health Study

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The Agricultural Health Study (AHS), a large prospective cohort, was designed to elucidate associations between pesticide use and other agricultural exposures and health outcomes. The cohort includes 57,310 pesticide applicators who were enrolled between 1993 and 1997 in Iowa and North Carolina. A follow-up questionnaire administered 5 years later was completed by 36,342 (63%) of the original participants. Missing pesticide use information from participants who did not complete the second questionnaire impedes both long-term pesticide exposure estimation and statistical inference of risk for health outcomes. Logistic regression and stratified sampling were used to impute key variables related to the use of specific pesticides for 20,968 applicators who did not complete the second questionnaire. To assess the imputation procedure, a 20% random sample of participants was withheld for comparison. The observed and imputed prevalence of any pesticide use in the holdout dataset were 85.7% and 85.3%, respectively. The distribution of prevalence and days/year of use for specific pesticides were similar across observed and imputed in the holdout sample. When appropriately implemented, multiple imputation can reduce bias and increase precision and can be more valid than other missing data approaches.

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INTRODUCTION

Missing data is a common problem in epidemiological studies and the statistical implications of ignoring missing data are well known, including loss of statistical power and potentially biased estimates of association. The multiple imputation technique[1] is an approach whereby the investigator replaces each missing value with several plausible values sampled from a probability distribution, conducts multiple analyses for replicate datasets built from each plausible value, then combines the multiple results to account for the fact that the replacement data were imputed. Multiple imputation has been widely accepted and has been used to account for missing data in large national surveys and studies, including NHANES III,[2] National Assessment of Educational Progress,[3] Children's Mental Health Initiative,[4] and the Framingham Heart Study;[5] however, detailed accounts of the application of multiple imputation and particularly the evaluation and validation of the methods are not often published. This paper demonstrates a practical implementation of multiple imputation and is vital for investigators of the Agricultural Health Study (AHS).

The AHS is a prospective cohort study designed to evaluate the effect of agriculturally related exposures on health outcomes. The study includes 57,310 licensed pesticide applicators from Iowa and North Carolina, as well as 32,345 spouses of licensed applicators, who are not included in this imputation. In Iowa, both private applicators, who are primarily farmers, and commercial applicators were included. In North Carolina, only private applicators were enrolled. Cancer incidence and mortality are obtained by annual linkage to state cancer and mortality registries and to the National Death Index. Exposure information is collected by questionnaire. In the Phase 1 enrollment period (1993–97), applicators provided information on the use of 50 specific pesticides through completion of two self-administered questionnaires that included information on demographics, health history, and lifetime farming and pesticide use practices.[6–8] The study was approved by the Institutional Review Boards of the National Institutes of Health (Bethesda, Maryland) and its contractors. From the enrollment data, two exposure metrics were developed; the first was lifetime days of pesticide use, calculated as the product of years of use of each specific pesticide and average number of days used per year. The second metric, intensity-weighted lifetime days of use, incorporated information about factors that might impact exposure, such as the use of personal protective equipment, whether the applicator mixed pesticides, performed equipment repair, and methods of application.[9] Five years later in Phase 2 (1999–2005), we administered a computer-assisted telephone interview questionnaire that described pesticide use since enrollment. Specifically,

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participants were asked about the last year that they applied pesticides, which was denoted as the Phase 2 reference year, and the type and frequency of use of specific pesticides. A total of 36,342 (63%) of the original participants completed the questionnaire; 8% had died between enrollment and the administration of Phase 2, 15% refused, and 14% could not be reached.[10] For epidemiological analyses, pesticide use information collected in Phase 2 was cumulatively added to information collected in Phase 1 for both aforementioned exposure metrics, using details of specific pesticide use.

When using pesticide exposure in an analysis, there are several ways to handle missing Phase 2 information, including omission of those subjects, simple imputation (e.g., mean value substitution), or ignoring non-response in Phase 2 and implicitly assume zero pesticide exposure after Phase 1, which would be erroneous for most participants who did not complete the Phase 2 questionnaire. To correct for this potential bias, a data-driven multiple imputation for the 20,968 applicators (37%) who did not complete the Phase 2 questionnaire was employed. This paper describes the complex, multi-step process used to impute missing information on pesticide use from Phase 2 and an evaluation of the imputation procedure based on a holdout subset of participants with complete data (i.e., individuals who completed both Phase 1 and Phase 2). We also discuss the assumptions and advantages of multiple imputations.

MATERIALS AND METHODS

Imputation Strategy

An overarching principal of multiple imputation is to model the response of interest, in this case the use of pesticides in the interim period between the administration of the Phases 1 and 2 questionnaires. We used covariates from participants with complete data from both phases, and then applied that model to participants missing Phase 2 to obtain estimates of the missing data. Our specific multiple imputation procedure imputes four primary AHS exposure metric variables of interest: (1) use (yes/no) of any pesticide in the interim period between Phases 1 and 2; (2) use (yes/no) of 50 specific pesticides in the interim period (see Table 1); (3) number of days of use for a specific pesticide during Phase 2; and (4) last year of application of any pesticides within the 5-year period between Phases 1 and 2 (Phase 2 reference year). Phase 2 respondents report use of many pesticides that were not specifically on the Phase 1 questionnaires; however, we limit this imputation to the subset of 50 pesticides that were chosen as the focus in Phase 1. The value of days of use per year on the Phase 2 questionnaire is a discrete count variable that was collapsed into categories and therefore skewed, and reference year is an ordinal variable. We use logistic regression and stratified sampling to impute the 102 variables (any use of pesticides: reference year of use, and for 50 specific pesticides: any use, and days per year) from Phase 2 that are needed to construct the pesticide-exposure metrics in the AHS.

We withheld a randomly selected subset (20%, $n = 7269$) of participants from both Phase 1 and Phase 2 data to assess the proposed imputation method. We compared true and imputed percent usage and days/year of pesticide use within this subset using graphical displays and calculated the Brier score and Brier skill score[11–13] — measures of prediction accuracy. After assessment, the complete data were used to generate the final imputed datasets; nothing was withheld. All analyses were based on AHS data releases P1REL201005.00 and P2REL201007.00 and performed using SAS Version 9.1.

Use of any Pesticide

The first step in the imputation process was to impute the use of any pesticides since Phase 1 using subjects who completed both Phase 1 and 2 questionnaires. Both the enrollment and the take-home portions of the Phase 1 questionnaire were used in the modeling process. The use of any pesticides was a binary variable, and we therefore used logistic regression to model its probability based on Phase 1 responses. We considered all variables from Phase 1 that had the potential to be associated with either missingness or pesticide use (see Table 2 for candidate covariates). We first conducted a univariate analysis of Phase 1 variables, except the pesticide-specific variables. The variables most strongly predictive of use of any pesticide on the Phase 2 questionnaire were sex, marital status, farm ownership, farm size, days/year mixing pesticides, percent time personally mixing pesticides, percent time personally applying pesticides, and application of any pesticide in the prior year. Covariates associated with non-response to Phase 2 were continuous

Table 1. Phase 2 (1999–2005) pesticide usage in the AHS: observed and imputed.

	Prevalence estimates (%)		
	Observed (N = 36,342)	*Imputed[a] (N = 20,968)*	*Observed and imputed[a] (N = 57,310)*
Personally mix/load/apply any pesticides	85.21	82.82	84.33
METHYL BROMIDE	0.51	0.49	0.51
ALUMINUM PHOSPHIDE	0.79	0.84	0.81
CARBON TETRACHLORIDE/ DISULFIDE	0.00	0.00	0.00
ETHYLENE-DIBROMIDE	0.03	0.02	0.03
BENOMYL	0.40	0.30	0.36
CHLOROTHALONIL	2.53	2.75	2.61
CAPTAN	2.37	1.65	2.11
MANEB/MANCOZEB	0.18	0.14	0.16
METALAXYL	2.52	2.60	2.55
ZIRAM	0.10	0.08	0.10
ATRAZINE	31.16	25.86	29.22
DICAMBA	19.35	15.31	17.87
CYANAZINE	1.64	1.44	1.57
CHLORIMURON-ETHYL	3.24	3.19	3.22
METOLACHLOR	14.74	13.03	14.11
EPTC	0.35	0.30	0.33
ALACHLOR	2.81	2.49	2.69
METRIBUZIN	1.96	1.62	1.84
PARAQUAT	2.08	2.19	2.12
PETROLEUM OIL/PETROL. DISTILLATES	0.58	0.41	0.52
PENDIMETHALIN	11.71	10.77	11.37
IMAZETHAPYR	8.16	6.68	7.62
GLYPHOSATE	51.82	43.98	48.95
SILVEX	0.00	0.00	0.00
BUTYLATE	0.09	0.08	0.09
TRIFLURALIN	11.10	9.13	10.38
2,4-D	37.32	29.54	34.47
2,4,5-T	0.14	0.11	0.13
PERMETHRIN (for crops)	3.17	2.73	3.01
PERMETHRIN (for animals)	3.12	2.29	2.82
TERBUFOS	3.79	3.47	3.67
FONOFOS	0.17	0.17	0.17
TRICHLORFON	0.20	0.19	0.20
LINDANE	1.31	0.92	1.17
CARBOFURAN	1.35	1.21	1.30
CHLORPYRIFOS	8.93	7.97	8.58
MALATHION	12.78	10.00	11.76
PARATHION	0.00	0.00	0.00
CARBARYL	9.06	6.63	8.17
DIAZINON	2.91	2.42	2.73
ALDICARB	1.67	2.31	1.91
PHORATE	0.72	0.82	0.75
ALDRIN	0.00	0.00	0.00
CHLORDANE	0.05	0.00	0.03
DIELDRIN	0.00	0.00	0.00
DDT	0.00	0.00	0.00
HEPTACHLOR	0.01	0.00	0.00
TOXAPHENE	0.01	0.00	0.01
COUMAPHOS	0.44	0.28	0.38
DICHLORVOS	0.61	0.47	0.56

[a]Imputed prevalence is average of five imputations.

Table 2. Phase 1 candidate covariates to predict use of any pesticide in Phase 2 (1999–2005) of AHS.

Demographics
Age (AGE_AT_ENROLLMENT)[a]
Sex (GENDER)[a]
State (SITE)[a]
County (COUNTY)
Professional/private license type (APP_TYPE)[a]
Marital status / family size (AMARITAL)[a]
Education (ASCHOOL, collapsed)[a]
Farm characteristics
Owner (AOWNFARM)[a]
Farm size (AACRES)[a]
Pesticide use
Years mixing pesticides (AYRSMIX)[a]
Days/year mixing pesticides (AMIXDPY)[a]
Percent Mix (APCTMIX)[a]
Percent Apply (APCTAPPL)[a]
Application Methods (AAPMTH1 - AAPMTH21)
Do not personally apply (AAPMTH 1)[b]
Hand spray gun application (AAPMTH 4)[b]
Backpack spray application (AAPMTH 5)[b]
In furrow or banded application (AAPMTH 8)[b]
Application Uses (APSTAP1 - APSTAP17)
Rodent control (APSTAP2)[b]
Highway right-of-way weed control (APSTAP6)[b]
Herbicide (weed killers) applications to farm crops (APSTAP9)[b]
Insecticide applications to farm animals/animal shelters (APSTAP12)[b]
Fungicides (chemicals for controlling disease on crops) (APSTAP16)[b]
Fumigants (gases or liquids that turn into gas when released) (APSTAP17)[b]
Application in past 12 mos (APSTAP18)[a]
Personal Protective Equipment (APROTEQ1- APROTEQ8)
Chemical resistant gloves (APROTEQ7)[b]
Crops and Amimals (ACRPAN1 - ACRPAN8)
No Crops or animals (ACRPAN2)[b]
Medical conditions
Diagnosis of various conditions and diseases (A_MEDCOND5 - A_MEDCOND56)
Ever diagnosed with other chronic lung disease (A_MEDCOND10)[b]
Ever diagnosed with Diabetes (A_MEDCOND16E)[b]

[a]Covariates forced into the model.
[b]Covariates selected for the final model in step-wise selection process.

age, education, state, applicator type, and years mixing chemicals.[10] These variables and covariates were forced into the logistic regression model. Other potential covariates from Phase 1 (Table 2) were included or excluded based on the SAS step-wise regression procedure, with entrance and removal criteria of $P \leq 0.001$ and $P > 0.01$, respectively. Strict criteria were set because the dataset of individuals with complete data was so large. See Table 2 for final covariates in the model.

We used the aforementioned logistic model with covariates based on Phase 1 data to compute a predicted probability of the use of any pesticides for each individual who did not complete Phase 2 ($\hat{p}_i$, $i = 1, \ldots, 20{,}968$). For the i^{th} individual, we imputed use (yes/no) of any pesticides as follows. With $\hat{p}_i$between 0 and 1, we generated five uniform random variables between 0 and 1, Z_{ij}, $j = 1, \ldots, 5$. If $Z_{ij} \leq \hat{p}_i$, then we assigned $U_{ij} = 1$, otherwise we assigned $U_{ij} = 0$, where $U_{i1}, \ldots, U_{i5}$ were the imputed values for use of any pesticides in Phase 2.

For each individual and each imputation with an imputed "no" ($U_{ij} = 0$), the 50 pesticide-specific use variables (yes/no) and the 50 chemical-specific days/year variables in Phase 2 (Table 1) were set to zero. For each individual and each imputation with an imputed "yes" to use of any pesticide ($U_{ij} = 1$), the 50 missing chemical specific use variables and days/year were then imputed.

Use of Specific Pesticides

Using data from participants who completed both Phase 1 and 2 questionnaires, we applied the same process to generate a model for the probability of use of a specific pesticide in the interim period between Phases 1 and 2. However, we forced pesticide-specific covariates from Phase 1 (use of the specific chemical in the past year, ever mixed or applied the chemical in the past, number of years using the chemical, and days per year using the chemical) into the logistic model in addition to the 13 covariates for the model of use of any pesticide (see Table 2). The stepwise procedure in SAS identified other meaningful covariates for each pesticide, based on the entrance and removal criteria and likelihood ratio statistics. For each participant missing Phase 2 information for whom we imputed a "yes" to use of any pesticide, $U_{ij} = 1$, we generated a predicted probability for the use of a specific pesticide and randomly imputed five binary responses based on a uniform random number generator. Five responses (yes/no) were imputed for each of the 50 specific pesticides, V_{ijk} with $k = 1, \ldots, 50$. For those with Phase 1 and 2 data, it was not uncommon for participants to indicate applying or mixing of pesticides in Phase 2, while providing no affirmative response for any of 50 specific pesticides considered. This could suggest use of other pesticides or the inability to recall a specific pesticide. For that reason, we did not require that at least 1 specific pesticide be imputed as "yes", nor did we reverse the order by first imputing the 50 pesticides and then infer overall usage.

Days Per Year Use of Specific Pesticides

For each individual with an imputed "yes" to use of a specific pesticide, $V_{ijk} = 1$, we next developed a procedure to impute days/year of use. Because the Phase 2 question for days/year had an ordinal response and because data were skewed and sparse, we implemented a stratified sampling scheme using participants who completed both Phase 1 and 2 and who reported the number of days/year they used the pesticide of interest. For those missing Phase 2 data and imputed to have used a specific pesticide, we randomly selected days/year of use from the empirical frequency distribution derived from those with Phase 1 and 2 data who used the pesticide and who were in an appropriate stratum. The first step in this process was to identify an informative stratification. Table 1 indicates that the prevalence of the use of specific pesticides in Phase 2 ranged from 0% (pesticide use was discontinued) to >50%. For infrequently used pesticides, which were the majority, we could use only a limited number of Phase 1 stratification variables. By contrast, for widely used pesticides (e.g., 2,4-dichlorophenoxyacetic acid (2,4-D)), we could potentially use many stratification variables. However, to maintain consistency of methods across variables, we selected only variables most strongly associated with Phase 2 days/year use as stratification factors. After considering several possible stratification variables (age, state, applicator type, Phase 1 days use, and others; data not shown), we based the imputation of Phase 2 days/year of use of a specific pesticide on a stratification by Phase 1 days/year of use of a specific pesticide. Thus, for an applicator missing Phase 2 days/year of use of a specific pesticide, we identified the Phase 1 days/year of use category, then randomly sampled (with replacement) a value from the frequency distribution for Phase 2 days/year of use that corresponded to the same Phase 1 days/year of use category.

Finally, for those missing Phase 2 data, we also needed to impute the most recent year of farming activity. This year (see questions 10 and 13 of the private and commercial Phase 2 Questionnaires,[7] respectively at www.aghealth.org/questionnaires.html) was critical for calculating cumulative exposure to pesticides. Because reference year is an integer with a 12-year range (1993–2004), we again employed stratified sampling with replacement. The primary stratification variable was the use of any pesticide in Phase 2. If the imputed value for use of any pesticide was "no", then we defined 10 strata (applicator type [commercial or private] by enrollment year [1993–1997]). If the imputed value for use of any pesticide was "yes", then we defined 50 strata (applicator type by enrollment year by age at AHS enrollment in quintiles). For each stratum, we computed the frequency distribution of the most recent year of farming activity from those with complete Phase 1 and 2 data. We constrained the imputed reference year to occur after the enrollment year and, when an individual

was known to have died, before the year of death. If the enrollment year was equal to or within 1 year of death, we set the reference year to the enrollment year.

RESULTS

Imputation Assessment

We assessed the imputation method by holding out a randomly selected subset (20%, $n = 7269$) of the observed complete data and imputing multiple values for Phase 2 as though the data were missing. The "true" use of any pesticides in this subset was 85.68% with standard error 0.41%. The average of the five imputations indicated a prevalence of 85.25% with imputation adjusted standard error of 0.59%. This indicates that the logistic regression model underpinning the multiple imputation procedure did indeed preserve essential features of the data. Recall, the modeling process we used first generated a probability of use (the use of any pesticide, or the use of a specific pesticide) for each individual, $\hat{p}_i$. To assess the accuracy of the implemented prediction model, and how it compares with a "naïve" reference prediction (e.g., change prediction based on observed prevalence), we calculated the Brier[11] and Brier skill scores,[12] commonly utilized in atmospheric probability forecasting and risk prediction modeling. In the holdout set, let X_i be the observed use of any pesticides, $X_i = 0$ or 1, $i = 1, \ldots, n$, for the i^{th} individual in the holdout data. Let $\hat{p}_i$ be the predicted probability of use from the logistic model. The Brier score estimator is $B = 1/n \times \sum_{i=1}^{n} (X_i - \hat{p}_i)^2$ and is equivalent to the mean squared error of prediction; the smaller the value the better the prediction. To assess the utility of any prediction model, it can be compared to a naïve prediction using the skill score, $SS = 1 - B/B_{Rf}$, where B_{Rf} is the Brier score estimator using a reference, or naïve forecast, p' in place of the model $\hat{p}_i$ prediction. In this evaluation, we use the observed Phase 2 prevalence of pesticide use in the complete data ($N = 36{,}342$) less the holdout observations ($n = 7269$) as the reference prediction, $p' = 1/n' \times \sum_{i=1}^{n'} X_i$, where $n' = N - n$. For use of any chemicals, $B = 0.1092$, $B_{Rf} = 0.1227$, for a $SS = 0.1103$, an 11% improvement in accuracy using the predictive model over simple prediction based on observed Phase 2 usage. Parker and Davis[13] proposed a similar metric to the skill score, which was the sum of sensitivity and specificity, whereby the sum must be > 1 for the observed accuracy to be larger than chance. Figure 1 is a plot of Brier skill score *versus* the sum of sensitivity and specificity

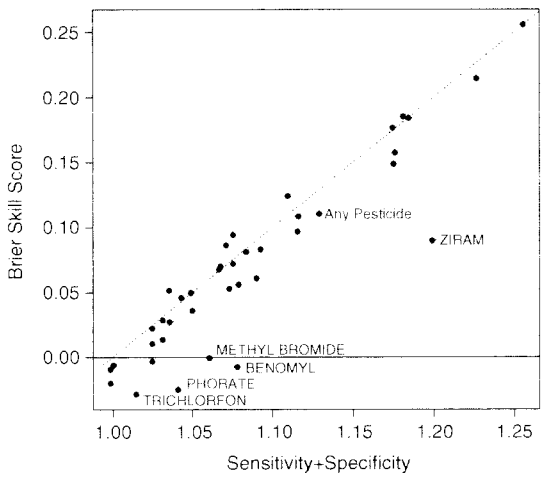

Figure 1. Scatterplot of Brier skill score *versus* sensitivity + specificity for commonly used pesticides ($P > 0.05\%$).

(pooling all five imputations for calculations) for overall pesticide use and commonly used pesticides (percent usage $> 0.05\%$). The two metrics are highly correlated ($r = 0.925$) and essentially measure the same thing, proportional improvement of prediction model over naïve/chance prediction.

Use of Specific Pesticides

Table 3 gives the observed ("true") and imputed prevalence for the 38 pesticides where observed prevalence $> 0.05\%$. The mean and standard error of a variable that includes multiply imputed values is well known.[1] Therefore, for any chemical, let X_i be the observed use of the pesticide of interest, $X_i = 0$ or 1, $i = 1, \ldots, n$ for the i^{th} individual in the holdout data. The estimated mean and variance of the percent usage (prevalence) in the holdout data is: $p = (1/n) \times \sum_{i=1}^{n} X_i$ and $s^2 = p \times (1-p)/n$, respectively. It follows that the usual standard error of the estimated prevalence p, is s. The prevalence from one of the m multiply imputed datasets is $\tilde{p}_j = (1/n) \times \sum_{i=1}^{n} \tilde{X}_{ij}$ where $\tilde{X}_{ij} = 0$ or 1, the imputed use of the pesticide of interest for individual i. Then, the overall prevalence estimate and its variance from the m (in this case 5) imputed datasets are $\tilde{p} = (1/m) \times \sum_{j=1}^{m} \tilde{p}_j$ and $\tilde{s}^2 = 1^m (\tilde{p}_j - \tilde{p})^2$, where $\tilde{s}_j^2 = (1/n) \times \tilde{p}_j \times (1 - \tilde{p}_j)$ and $\tilde{s}$ is the standard error of $\tilde{p}$.

As expected, the multiple imputation estimates of the standard error are slightly higher than the "true" standard error because the variability of the random imputations are included in the estimates, and pesticides with the highest prevalence (e.g., atrazine, 31.47%) have the largest standard errors while rarely used pesticides (e.g., methyl bromide, 0.41%) have little variability. Imputed prevalence is generally lower than observed both in Table 1 (across Phase 2 responders and non-responders) and Table 3 (the validation set). The Brier skill scores in Table 3 show a range of improvement from none to 25% over the naïve, or reference prediction model. Models for aldicarb and chlorothalonil appear to perform the best (SS of 0.256 and 0.214, respectively), while the majority of pesticides fall between $SS = 0.05$ and 0.20, including 2,4-D and atrazine with an 18% improvement in accuracy over naïve predictions. Some of the least prevalent pesticides did not benefit much from the implemented modeling scheme, and some of their skill scores were slightly negative (e.g., EPTC, phorate, benomyl, fonofos, and trichlorphon). The variability corresponding to rare event predictions can be large relative to the naïve estimates, and can yield negative skill scores. Skill scores close to zero (negative or positive) indicate that the predictive model was of limited additional value for these pesticides.

Figure 2 is a plot of the relative errors of the imputed prevalence estimate, $\tilde{p}$ to their respective true estimate, p, i.e., $\varepsilon = (\tilde{p} - p)/p$, for the 38 pesticides with $> 0.05\%$ use. Relative errors, ε, are centered about zero, and mostly fall within ± 0.20. For only a few of the rare pesticides ($< 1.0\%$ usage) used in Phase 2 does the imputed prevalence differ from the "true" prevalence by more than 20% (e.g., petroleum oil/petroleum distillates, methyl bromide, maneb/mancozeb, trichlorfon, metalaxyl, dichlorvos, coumaphos, and phorate).

Days Per Year Use of Specific Pesticides

We imputed days per year for a specific pesticide by sampling with replacement from the observed Phase 2 data stratified by Phase 1 days use of that pesticide. Figure 3 shows the box plots of the observed data from the validation dataset alongside the imputed data for days/year for three pesticides. Alachlor, diazinon, and 2,4-D were chosen for illustration because they were widely used and represent common usage patterns in the AHS cohort. The distributions of the imputed values for the three pesticides were very similar to those of the "true" data. The means (solid

Table 3. Prevalence, standard error and Brier scores of pesticide use in holdout dataset ($N = 7269$) of the AHS.

Pesticide name	Observed		Imputed[a]		Reference Brier	Brier score	Brier skill score
	Prevalence (%)	Standard error	Prevalence (%)	Standard error			
METHYL BROMIDE	0.43	0.08	0.56	0.12	0.004	0.004	−0.001
ALUMINUM PHOSPHIDE	0.59	0.09	0.71	0.13	0.006	0.005	0.149
BENOMYL	0.37	0.07	0.29	0.08	0.004	0.004	−0.007
CHLOROTHALONIL	2.39	0.18	2.33	0.26	0.023	0.018	0.214
CAPTAN	2.12	0.17	2.11	0.28	0.021	0.020	0.053
MANEB/MANCOZEB	0.15	0.05	0.18	0.06	0.002	0.002	−0.020
METALAXYL	2.66	0.19	2.09	0.23	0.026	0.023	0.124
ZIRAM	0.12	0.04	0.11	0.05	0.001	0.001	0.090
ATRAZINE	31.85	0.55	27.64	0.69	0.217	0.177	0.185
DICAMBA	19.16	0.46	17.39	0.48	0.155	0.128	0.177
CYANAZINE	1.75	0.15	1.50	0.21	0.017	0.017	0.029
CHLORIMURON-ETHYL	2.93	0.20	2.93	0.36	0.028	0.027	0.050
METOLACHLOR	14.87	0.42	13.23	0.55	0.127	0.113	0.109
EPTC	0.30	0.06	0.30	0.09	0.003	0.003	−0.003
ALACHLOR	2.82	0.19	2.43	0.32	0.027	0.026	0.052
METRIBUZIN	2.19	0.17	1.75	0.22	0.021	0.021	0.022
PARAQUAT	1.91	0.16	1.88	0.22	0.019	0.017	0.086
PETRO. OIL/PETRO. DISTILLATES	0.47	0.08	0.60	0.13	0.005	0.005	−0.006
PENDIMETHALIN	11.24	0.37	10.36	0.48	0.100	0.093	0.068
IMAZETHAPYR	7.76	0.31	7.36	0.39	0.072	0.067	0.070
GLYPHOSATE	52.73	0.59	45.42	0.83	0.249	0.225	0.097
TRIFLURALIN	10.58	0.36	10.21	0.58	0.095	0.080	0.157
2,4-D	36.92	0.57	33.30	0.86	0.233	0.190	0.184
PERMETHRIN (for crops)	3.36	0.21	2.71	0.24	0.032	0.031	0.036
PERMETHRIN (for animals)	3.05	0.20	2.83	0.33	0.030	0.028	0.061
TERBUFOS	3.80	0.22	3.38	0.33	0.037	0.033	0.095
FONOFOS	0.17	0.05	0.15	0.07	0.002	0.002	−0.009
TRICHLORFON	0.17	0.05	0.13	0.05	0.002	0.002	−0.028
LINDANE	1.39	0.14	1.07	0.18	0.014	0.013	0.046
CARBOFURAN	1.36	0.14	1.14	0.24	0.013	0.013	0.014
CHLORPYRIFOS	8.87	0.33	7.90	0.46	0.081	0.074	0.081
MALATHION	12.88	0.39	11.50	0.49	0.112	0.103	0.083
CARBARYL	9.34	0.34	7.69	0.65	0.085	0.079	0.072
DIAZINON	2.94	0.20	2.71	0.28	0.029	0.028	0.027
ALDICARB	1.66	0.15	1.57	0.18	0.016	0.012	0.256
PHORATE	0.59	0.09	0.69	0.17	0.006	0.006	0.024
COUMAPHOS	0.56	0.09	0.33	0.10	0.006	0.005	0.056
DICHLORVOS	0.65	0.09	0.48	0.12	0.006	0.006	0.010

[a]Imputed prevalence is average of five imputations and standard error is calculated via equation in text.

squares) were more sensitive to outliers for the less frequently used pesticides since fewer than 200 individuals reported use of those pesticides in the 20% holdout set. Comparing the observed reference year with its imputed value, Figure 4 indicates that for 90% of participants with reference year 1998 through 2004, the imputed years were centered around the expected year. When the "true" reference year is 1994–1997 the sampled imputation values were higher than expected and indicated bimodality. This was due to the ordinal nature of reference year and the scheduled pattern of interviews. The first interviews were conducted between 1993 and 1997 (Phase 1), while the follow-up Phase 2 interviews occurred between 1999 and 2005. When an individual participated in Phase 2, the most likely responses for reference year were 1) the year prior to the Phase 2 interview, 2) 5 years prior (year of Phase 1), or 3) the last year of farming prior to enrollment. This bimodal behavior seen in approximately 10% of the holdout dataset tended to occur in individuals who reported "no farming" or "no pesticide application" in Phase 2, and therefore a reference year for pesticide use in Phase 2 was irrelevant.

Post-assessment of the holdout dataset, all of the observed data were used to generate the complete predictive model and populate the sampling data. The final multiple imputations were generated and prevalence estimates for the 50 pesticides in the imputed subset and overall are shown in Table 1.

DISCUSSION

The lifetime exposure of an individual to a specific pesticide or set of pesticides is the primary quantity of interest in the AHS for studying the association between exposure and disease outcomes. A substantial number of AHS participants were non-responders to a Phase 2 questionnaire used to update lifetime pesticide use following enrollment. In analyses, imputation is generally preferable to omitting individuals who did not complete Phase 2 (in our case, 37% of enrolled individuals) due to possible selection bias in the subset with complete data and decreased precision of parameter estimates using only a subset of the data. This paper illustrates the use of a multi-step, conditional imputation procedure combining parametric modeling and sampling from an empirical distribution for several variable types. Using multiple imputation, the variables necessary to calculate exposure for those missing Phase 2 data are replaced by five imputed values. For validation purposes, we estimated prevalence of pesticide use and showed the form of the variance estimate for prevalence resulting from multiple imputation. Prevalence estimates for the Phase 2 non-responders were slightly lower than in the responders and this is likely due to the slightly different makeup of individuals in each. Logistic regression is known to perform sub-optimally when modeling rare events,[14] which may

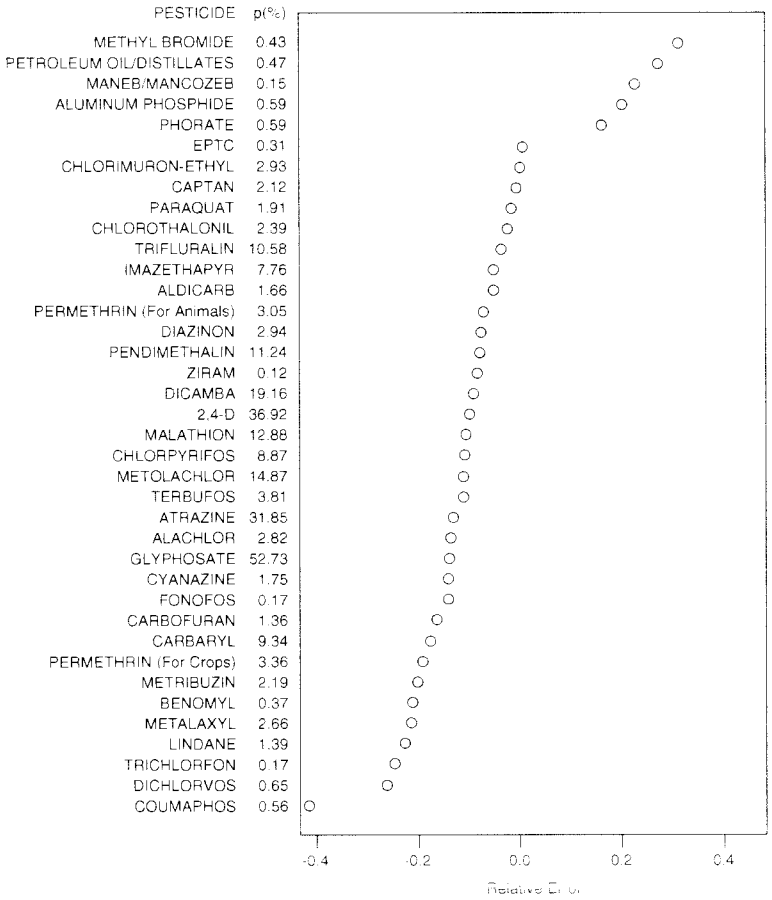

Figure 2. Relative errors of imputed prevalence or percent usage (p) for commonly used pesticides ($P > 0.05\%$).

explain the low imputed prevalence estimates in the validation set; the underestimation makes our imputation slightly conservative, favoring specificity over sensitivity.

Rubin's method of scalar estimands in multiple imputation procedures[15] is generalizable and can be used to calculate standard errors and confidence intervals for any estimator including risk ratios, absolute risk, and hazard ratios. We applied fractional hot deck imputation[16] to impute days/year use of a pesticide, for which other variance estimators have been proposed;[16–19] however, their utility has not been explored here.

Multiple imputation, in contrast to single imputation, accounts for the uncertainty of predicting missing data with limited loss of efficiency (nearly 94% efficient when imputed five times with 35% missing data, as opposed to 74% efficiency with a single imputation[1]). The observed data, together with the five imputed values for missing variables, generate five complete datasets to be analyzed by standard statistical techniques resulting in five slightly different results. These results and their variance/covariance matrices are combined to represent the variability induced by the imputing process. For simplicity, modeling and sampling were performed using the single set of observed complete data, as opposed to first bootstrapping the complete data to perform a proper imputation, which accounts for variability of regression parameter estimates used in the imputation.[1] An assessment of proper *versus* improper imputation on a dataset similar to the AHS shows mixed results.[20] Multiple imputation was chosen for pesticide use in the AHS over other approaches such as probability weighting or the EM algorithm[21] because of its familiarity and ease of use. Providing a single set of multiply imputed data will facilitate consistent results in future analyses.

A key assumption of any imputation is that missingness is independent of the unobserved outcome of interest or unobservable confounders (i.e., missing at random). The reduction of bias and increase in precision from multiple imputations is dependent on the covariates associated with both non-response and the endpoint variable,[22] and factors associated with non-participation, which were included in our imputation model. For our imputation analysis, the "outcome" of interest is the missing pesticide use itself; Montgomery et al.[10] show there is little evidence for selection bias in Phase 2 of the AHS, however missing at random is an untestable assumption without additional data; thus it is possible that non-responders differ from responders in variables we have not measured. It is worth emphasizing that the set of individuals with both Phase 1 and 2 responses had a full range of exposure, including those who were no longer farming, and therefore our data-driven imputation approach did not necessitate that non-responders be imputed as active pesticide users. To implement multiple imputation, missingness may be conditional on observable covariates from Phase 1 and our models incorporated covariates associated with Phase 2 pesticide use in constructing the values for missing data.

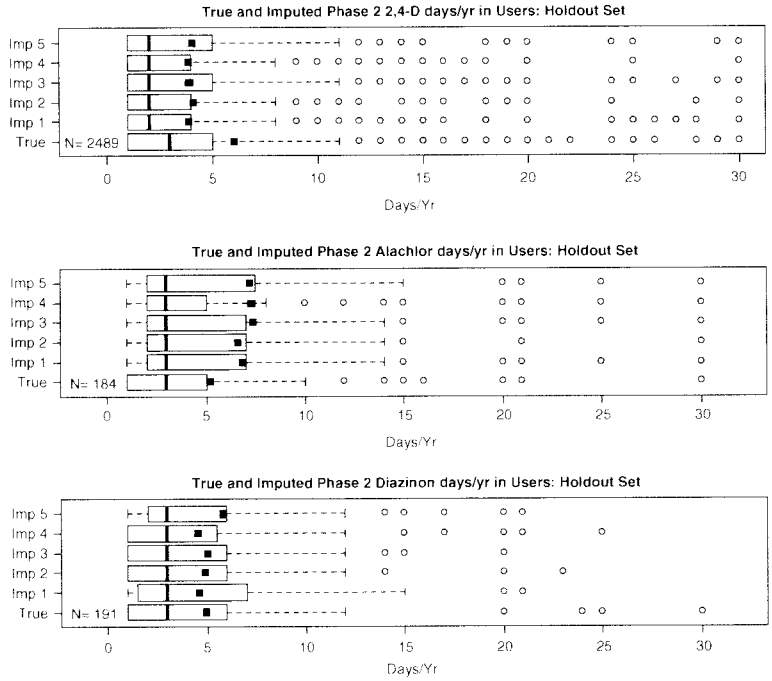

Figure 3. Box plots of observed and imputed days/year use of 2,4-D, alachlor, and diazinon in the holdout subset of the AHS.

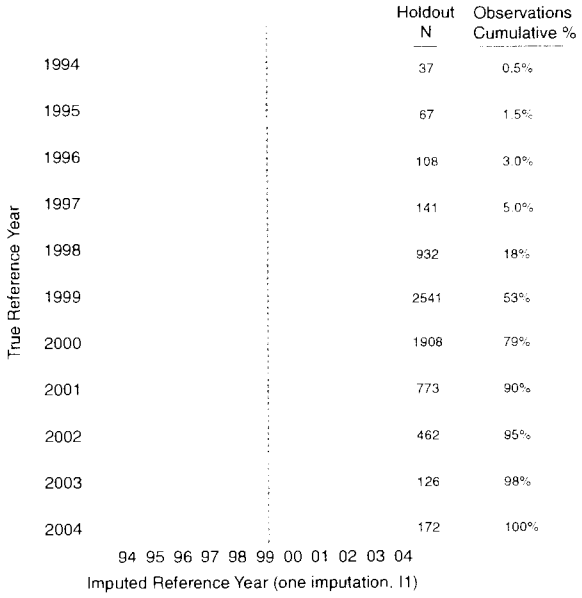

Figure 4. Histogram display of the distribution of imputed Phase 2 reference year by true, observed reference year in the holdout dataset of the AHS.

As was done for information collected from participants who completed the Phase 2 questionnaire, for epidemiologic analyses, the imputed pesticide use information has been cumulatively added to information collected in Phase 1. This multiple imputation will allow for bias reduction and improved efficiency in future analyses of the AHS.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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REFERENCES

1 Rubin D.B. *Multiple Imputation of Nonresponse in Surveys*. J.Wiley and Sons: New York, NY, 1987.
2 Schafer J.L., Ezzatti-Rice T.M., Johnson W., Khare M., Little R.J.A., and Rubin D.B. The NHANES III multiple imputation project. *Proc Survey Res Methods Section Am Stat Assoc* 1996, 28–37.
3 Mislevy R.J., Johnson E.G., and Muraki E. Scaling procedures in NAEP. *J Educational Stat* 1992: **17**: 131–154.
4 Stuart E.A., Azur M., Frangakis C., and Leaf P. Multiple imputation with large data sets: a case study of the children's mental health initiative. *Am J Epidemiol* 2009: **169**(9): 1133–1139.
5 Kang T., Kraft P., Gauderman W.J., and Thomas D. Multiple imputation methods for longitudinal blood pressure measurements from the Framingham Heart Study. *BMC Genet* 2003: **4**(suppl 1): S43.
6 Alavanja M.C., Sandler D.P., McMaster S.B., Zahm S.H., McDonnell C.J., and Lynch C.F., et al. The Agricultural Health Study. *Environ Health Perspect* 1996: **104**: 362–369.
7 National Cancer Institute, National Institutes of Health. Agricultural Health Study (AHSQ). Full Text of Questionnaires. 2010. (www.aghealth.org/questionnaires.html). (Accessed November 8, 2010).
8 Tarone R.E., Alavanja M.C., Zahm S.H., Lubin J.H., Sandler D.P., and McMaster S.B., et al. The Agricultural Health Study: factors affecting completion and return of self-administered questionnaires in a large prospective cohort study of pesticide applicators. *Am J Ind Med* 1997: **31**: 223–242.

9 Dosemeci M., Alavanja M.C., Rowland A.S., Mage D., Zahm S.H., and Rothman N., et al. A quantitative approach for estimating exposure to pesticides in the agricultural health study. *Ann Occup Hyg* 2002: **46**(2): 245–260.
10 Montgomery M.P., Kamel F., Hoppin J.A., Beane Freeman L.E., Alavanja M.C., and Sandler D.P. Effects of self-reported health conditions and pesticide exposures on probability of follow-up in a prospective cohort study. *Am J Ind Med* 2010: **53**: 486–496.
11 Brier G.W. Verification of forecasts expressed in terms of probability. *Monthly Weather Rev* 1950: **78**(1): 1–3.
12 Murphy S.H. Hedging and skill scores for probability forecasts. *J Appl Meteor* 1973: **12**(1): 215–223.
13 Parker R.A., and Davis R.B. Evaluating whether a binary decision rule operates better than chance. *Biom J* 1999: **41**: 25–31.
14 King G., and Zeng L. Logistic regression in rare events data. *Political Anal* 2001: **9**: 137–163.
15 Little R.J.A., and Rubin D.B. *Statistical Analysis with Missing Data*, 2nd edn J.Wiley and Sons: New York, NY, 2002.
16 Kim J.K., and Fuller W.A. Fractional hot deck imputation. *Biometrics* 2004: **91**(3): 559–578.
17 Rao J.N.K., and Shao J. Jackknife variance estimation with survey data under hot deck imputation. *Biometrika* 1992: **79**: 811–822.
18 Rubin D.B., and Schenker N. Multiple imputation for interval estimation from simple random samples with ignorable nonresponse. *J Am Stat Assoc* 1986: **81**: 366–374.
19 Tollefson M., and Fuller W.A. Variance estimation for samples with random imputation. *American Statistical Association Proceedings of the Section of Survey Research Methods* 1992: **15**: 758–763.
20 Heitjan D.F., and Little R.J.A. Multiple imputation for the fatal accident reporting system. *Appl Stat* 1991: **40**: 13–29.
21 Dempster A.P., Laird N.M., and Rubin D.B. Maximum likelihood from incomplete data via the EM algorithm. *J R Stat Soc Ser B* 1977: **39**(1): 1–38.
22 Spratt M., Carpenter J., Sterne J.A., Carlin J.B., Heron J., and Henderson J., et al. Strategies for multiple imputation in longitudinal studies. *Am J Epidemiol* 2010: **172**(4): 478–487.

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Non-Hodgkin Lymphoma Risk and Insecticide, Fungicide and Fumigant Use in the Agricultural Health Study

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Abstract

Farming and pesticide use have previously been linked to non-Hodgkin lymphoma (NHL), chronic lymphocytic leukemia (CLL) and multiple myeloma (MM). We evaluated agricultural use of specific insecticides, fungicides, and fumigants and risk of NHL and NHL-subtypes (including CLL and MM) in a U.S.-based prospective cohort of farmers and commercial pesticide applicators. A total of 523 cases occurred among 54,306 pesticide applicators from enrollment (1993–97) through December 31, 2011 in Iowa, and December 31, 2010 in North Carolina. Information on pesticide use, other agricultural exposures and other factors was obtained from questionnaires at enrollment and at follow-up approximately five years later (1999–2005). Information from questionnaires, monitoring, and the literature were used to create lifetime-days and intensity-weighted lifetime days of pesticide use, taking into account exposure-modifying factors. Poisson and polytomous models were used to calculate relative risks (RR) and 95% confidence intervals (CI) to evaluate associations between 26 pesticides and NHL and five NHL-subtypes, while adjusting for potential confounding factors. For total NHL, statistically significant positive exposure-response trends were seen with lindane and DDT. Terbufos was associated with total NHL in ever/never comparisons only. In subtype analyses, terbufos and DDT were associated with small cell lymphoma/chronic lymphocytic leukemia/marginal cell lymphoma, lindane and diazinon with follicular lymphoma, and permethrin with MM. However, tests of homogeneity did not show significant differences in exposure-response among NHL-subtypes for any pesticide. Because 26 pesticides were evaluated for their association with NHL and its subtypes, some chance finding could have occurred. Our results showed pesticides from different chemical and functional classes were associated with an excess risk of NHL and NHL subtypes, but not all members of any single class of pesticides were associated with an elevated risk of NHL or NHL subtypes. These findings are among the first to suggest links between DDT, lindane, permethrin, diazinon and terbufos with NHL subtypes.

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Data Availability: The authors confirm that all data underlying the findings are fully available without restriction. All relevant data are within the paper and the Supporting Information files.

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Introduction

Since the 1970s, epidemiologic studies of non-Hodgkin lymphoma (NHL) and multiple myeloma (MM) have shown increased risk among farmers and associations with the type of farming practiced [1–6]. While farmers are exposed to many agents that may be carcinogenic [7]; there has been a particular focus on pesticides. Studies from around the world have suggested increased risk of NHL or MM [8,9] and other NHL subtypes [10] in relation to the use of specific pesticides in different functional classes (i.e., insecticides, fungicides, fumigants and herbicides). A meta-analysis of 13 case-control studies published between 1993–2005 observed an overall significant meta-odds ratio (OR) between occupational exposure to pesticides and NHL (OR = 1.35; 95% CI: 1.2–1.5) [11]. This risk was greater among individuals with more than 10 years of exposure (OR = 1.65; 95% CI: 1.08–1.95) [11], but the meta-analysis lacked details about the use of specific pesticides and other risk factors [11]. Although the International Agency for Research on Cancer (IARC) has classified "Occupational exposures in spraying and application of non-arsenical insecticides" as "probably carcinogenic to humans", the human

evidence for the 17 individual pesticides evaluated in this monograph was determined to be inadequate for nine and there were no epidemiological studies for eight pesticides [12]. Since then, more studies have focused on cancer risk from specific pesticides, although the information is still relatively limited for many cancer-pesticide combinations [8,9].

To help fill the current information gap we evaluated the relationships between the use of specific insecticides, fungicides and fumigants and NHL in the Agricultural Health Study (AHS), a prospective cohort of licensed private (i.e., mostly farmer) and commercial pesticide applicators. Because the etiology of NHL and its B and T cell subtypes may differ by cell type[13], we also evaluated risk by subtype while controlling for potential confounding factors suggested from the literature [13], and the AHS data.

Novelty and Impact

These findings on occupationally exposed pesticide applicators with high quality exposure information are among the first to suggest links between DDT, lindane, permethrin, diazinon and terbufos and specific NHL subtypes in a prospective cohort study.

Materials and Methods

Study Population

The AHS is a prospective cohort study of 52,394 licensed private pesticide applicators (mostly farmers) in Iowa and North Carolina and 4,916 licensed commercial applicators in Iowa (individuals paid to apply pesticides to farms, homes, lawns, etc.), and 32,346 spouses of private applicators. Only applicators are included in this analysis. The cohort has been previously described in detail [14,15] and study questionnaires are available on the AHS website (www.aghealth.nih.gov). Briefly, individuals seeking licenses to apply restricted use pesticides were enrolled in the study from December 1993 through December 1997 (82% of the target population enrolled). At enrollment, subjects did not sign a written informed consent form. However, the cover letter of the questionnaire booklet informed subjects of the voluntary nature of participation, the ability to not answer any question, and it provided an assurance of confidentiality (including a Privacy Act Notification statement). The letter also included a written summary of the purpose of research, time involved, benefits of research, and a contact for questions about the research. The cover letter to the take-home questionnaire included all of the above and also informed the participant that they had the right to withdraw at any time. Finally, subjects were specifically informed that their contact information (including Social Security Number) would be used to search health and vital records in the future. The participants provided consent by completing and returning the questionnaire booklet. These documents and procedures were approved in 1993 by all relevant institutional review boards (i.e., National Cancer Institute Special Studies Institutional Review Board, Westat Institutional Review Board, and the University of Iowa Institutional Review Board-01).

Excluded from this analysis were study participants who had a history of any cancer at the time of enrollment (n = 1094), individuals who sought pesticide registration in Iowa or North Carolina but did not live in these states at the time of registration (n = 341) and were thus outside the catchment area of these cancer registries and individuals that were missing information on potential confounders (i.e., race or total herbicides application days [n = 1,569]). This resulted in an analysis sample of 54,306. We obtained cancer incidence information by regular linkage to the population-based cancer registry files in Iowa and North Carolina. In addition, we linked cohort members to state mortality registries of Iowa and North Carolina and the nation-wide National Death Index to determine vital status, and to the nation-wide address records of the Internal Revenue Service, state-wide motor vehicle registration files, and pesticide license registries of state agricultural departments to determine residence in Iowa or North Carolina. The current analysis included all incident primary NHL, as well as CLL and MM (which are now classified as NHL) [13] ($n = 523$) diagnosed from enrollment (1993–1997) through December 31, 2010 in North Carolina and from enrollment (1993–1997) through December 31, 2011 in Iowa, the last date of complete cancer incidence reports in each state. We ended follow-up and person-year accumulation at the date of diagnosis of any cancer, death, movement out of state, or December 31, 2010 in North Carolina and December 31, 2011 in Iowa, whichever was earlier.

Tumor Characteristics

Information on tumor characteristics was obtained from state cancer registries. We followed the definition of NHL and six subtypes of NHL used by the Surveillance Epidemiology and End Results (SEER) coding scheme [16] which was based on the Pathology Working Group of the International Lymphoma Epidemiology Consortium (ICD-O-3 InterLymph modification) classification (Table S1 in File S1, [17], i.e., 1. Small B-cell lymphocytic lymphomas (SLL)/chronic B-cell lymphocytic lymphomas (CLL)/mantle-cell lymphomas (MCL); 2. Diffuse large B-cell lymphomas; 3. Follicular lymphomas; 4. 'Other B-cell lymphomas' consisting of a diverse set of B-cell lymphomas; 5. Multiple myeloma; and 6. T-cell NHL and undefined cell type). There were too few T-cell NHL cases available for analysis [n = 19] so this cell type was not included in the subtype analysis). The ICD-O-3 original definition (used in many earlier studies of pesticides and cancer) of NHL [18] was also evaluated in relation to pesticide exposure to allow a clearer comparison of our results with previous studies.

Exposure Assessment

Initial information on lifetime use of 50 specific pesticides (Table S2 in File S1), including 22 insecticides, 6 fungicides and 4 fumigants was obtained from two self-administered questionnaires [14,15] completed during cohort enrollment (Phase 1). All 57,310 applicators completed the first enrollment questionnaire, which inquired about ever/never use of 50 pesticides, as well as duration (years) and frequency (average days/year) of use for a subset of 22 pesticides including 9 insecticides, 2 fungicides and 1 fumigant. In addition, 25,291 (44%) of the applicators returned the second (take-home) questionnaire, which inquired about duration and frequency of use for the remaining 28 pesticides, including 13 insecticides, 4 fungicides and 3 fumigants.

A follow-up questionnaire, which ascertained pesticide use since enrollment, was administered approximately 5 years after enrollment (1999–2005, Phase 2) and completed by 36,342 (63%) of the original participants. The full text of the questionnaires is available at www.aghealth.nih.gov. For participants who did not complete the Phase 2 questionnaire (20,968 applicators, 37%), a data-driven multiple imputation procedure which used logistic regression and stratified sampling [19] was employed to impute use of specific pesticides in Phase 2. Information on pesticide use from Phase 1, Phase 2 and imputation for Phase 2 was used to construct three cumulative exposure metrics: (i) lifetime days of pesticide use (i.e., the product of years of use of a specific pesticide and the number of days used per year); (ii) intensity-weighted lifetime days of use (i.e., the product of lifetime days of use and a measure of exposure

intensity) and (iii) ever/never use data for each pesticide. Intensity was derived from an exposure-algorithm, which was based on exposure measurements from the literature and individual information on pesticide use and practices (e.g., whether or not they mixed pesticides, application method, whether or not they repaired equipment and use of personal protective equipment) obtained from questionnaires completed by study participants [20].

Statistical Analyses

We divided follow-up time into 2-year intervals to accumulate person-time and update time-varying factors, such as attained age and pesticide use. We fit Poisson models to estimate rate ratios (RRs) and 95% confidence intervals (95% CI) to evaluate the effects of pesticide use on rates of overall NHL and the five NHL subtypes.

We evaluated pesticides with 15 or more exposed cases of total NHL, thereby excluding aluminum phosphide, carbon tetrachloride/carbon disulfide, ethylene dibromide, trichlorfon, and ziram leaving 26 insecticides, fungicides and fumigants for analysis (permethrin for animal use and crop use were combined into one category, all insecticides, fungicides and fumigants are listed in Table S2 in File S1). For each pesticide, we evaluated ever vs. never exposure, as well as tertiles of exposure which were created based on the distribution of all NHL exposed cases and compared to those unexposed. In the NHL subtype analysis and in circumstances where multiple pesticides were included in the model we categorized exposure for each pesticide into unexposed (i.e., never users) and two exposed groups (i.e., low and high) separated at the median exposure level. The number of exposed cases included in the ever/never analysis and in the trend analysis can differ because of the lack of information necessary to construct quantitative exposure metrics for some individuals.

Several lifestyle and demographic factors associated with NHL in the AHS cohort or previously suggested as possible confounders in the NHL literature[13] were evaluated as potential confounders in this analysis. These included: age at enrollment, gender, race, state, license type, education, autoimmune diseases, family history of lymphoma in first-degree relatives, body mass index, height, cigarette smoking history, alcohol consumption per week and several occupational exposures[1–13] including number of livestock, cattle, poultry, whether they raised poultry, hogs or sheep, whether they provided veterinary services to their animals, number of acres planted, welding, diesel engine use, number of years lived on the farm, total days of any pesticide use, and total days of herbicide use. However, since most of these variables did not change the risk estimates for specific pesticides, we present results adjusted for age, race, state and total days of herbicide use, which impacted risk estimates by more than 10% for some subtypes. We also performed analyses adjusting for specific insecticides, fungicides and fumigants shown to be associated with NHL or a specific NHL subtype in the current analysis. Tests for trend used the median value of each exposure category. All tests were two-sided and conducted at $\alpha = 0.05$ level. Analysis by NHL subtype was limited to insecticides, fungicides, and fumigants with 6 or more exposed cases.

We also fit polytomous logit models, where the dependent variable was a five-level variable (i.e., five NHL subtypes) and a baseline level (i.e., no NHL) to estimate exposure-response odds ratios (ORs) and 95% confidence intervals (CIs) for each subtypes of NHL. We then used polytomous logit models to estimate exposure-response trend while adjusting for age, state, race and total days of herbicide use, as in the Poisson models, and tested homogeneity among the 5 NHL subtypes.

Poisson models were fit using the GENMOD procedure and polytomous logit models were fit using the LOGISTIC procedure of the SAS 9.2 statistical software package (SAS Institute, Cary, NC). Summary estimates of NHL and NHL subtype risks for both Poisson models and polytomous logit models incorporated imputed data and were calculated along with standard error estimates, confidence intervals, and p-values, using multiple imputation methods implemented in the MIANALYZE procedure of SAS 9.2.

We also evaluated the impact of the additional pesticide exposure information imputed for Phase 2 on risk estimates. We compared risk estimates for those who completed both the phase 1 enrollment and take-home questionnaires and the phase 2 questionnaires (n = 17,545) with risk estimates obtained from the combined completed questionnaire data plus the imputed phase 2 data (n = 54,306). We also explored the effect of lagging exposure data 5 years because recent exposures may not have had time to have an impact on cancer development. For comparison to previous studies, we also assessed the exposure-response association for NHL using the original ICD-O-3 definition of NHL [18] and the new definition [16] in Table S3 in File S1. Unless otherwise specified, reported results show un-lagged exposure information from both Phase 1 and Phase 2 including Phase 2 imputed data for lifetime exposure-days and intensity-weighted lifetime days of use and NHL defined by the InterLymph modification of ICD-O-3 [17]. Data were obtained from AHS data release versions P1REL201005.00 (for Phase 1) and P2REL201007.00 (for Phase 2).

Results

The 54,306 applicators in this analysis contributed 803,140 person-years of follow-up from enrollment through December 31, 2010 in North Carolina and December 31, 2011 in Iowa (Table 1). During this period, there were 523 incident cases of NHL, including 148 SLL/CLL/MCL, 117 diffuse large B-cell lymphomas, 67 follicular lymphomas, 53 'other B-cell lymphomas' (consisting of a diverse set of B-cell lymphomas) and 97 cases of MM. Another 41 cases consisting of T-cell lymphomas (n = 19) and non-Hodgkin lymphoma of unknown lineage (n = 22) were excluded from cell type-specific analyses because of small numbers of cases with identified cell types. Between enrollment and the end of follow-up, 6,195 individuals were diagnosed with an incident cancer other than NHL, 4,619 died without a record of cancer in the registry data, and 1,248 cohort members left the state and could not be followed-up for cancer. Person-years of follow-up accumulated for all of these study participants after enrollment until they were censored for the incident cancer, death or moving out of the state (data not shown). The risk of NHL increased significantly and monotonically with age in the AHS cohort in this analysis (p = 0.001) and age-adjusted risks were significant for state and NHL overall and race for multiple myeloma (data not shown). Total days of herbicide use had a small but significant effect on the risk of some NHL subtypes, but not on NHL overall. No other demographic or occupational factors showed evidence of confounding so they were not included in the final models.

In Table 2 we present ever/never results for 26 insecticides, fungicides and fumigants by total NHL and by NHL subtype adjusted for age, race, state and herbicide use (total life-time days). Terbufos was the only pesticide associated with an increased risk of total NHL in the ever/never use analysis (RR = 1.2 [1.0–1.5]), although the trend for increasing use and risk of total NHL was not significant (p trend = 0.43) (Table 3). In contrast, there were a few chemicals that were not associated with ever/never use, but

Table 1. Baseline characteristics of AHS study participants in the NHL incidence analysis[1,2].

Variables	All NHL cases (%)	Cohort Person-years.
Age at Enrollment		
<45	84 (16.1)	426,288
45–49	51 (9.8)	101,018
50–54	75 (14.3)	84,998
55–59	90 17.2)	74,440
60–64	78 (14.9)	56,978
65–69	79 (15.1)	35,071
≥70	66 (12.6)	24,347
Race		
White	509 (97.3)	787,799
Black	14 (2.7)	15,341
State		
IA	332 (63.5)	537,252
NC	191 (36.5)	265,888
Lifetime Total Herbicide Exposure Days		
0–146 days	170 (32.5)	251,401
147–543 days	169 (32.3)	273,107
544–2453 days	184 (35.2)	278,632

[1]During the period from enrollment (1993–1997) to December 31, 2010 in NC and December 31, 2011 in Iowa.
[2]Individuals with missing ever/never exposure information or missing confounding variable information were not included in the table.
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did show evidence of an exposure-response association. Lindane was the only pesticide that showed a statistically significant increasing trend in risk for NHL with both exposure metrics, for lifetime-days of lindane use the RR were = 1.0 (ref), 1.2 (0.7–1.9), 1.0 (0.6–1.7), 2.5 (1.4–4.4); p trend = 0.004 and intensity-weighted lifetime-days of use the: RR were: = 1.0 (ref), 1.3 (0.8–2.2), 1.1 (0.7–1.8), 1.8 (1.0–3.2); p trend = 0.04. DDT showed a significant trend for NHL risk with life-time days of use RR = 1.0 (ref), 1.3 (0.9–1.8), 1.1 (0.7–1.7), 1.7 (1.1–2.6); p trend = 0.02, while the intensity weighted lifetime days of use of DDT was of borderline significance: RR = 1.0 (ref), 1.2 (0.8–1.8), 1.1 (0.8–1.7), 1.6 (1.0–2.3); p trend = 0.06. The number of lifetime days of use of lindane and DDT was weakly correlated (coefficient of determination = 0.04), and the pattern of NHL risk showed little change when both were included in the model. The results for lindane adjusted for DDT were, RR = 1.0 (ref), 1.2 (0.7–2.0), 1.0 (0.5–1.8), 1.6 (0.9–3.3); p trend = 0.07 and the results for DDT adjusted for lindane were, RR = 1.0 (ref), 1.3 (0.9–2.0), 0.9 (0.6–1.6), 1.6 (0.9–2.6); p trend = 0.08).

We also evaluated pesticides by NHL sub-type. In the ever/never analyses (Table 2), permethrin was significantly associated with multiple myeloma, RR = 2.2 (1.4–3.5) and also demonstrated an exposure-response trend (RR = 1.0 (ref), 1.4 (0.8–2.7), 3.1 (1.5–6.2); p trend = 0.002) (Table 4). Similarly, there was an elevated risk of SLL/CLL/MCL with terbufos in ever/never analyses RR = 1.4 (0.97–2.0) and an exposure response trend (RR = 1.0 (ref), 1.3 (0.8–2.0), 1.6 (1.0–2.5); p trend = 0.05). For follicular lymphoma, lindane showed an elevated but non-significant association for ever use, RR = 1.7 (0.96–3.2) and a significant exposure-response association (RR = 1.0 (ref), 4.9 (1.9–12.6), 3.6 (1.4–9.5); p trend = 0.04). There were also two chemicals with evidence of exposure-response that were not associated with specific subtypes in the ever/never analyses: DDT (Dichlorodiphenyltrichloroethane) with SLL/CLL/MCL (RR = 1.0 (ref), 1.0 (0.5–1.8), 2.6 (1.3–4.8; p trend = 0.04); and diazinon with follicular lymphoma (RR = 1.0 (ref), 2.2 (0.9–5.4), 3.8 (1.2–11.4); p trend = 0.02) (Table 4).

The pattern of increased CLL/SLL/MCL risk with increased use of DDT and terbufos remained after both insecticides were placed in our model concurrently. CLL/SLL/MCL risk increased with DDT use (RR = 1.0 (ref), 0.9 (0.5–4.7); 2.4 (1.1–4.7); p trend = 0.04), and a pattern of increased CLL/SLL/MCL risk was also observed with terbufos use (RR = 1.0 (ref), 1.1 (0.6–2.1), 1.7 (0.9–3.3) p trend = 0.07), although the trend was not significant for terbufos. Similarly, the pattern of increased follicular lymphoma risk with lindane use and diazinon use remained after both insecticides were placed in our model concurrently. Follicular lymphoma risk increased with diazinon use (RR = 1.0 (ref), 4.1 (1.5–11.1); 2.5 (0.9–7.2); p trend = 0.09), and a similarly, pattern of increased follicular lymphoma risk was observed with lindane use (RR = 1.0 (ref), 1.6 (0.6–4.1), 2.6 (0.8–8.3) p trend = 0.09), although neither remained statistically significant (Table 4).

Three chemicals showed elevated risks in ever/never analyses for certain subtypes, with no apparent pattern in exposure-response analyses: metalaxyl and chlordane with SLL/CLL/MCL, RR = 1.6 (1.0–2.5) and RR = 1.4 (0.97–2.0) respectively, and methyl bromide with diffuse large B-cell lymphoma RR = 1.9 (1.1–3.3). Although there was evidence of association by subtype, and polytomous logit models indicated homogeneity across subtypes for lindane (p = 0.54), DDT (p = 0.44) and any other pesticide evaluated in this study (e.g., permethrin (p = 0.10), diazinon (p = 0.09), terbufos (p = 0.63), (last column in Table 4).

There was no evidence of confounding of the total NHL associations with either lindane or DDT. We also calculated RR for those who completed both the phase 1 enrollment and take-home questionnaires and the phase 2 questionnaire (n = 17,545) and found no meaningful difference in the RR that also included imputed exposures, although there was an increase in precision of

Table 2. Pesticides exposure (ever/never) and adjusted Relative Risk of total NHL and NHL Subtype[1].

Insecticide	Total NHL Cases[2]		SLL/CLL/MCL Cases[2]		Diffuse Large B-Cell Cases[2]		Follicular B-Cell Cases[2]		Other B-cell Cases[2]		Multiple Myeloma Cases[2]	
Pesticide (chemical-functional class)	Ever/Never Exposed	RR[3,4] (95% CI)	Ever/Never Exposed	RR[3,4] (95% CI)	Ever/Never Exposed	RR[3,4] (95% CI)	Ever/Never Exposed	RR[3,4] (95% CI)	Ever/Never Exposed	RR[3,4] (95% CI)	Ever/Never Exposed	RR[3,4] (95% CI)
Aldicarb	47/435	1	14/124	1.1	8/98	0.7	6/54	0.9	7/41	1.6	10/82	1.2
(carbamate-insecticide)		(0.7–1.4)		(0.6–1.8)		(0.4–1.5)		(0.3–2.2)		(0.7–3.5)		(0.6–2.2)
Carbofuran	147/317	1.1	48/86	1.2	26/78	0.8	18/39	1	13/31	0.8	31/56	1.3
(carbamate-insecticide)		(0.9–1.3)		(0.8–1.8)		(0.5–1.3)		(0.5–1.7)		(0.4–1.6)		(0.8–2.1)
Carbaryl	272/225	1	75/66	1	58/53	0.8	37/24	0.8	24/28	0.9	58/34	0.9
(carbamate-insecticide)		(0.8–1.2)		(0.7–1.5)		(0.5–1.3)		(0.5–1.3)		(0.5–1.6)		(0.6–1.4)
Chlorpyrifos	210/300	1	62/84	1	44/70	0.9	32/33	1.3	21/31	0.8	36/58	1
(organophosphate-insecticide)		(0.8–1.2)		(0.7–1.4)		(0.6–1.4)		(0.8–2.2)		(0.5–1.5)		(0.6–1.5)
Coumaphos	46/411	1.1	15/120	1.2	10/93	1	8/48	1.6	5/40	xxx	7/78	1
(organophos-phate-insecticide)		(0.8–1.5)		(0.7–2.1)		(0.5–2.1)		(0.8–3.5)				(0.1–2.1)
DDVP	55/407	1.1	13/124	0.8	10/93	1	8/48	1.3	6/39	1	12/73	1.7
(dimethyl phosphate-insecticide)		(0.8–1.5)		(0.5–1.5)		(0.5–1.9)		(0.6–2.7)		(0.4–2.4)		(0.9–3.2)
Diazinon	144/342	1	46/93	1.3	30/78	0.9	22/38	1.3	12/37	0.8	27/64	1
(organophosphorous-insecticide)		(0.8–1.3)		(0.9–1.9)		(0.6–1.4)		(0.7–2.3)		(0.4–1.6)		(0.6–1.6)
Fonofos	115/349	1.1	35/100	1.1	25/81	1.2	13/45	0.9	15/30	1.3	19/66	1.3
(organophosphorous-insecticide)		(0.9–1.4)		(0.7–1.6)		(0.7–1.9)		(0.5–1.7)		(0.7–2.5)		(0.8–2.3)
Malathion	332/163	0.9	99/43	1	72/37	0.9	46/14	1.3	30/21	0.6	61/32	0.9
(organophosphorous-insecticide)		(0.8–1.1)		(0.7–1.4)		(0.6–1.4)		(0.7–2.4)		(0.3–1.0)		(0.6–1.5)
Parathion (ethyl or methyl)	69/411	1.1	20/117	1	14/91	1	10/48	1.1	7/44	1.1	14/77	1
(organophosphorous insecticide		(0.8–1.4)		(0.7–1.4)		(0.6–1.4)		(0.8–1.5)		(0.7–1.5)		(0.8–1.5)
Permethrin (animal and crop applications)	112/363	1.1	32/106	1	18/81	0.7	18/81	1.1	9/14	0.8	20/72	**2.2**
(pyrethroid insecticide)		(0.8–1.3)		(0.6–1.5)		(0.4–1.2)		(0.6–2.0)		(0.4–1.6)		**(1.4–3.5)**
Phorate	160/325	1	53/87	1.1	31/76	0.9	20/40	0.9	19/31	0.9	26/64	1
(organophosphorous-insecticide)		(0.8–1.2)		(0.8–1.6)		(0.5–1.3)		(0.5–1.6)		(0.5–1.6)		(0.6–1.7)
Terbufos	201/267	**1.2**	64/72	1.4	42/63	1.1	31/26	1.2	26/19	1.8	32/59	1.2
(organophosphorous-insecticide)		**(1.0–1.5)**		(0.97–2.0)		(0.7–1.7)		(0.7–2.1)		(0.94–3.2)		(0.7–1.9)
Chlorinated Insecticides												
Aldrin	116/364	0.9	53/99	0.9	15/91	0.8	13/45	0.8	12/37	0.6	29/62	1.5
(chlorinated insecticide)		(0.7–1.1)		(0.6–1.4)		(0.4–1.6)		(0.4–1.6)		(0.3–1.3)		(0.9–2.5)
Chlordane	136/344	1	49/90	1.4	20/86	0.6	18/41	1.2	13/36	1	31/60	1.2
(chlorinated insecticide)		(0.8–1.3)		(0.99–2.1)		(0.4–1.0)		(0.7–2.1)		(0.7–2.0)		(0.8–1.9)
DDT	182/300	1	59/79	1.2	34/73	0.8	18/41	0.9	20/31	1.1	40/50	1.1

Table 2. Cont.

Insecticide												
	Total NHL Cases[2]		SLL/CLL/MCL Cases[2]		Diffuse Large B-Cell Cases[2]		Follicular B-Cell Cases[2]		Other B-cell Cases[2]		Multiple Myeloma Cases[2]	
Pesticide (chemical-functional class)	Ever/Never Exposed	RR[3,4] (95% CI)	Ever/Never Exposed	RR[3,4] (95% CI)	Ever/Never Exposed	RR[3,4] (95% CI)	Ever/Never Exposed	RR[3,4] (95% CI)	Ever/Never Exposed	RR[3,4] (95% CI)	Ever/Never Exposed	RR[3,4] (95% CI)
(chlorinated insecticide)		(0.8–1.3)		(0.8–1.8)		(0.5–1.3)		(0.5–1.6)		(0.6–2.1)		(0.7–1.8)
Dieldrin	35/442	0.9	5/130	xxx	4/101	xxx	4/54	xxx	7/42	1	10/81	0.9
(chlorinated insecticide)		(0.6–1.2)								(0.7–2.0)		(0.5–1.4)
Heptachlor	90/384	1	33/104	1.1	10/95	1.1	9/48	1.1	13/36	0.9	17/72	1.1
(chlorinated insecticide)		(0.7–1.2)		(0.7–3.0)		(0.3–3.1)		(0.5–3.2)		(0.5–2.7))		(0.6–2.0)
Lindane	85/396	1	27/113	1.2	12/95	0.6	16/41	1.7	9/40	0.7	13/73	1.1
(chlorinated insecticide)		(0.8–1.2)		(0.6–1.5)		(0.3–1.1)		(0.96–3.2)		(0.4–1.2)		(0.5–2.0)
Toxaphene	79/397	1	21/116	0.9	14/90	0.8	9/47	1	10/40	1.1	19/73	1.1
(chlorinated insecticide)		(0.7–1.2)		(0.5–1.5)		(0.4–1.4)		(0.6–2.0)		(0.6–2.0)		(0.6–1.9)
Fungicides												
Benomyl	54/428	1.1	18/123	1.2	12/95	1.1	4/51	xxx	4/51	xxx	11/80	1.1
(carbamate fungicide)		(0.8–1.5)		(0.7–2.0)		(0.6–1.9)						(0.6–2.0)
Captan	60/406	1.1	18/118	1.1	12/91	0.9	5/51	xxx	6/39	1.1	12/76	1.2
(phthalimide fungicide)		(0.8–1.4)		(0.6–1.8)		(0.5–1.8)				(0.5–2.7)		(0.6–2.2)
Chloro-thalonil	35/474	0.8	9/135	0.9	6/107	0.5	5/60	xxx	2/50	xxx	11/84	1.2
(poly-chlorinated aromatic thalonitrile fungicide)		(0.5–1.2)		(0.4–1.9)		(0.2–1.3)						(0.6–2.3)
Maneb/	44/437	0.9	13/127	1.1	12/95	1.1	4/60	xxx	5/49	xxx	10/79	0.8
Mancozeb		(0.7–1.3)		(0.6–2.1)		(0.6–2.1)						(0.4–1.7)
(dithiocarbamate fungicide)												
Metalaxyl	108/381	1	34/106	**1.6**	27/82	1.1	10/48	0.7	10/40	0.9	21/71	0.8
(acylalanine fungicide)		(0.8–1.3)		**(1.0–2.5)**		(0.6–1.8)		(0.4–1.4)		(0.4–1.7)		(0.4–1.3)
Fumigant												
Methyl bromide	85/425	1.1	18/126	0.9	28/86	**1.9**	7/58	0.6	8/44	2.2	19/76	1
(methyl halide fumigant)		(0.9–1.5)		(0.5–1.7)		**(1.1–3.3)**		(0.2–1.4)		(0.9–5.7)		(0.6–1.8)

[1]During the period from enrollment (1993–1997) to December 31, 2010 in NC and December 31, 2011 in Iowa.
[2]Numbers of cases by NHL subtype do not sum to total number of NHL cases (n = 523) due to missing data.
[3]Adjusted RR: age (<45, 45–49, 50–54, 55–59, 60–64, 65–69, ≥70), State (NC vs. IA), Race (White vs. Black), AHS herbicides (tertiles of total herbicide use-days). Statistically significant RR and 95% confidence limits are bolded.
[4]RR was not calculated if the number of exposed cases in a pesticide-NHL subtype cell was <6 and the missing RR was marked with an XXX. Statistically significant RRs and 95% confidence limits are bolded.
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Table 3. Pesticide exposure (lifetime-days & intensity weighted life-time days) and adjusted risks of total NHL incidence[1].

Insecticides						
Pesticide (chemical-functional class) [days of lifetime exposure for each category]	**NHL Cases[2]**	**Non-Cases[2]**	**RR[3,4] (95% CI) by Total Days of Exposure**	**NHL Cases[2,]**	**Non-Cases**	**RR[3,4] (95% CI) Intensity-weighted days of exposure**
Aldicarb (carbamate-insecticide)						
None	238	21557	1.0 (ref)	238	21557	1.0 (ref)
Low [≤8.75]	7	633	1.1 (0.5–2.3)	6	383	1.3 (0.6–3.3))
Medium [>8.75–25.5]	5	522	0.9 (0.3–2.5)	6	853	0.9 (0.4–1.9)
High [>25.5–224.75]	5	1266	0.5 (0.2–1.3)	5	1183	0.5 (0.2–1.3)
			P trend = 0.23			P trend = 0.22
Carbofuran (carbamate-insecticide)						
None	317	36296	1.0 (ref)	317	36296	1.0 (ref)
Low [≤8.75]	63	4775	1.2 (0.9–1.6)	46	3695	1.2 (0.9–1.6)
Medium [>8.75–38.75]	32	3648	0.8 (0.6–1.2)	46	4590	1.0 (0.7–1.3)
High [>38.75–767.25]	44	4370	0.97 (0.7–1.4)	45	4477	1.0 (0.7–1.4)
			P trend = 0.69			P trend = 0.74
Carbaryl (carbamate-insecticide)						
None	128	12864	1.0 (ref)	128	12864	1.0 (ref)
Low [≤8.75]	54	4128	1.1 (0.7–1.6)	46	3962	1.0 (0.7–1.5)
Medium [8.75–56]	43	5096	0.9 (0.6–1.2)	45	4433	0.9 (0.7–1.5)
High [>56–737.5]	39	3281	1.0 (0.7–1.6)	44	4029	1.0 (0.6–1.5)
			P trend = 0.87			P trend = 0.94
Chlorpyrifos (organophosphate-insecticide)						
None	300	30393	1.0 (ref)	300	30393	1.0 (ref)
Low [≤8.75]	71	6493	1.1 (0.9–1.5)	61	6383	1.1 (0.8–1.4)
Medium [>8.75–44]	65	6892	1.1 (0.8–1.4)	60	7549	0.9 (0.7–1.2)
High [>44–767.25]	67	9380	0.8 (0.6–1.1)	60	7044	1.0 (0.7–1.3)
			P trend = 0.11			P trend = 0.85
Coumaphos (organophosphate-insecticide)						
None	411	44846	1.0 (ref)	411	44846	1.0 (ref)
Low [<8.75]	16	1510	1.0 (0.6–1.7)	15	1132	1.3 (0.8–2.1)
Medium [>8.75–38.75]	14	1076	1.2 (0.7–2.1)	14	1452	1.0 (0.6–1.6)
High [>38.75–1627.5]	13	1175	1.2 (0.7–2.0)	14	1170	1.2 (0.7–2.1)
			P for trend = 0.50			P trend = 0.48
DDVP (dimethyl phosphate-insecticide)						
None	407	44551	1.0 (ref)	407	44551	1.0 (ref)
Low [≤8.75]	19	1342	1.4 (0.9–2.1)	18	1281	1.4 (0.9–2.3)
Medium [>8.75–87.5]	17	1519	1.2 (0.7–1.9)	18	1633	1.1 (0.7–1.8)
High [>87.5–2677.5]	17	1893	0.9 (0.6–1.5)	17	1824	1.0 (0.6–1.6)
			P trend = 0.78			P trend = 0.83
Diazinon (organophosphorous-insecticide)						
None	187	17943	1.0 (ref)	187	17943	1.0 (ref)
Low [≤8.75]	28	2506	1.1 (0.7–1.6)	23	2047	1.1 (0.7–1.8)
Medium [>8.75–25]	19	1515	1.0 (0.6–1.8)	24	2246	0.9 (0.5–1.5)
High [>25–457.25]	23	1990	1.2 (0.7–1.9)	22	1708	1.3 (0.8–2.1)
			P trend = 0.52			P trend = 0.33

Table 3. Cont.

Insecticides						
Pesticide (chemical-functional class) [days of lifetime exposure for each category]	**NHL Cases[2]**	**Non-Cases[2]**	**RR[3,4] (95% CI) by Total Days of Exposure**	**NHL Cases[2,]**	**Non-Cases**	**RR[3,4] (95% CI) Intensity-weighted days of exposure**
Fonofos (organophosphorous-insecticide)						
None	349	39570	1.0 (ref)	349	39570	1.0 (ref)
Low [≤20]	47	3812	1.3 (0.96–1.8)	37	2906	1.4 (0.97–1.9)
Medium [>20–50.75]	28	2819	1.1 (0.7–1.6)	38	3487	1.1 (0.8–1.6)
High [>50.75–369.75]	37	3385	1.1 (0.7–1.5)	36	3606	1.0 (0.7–1.4)
			P trend = 0.83			P trend = 0.87
Malathion (organophosphorous-insecticide)						
None	90	8368	1.0 (ref)	90	8368	1.0 (ref)
Low [≤8.75]	75	7284	0.97 (0.7–1.3)	60	5535	1.0 (0.7–1.4)
Medium [>8.75–38.75]	47	5779	0.7 (0.5–1.1)	59	6899	0.8 (0.6–1.1)
High [>38.75–737.5]	57	5037	0.9 (0.6–1.3)	59	5588	0.9 (0.6–1.2)
			P trend = 0.63			P trend = 0.46
Parathion (ethyl or methyl) (organophosphorous insecticide)						
None	228	21457	1.0 (ref)	228	21457	1.0 (ref)
Low [≤8.75]	9	693	1.0 (0.5–2.0)	7	612	0.9 (0.4–2.0)
Medium [>8.75–24.5]	6	351	1.4 (0.6–3.2)	8	462	1.4 (0.7–2.9)
High [>24.5–1237.5]	6	652	0.8 (0.3–1.8)	6	621	0.8 (0.4–1.9)
			P trend = 0.64			P trend = 0.74
Permethrin (animal and crop applications)						
(pyrethroid insecticide)						
None	371	37496	1.0 (ref)	371	37496	1.0 (ref)
Low [≤8.75]	38	4315	1.1 (0.8–1.5)	33	4263	0.9 (0.6–1.3)
Medium [>8.75–50.75]	31	4611	0.8 (0.5–1.2)	33	4200	1.0 (0.7–1.4)
High [>50.75–1262.25]	33	4121	1.2 (0.8–1.7)	32	4553	1.0 (0.7–1.5)
			P trend = 0.54			P trend = 0.99
Phorate (organophosphorous-insecticide)						
None	171	16834	1.0 (ref)	171	16834	1.0 (ref)
Low [≤8.75]	27	2621	0.8 (0.5–1.2)	26	2320	0.9 (0.6–1.4)
Medium [8.75–24.5]	33	1819	1.4 (0.96–2.1)	27	1951	1.1 (0.7–1.7)
High [>24.5–224.75]	18	2246	0.6 (0.4–1.1)	25	2409	0.8 (0.5–1.3)
			P trend = 0.25			P trend = 0.44
Terbufos (organophosphorous-insecticide)						
None	267	31076	1.0 (ref)	267	31076	1.0 (ref)
Low [≤24.5]	82	8410	1.2 (0.9–1.5)	64	6895	1.1 (0.9–1.5)
Medium [>24.5–56]	54	3925	1.6 (1.2–2.1)	64	4642	1.6 (1.2–2.2)
High [>56–1627.5]	57	6080	1.1 (0.8–1.5)	63	6842	1.1 (0.8–1.5)
			P trend = 0.43			P trend = 0.44
Chlorinated Insecticides						
Aldrin (chlorinated insecticide)						
None	193	19743	1.0 (ref)	193	19743	1.0 (ref)
Low [≤8.75]	27	1613	0.9 (0.6–1.4)	20	1212	0.9 (0.6–1.4)
Medium [>8.75–24.5]	16	1002	0.8 (0.5–1.3)	20	1279	0.8 (0.5–1.3)

Table 3. Cont.

Insecticides						
Pesticide (chemical-functional class) [days of lifetime exposure for each category]	**NHL Cases[2]**	**Non-Cases[2]**	**RR[3,4] (95% CI) by Total Days of Exposure**	**NHL Cases[2,]**	**Non-Cases**	**RR[3,4] (95% CI) Intensity-weighted days of exposure**
High [>24.5–457.25]	17	903	0.9 (0.5–1.5)	19	1026	0.9 (0.6–1.5)
			P trend = 0.58			P trend = 0.74
Chlordane (chlorinated insecticide)						
None	179	19115	1.0 (ref)	179	19115	1.0 (ref)
Low [≤8.75]	47	2687	1.3 (0.97–1.9)	23	1303	1.4 (0.9–2.2)
Medium[5]	0	0	xxx	24	1747	1.0 (0.6–1.5)
High [>8.75–1600]	23	1450	1.1 (0.7–1.7)	22	1085	1.4 (0.9–2.2)
			P trend = 0.43			P trend = 0.16
DDT (chlorinated insecticide)						
None	152	18543	1.0 (ref)	152	18543	1.0 (ref)
Low [≤8.75]	43	2121	1.3 (0.9–1.8)	33	1601	1.2 (0.8–1.8)
Medium [>8.75–56]	28	1598	1.1 (0.7–1.7)	32	1760	1.1 (0.8–1.7)
High [>56–1627.5]	27	953	1.7 (1.1–2.6)	32	1305	1.6 (1.0–2.3)
			P trend = 0.02			P trend = 0.06
Dieldrin (chlorinated insecticide)						
None	235	22510	1.0 (ref)	235	22510	1.0 (ref)
Low [≤8.75]	7	472	0.7 (0.3–1.5)	6	363	0.8 (0.4–1.8)
Medium [>8.75–24.5]	8	154	2.3 (1.1–4.7)	5	106	2.2 (0.9–5.3)
High [>24.5–224.75]	2	140	0.7 (0.2–2.9)	5	298	0.8 (0.3–2.0)
			P trend = 0.47			P trend = 0.84
Heptachlor (chlorinated insecticide)						
None	205	20844	1.0 (ref)	205	20844	1.0 (ref)
Low [≤8.75]	21	1261	1.0 (0.6–1.6)	15	1110	0.8 (0.5–1.4)
Medium [>8.75–24.5]	18	679	1.5 (0.9–2.4)	16	425	2.0 (1.2–3.4)
High [>24.5–457.25]	7	600	0.7 (0.3–1.4)	14	1001	0.8 (0.5–1.4)
			P trend = 0.82			P trend = 0.88
Lindane (chlorinated insecticide)						
None	205	20375	1.0 (ref)	205	20375	1.0 (ref)
Low [≤8.75]	18	1285	1.2 (0.7–1.9)	15	976	1.3 (0.8–2.2)
Medium [>8.75–56]	13	1103	1.0 (0.6–1.7)	16	1205	1.1 (0.7–1.8)
High [>56–457.25]	14	467	2.5 (1.4–4.4)	14	673	1.8 (1.0–3.2)
			P trend = 0.004			**P trend = 0.04**
Toxaphene (chlorinated insecticide)						
None	214	20911	1.0 (ref)	214	20911	1.0 (ref)
Low [≤8.75]	14	1198	0.8 (0.5–1.4)	11	630	1.3 (0.7–2.3)
Medium [>8.75–24.5]	13	564	1.5 (0.9–2.7)	12	931	0.9 (0.5–1.6)
High [>24.5–457.25]	6	686	0.6 (0.3–1.4)	10	886	0.8 (0.4–1.5)
			P trend = 0.50			P trend = 0.38
Fungicides						
Benomyl (carbamate fungicide)						
None	219	21425	1.0 (ref)	219	21425	1.0 (ref)
Low [≤12.25]	14	896	1.7 (0.9–2.9)	9	432	2.2 (1.1–4.3)
Medium [>12.25–24.5]	4	214	2.4 (0.9–6.6)	10	732	1.7 (0.9–3.2)

Table 3. Cont.

Insecticides						
Pesticide (chemical-functional class)	**NHL Cases[2]**	**Non-Cases[2]**	**RR[3,4] (95% CI) by Total Days of Exposure**	**NHL**	**Non-Cases**	**RR[3,4] (95% CI)**
[days of lifetime exposure for each category]				**Cases[2,]**		**Intensity-weighted days of exposure**
High [>24.5–457.25]	8	834	1.0 (0.5–2.1)	7	779	0.9 (0.4–2.0)
			P trend = 0.93			P trend = 0.75
Captan (phthalimide fungicide)						
None	407	43433	1.0 (ref)	407	43433	1.0 (ref)
Low [≤0.25]	15	2334	0.8 (0.5–1.4)	15	2108	0.9 (0.6–1.5)
Medium [>0.25–12.25]	16	1004	1.5 (0.8–2.6)	15	1171	1.2 (0.7–2.2)
High [>12.25–875]	14	1823	0.8 (0.5–1.5)	14	1805	0.8 (0.5–1.5)
			P trend = 0.69			P trend = 0.52
Chlorothalonil (polychlorinated aromatic thalonitrile fungicide)						
None	474	48442	1.0 (ref)	474	48442	1.0 (ref)
Low [≤12.25]	13	1509	0.9 (0.5–1.6)	10	1800	0.6 (0.3–1.2)
Medium [>12.25–64]	9	1492	0.8 (0.4–1.6)	11	1501	0.9 (0.5–1.7)
High [>64–395.25]	9	1678	0.6 (0.3–1.3)	9	1362	0.8 (0.4–1.6)
			P trend = 0.16			PP trend = 0.52
Maneb/Mancozeb (dithiocarbamate fungicide)						
None	228	21512	1.0 (ref)	228	21512	1.0 (ref)
Low [≤7]	8	400	1.9 (0.9–3.9)	8	486	1.6 (0.8–3.3)
Medium [>7–103.25]	9	990	0.9 (0.4–1.7)	9	680	1.3 (0.6–2.6)
High [>103.25–737.5]	7	454	1.4 (0.6–2.9)	7	677	0.9 (0.4–1.9)
			P trend = 0.49			P trend = 0.78
Metalaxyl (acylalanine fungicide)						
None	209	18833	1.0 (ref)	209	18833	1.0 (ref)
Low [≤6]	16	1439	1.0 (0.6–1.8)	15	1079	1.3 (0.8–2.2)
Medium [>6–28]	15	2182	0.7 (0.4–1.3)	15	2203	0.8 (0.4–1.3)
High [>28–224.75]	13	1566	1.1 (0.6–2.1)	14	1893	0.9 (0.5–1.6)
			P trend = 0.76			P trend = 0.63
Fumigant						
Methyl bromide (methyl halide fumigant)						
None	425	45265	1.0 (ref)	425	45265	1.0 (ref)
Low [≤8]	37	2060	2.0 (1.4–2.9)	26	1680	1.8 (1.2–2.7)
Medium [>8–28]	24	3011	0.9 (0.6–1.4)	25	2501	1.1 (0.7–1.8)
High [>28–387.5]	17	2768	0.6 (0.4–1.0)	25	3571	0.8 (0.5–1.2)
			P trend = 0.04			P trend = 0.10

[1]During the period from enrollment (1993–1997) to December 31, 2010 in NC and December 31, 2011 in Iowa.
[2]Numbers of cases in columns do not sum to total number of NHL cases (n = 523) due to missing data. In the enrollment questionnaire, lifetime-days & intensity weighted life-time days of pesticide use was obtained for the insecticides: carbofuran, chlorpyrifos, coumaphos, DDVP, fonofos, permethrin and terbufos; the fungicides: captan, chlothalonil and the fumigant: methyl bromide. In the take home questionnaire lifetime-days & intensity weighted life-time days of pesticide use were obtained for the insecticides: aldicarb, carbaryl, diazinon, malathion, parathion, and phorate, the chlorinated insecticides: aldrin, chlordane, DDT, dieldrin, heptachlor, lindane, and toxaphene, the fungicides: benomyl, maneb/mancozeb and metalaxyl, therefore, numbers of NHL cases can vary among pesticides listed in the table.
[3]Adjusted RR: age (<45, 45–49, 50–54, 55–59, 60–64, 65–69, ≥70), State (NC vs. IA), Race (White vs. Black), AHS herbicides (tertiles of total herbicide use-days). Statistically significant P trends are bolded.
[4]Permethrin for animal use and crop use were combined into one category.
[5]The distribution of life-time days of chlordane exposure was clumped into two exposed groups those who with, ≤8.75 life-time days of exposure and those with >8.75 life-time days of exposure.
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Table 4. Pesticide exposure (Lifetime-Days of Exposure) and adjusted risks for NHL Subtypes.

Insecticides											
	SLL, CLL, MCL		Diffuse Large B-cell		Follicular B-cell		Other B-cell types		Multiple Myeloma		
	RR[3,4] (95% CI)	N[2]	RR[3,4] (95% CI)	N[2]	RR[3,4] (95% CI)	N[2]	RR[3,4] (95% CI)	N[2]	RR[3,4] (95% CI)	N[2]	NHL subtype Homo-geneity Test (p-value)
Carbaryl											
None	1.0 (ref)	42	1.0 (ref)	29	1.0 (ref)	11	1.0 (ref)	14	1.0 (ref)	22	
Low	1.1 (0.6–2.2)	19	0.8 (0.4–1.6)	17	1.6 (0.6–3.9)	10	1.8 (0.7–4.3)	10	0.7 (0.3–1.4)	14	
High	0.6 (0.3–1.3)	15	1.3 (0.6–2.8)	15	2.8 (1.0–7.4)	10	0.4 (0.1–1.5)	3	1.1 (0.7–1.8)	13	
	p trend = 0.16		p trend = 0.33		p trend = 0.06		p trend = 0.63		p trend = 0.98		0.19
Carbofuran											
None	1.0 (ref)	87	1.0 (ref)	78	1.0 (ref)	39	1.0 (ref)	33	1.0 (ref)	56	
Low	1.1 (0.7–1.8)	28	0.9 (0.5–1.7)	13	1.3 (0.7–2.4)	15	0.8 (0.4–1.8)	8	1.9 ((1.1–3.3)	16	
High	1.5 (0.9–2.5)	19	0.8 (0.5–1.3)	13	0.4 (0.1–1.4)	3	0.7 (0.2–2.0)	4	0.9 (0.4–1.6)	12	
	p trend = 0.16		p trend = 0.37		p trend = 0.31		p trend = 0.46		p trend = 0.57		0.52
Chlorpyrifos											
None	1.0 (ref)	84	1.0 (ref)	70	1.0 (ref)	33	1.0 (ref)	31	1 (ref)	58	
Low	1.2 (0.8–1.8)	31	0.9 (0.6–1.5)	22	1.6 (0.9–2.9)	20	1.2 (0.6–2.2)	14	1.0 (0.6–1.8)	17	
High	0.9 (0.6–1.3)	30	1.1 (0.6–1.7)	22	1.0 (0.5–2.1)	11	0.5 (0.2–1.3)	7	0.7 (0.4–1.3)	14	
	p trend = 0.45		p trend = 0.80		p trend = 0.94		p trend = 0.13		p trend = 0.27		0.90
Coumaphos											
None	1.0 (ref)	120	1.0 (ref)	92	1.0 (ref)	48	1.0 (ref)	40	1.0 (ref)	78	
Low	1.1 (0.5–2.2)	8	0.7 (0.3–1.9)	4	2.1 (0.7–5.8)	4	xxx-	4	0.7 (0.2–2.2)	3	
High	1.5 (0.6–3.4)	6	1.6 (0.6–4.5)	4	1.4 (0.5–4.0)	4	xxx-	1	1.2 (0.4–4.0)	3	
	p trend = 0.35		p trend = 0.42		p trend = 0.47		p trend = xxx		p trend = 0.84		0.63
Diazinon											
None	1.0 (ref)	53	1.0 (ref)	40	1.0 (ref)	15	1.0 (ref)	20	1.0 (ref)	41	
Low	1.4 (0.7–2.7)	14	1.5 (0.7–3.2)	9	2.2 (0.9–5.4)	8	xxx	3	0.4 (0.1–1.2)	4	
High	1.9 (0.98–3.6)	12	1.1 (0.5–2.4)	8	3.8 (1.2–11.4)	7	xxx	2	0.5 (0.2–1.7)	3	
	p trend = 0.06		p trend = 0.72		**p trend = 0.02**		p trend = xxx		p trend = 0.35		0.09
DDVP											
None	1.0 (ref)	124	1.0 (ref)	93	1.0 (ref)	48	1.0 (ref)	39	1.0 (ref)	73	
Low	0.8 (0.4–1.9)	6	1.1 (0.4–2.7)	5	1.5 (0.6–3.9)	5	1.1 (0.4–3.7)	3	2.7 (1.2–5.8)	7	
High	0.7 (0.3–1.7)	6	0.9 (0.4–2.3)	5	1.0 (0.3–3.4)	3	0.9 (0.3–3.1)	3	1.0 (0.3–2.7)	4	
	p trend = 0.49		p trend = 0.87		p trend = 0.90		p trend = 0.91		p trend = 0.81		0.96
Fonofos											
None	1.0 (ref)	100	1.0 (ref)	81	1.0 (ref)	45	1.0 (ref)	30	1.0 (ref)	66	
Low	1.2 (0.7–2.0)	20	1.2 (0.7–2.2)	13	1.5 (0.8–3.0)	11	1.4 (0.6–3.1)	8	1.2 (0.6–2.5)	9	
High	1.0 (0.6–1.8)	15	1.2 (0.6–2.3)	11	0.3 (0.1–1.2)	2	1.1 (0.4–2.7)	6	1.4 (0.7–3.0)	9	
	p trend = 0.96		p trend = 0.65		p trend = 0.19		p trend = 0.84		p trend = 0.33		0.35
Malathion											
None	1.0 (ref)	27	1.0 (ref)	20	1.0 (ref)	6	1.0 (ref)	11	1.0 (ref)	17	
Low	0.7 (0.4–1.3)	29	0.96 (0.5–1.8)	23	1.0 (0.4–2.9)	12	1.0 (0.5–2.4)	11	1.0 (0.5–2.1)	18	
High	1.0 (0.6–1.8)	22	1.0 (0.5–2.0)	20	1.6 (0.6–4.4)	11	0.3 (0.1–0.8)	6	1.0 (0.5–2.0)	17	
Ever/Never	1.0 (0.7–1.4)		0.9 (0.6–1.4)		1.3 (0.7–2.4)		0.6 (0.3–1.0)		0.9 (0.6–1.5)		
	p trend = 0.65		p trend = 0.88		p trend = 0.25		p trend = 0.17		p trend = 0.86		0.33
Permethrin											

Table 4. Cont.

Insecticides	SLL, CLL, MCL		Diffuse Large B-cell		Follicular B-cell		Other B-cell types		Multiple Myeloma		
	RR[3,4] (95% CI)	N[2]	RR[3,4] (95% CI)	N[2]	RR[3,4] (95% CI)	N[2]	RR[3,4] (95% CI)	N[2]	RR[3,4] (95% CI)	N[2]	NHL subtype Homo-geneity Test (p-value)
None	1.0 (ref)	108	1.0 (ref)	89	1.0 (ref)	41	1.0 (ref)	38	1.0 (ref)	64	
Low	1.1 (0.6–2.0)	15	0.6 (0.3–1.2)	8	1.3 (0.6–2.7)	8	0.9 (0.3–2.7)	5	1.4 (0.8–2.7)	13	
High	0.8 (0.5–1.5)	15	1.0 (0.5–2.1)	8	1.0 (0.5–2.4)	8	0.5 (0.2–1.7)	4	3.1 (1.5–6.2)	12	
	p trend = 0.53		p trend = 0.99		p trend = 0.88		p trend = 0.28		**p trend = 0.002**		0.10
Phorate											
None	1.0 (ref)	48	1.0 (ref)	37	1.0 (ref)	20	1.0 (ref)	16	1.0 (ref)	36	
Low	1.0 (0.6–1.9)	14	1.4 (0.7–2.7)	15	1.1 (0.4–3.0)	5	0.9 (0.3–2.2)	6	0.7 (0.3–1.8)	6	
High	0.8 (0.4–1.6)	11	0.7 (0.3–2.1)	4	0.8 (0.3–2.2)	5	1.1 (0.4–3.5)	4	0.8 (0.3–2.4)	4	
	p trend = 0.51		p trend = 0.80		p trend = 0.67		p trend = 0.91		p trend = 0.73		0.77
Terbufos											
None	1.0 (ref)	72	1.0 (ref)	63	1.0 (ref)	31	1.0 (ref)	19	1.0 (ref)	59	
Low	1.3 (0.8–2.0)	32	1.2 (0.8–1.9)	29	1.6 (0.9–3.1)	15	1.8 (0.9–3.6)	17	1.1 (0.6–1.9)	12	
High	1.6 (1.0–2.5)	31	1.0 (0.5–2.0)	12	0.8 (0.4–1.7)	10	1.6 (0.7–3.9)	8	1.3 (0.7–2.7)	5	
	p trend = 0.05		p trend = 0.90		p trend = 0.48		p trend = 0.29		p trend = 0.42		0.63
Chlorinated Insecticides											
Aldrin											
None	1.0 (ref)	53	1.0 (ref)	46	1.0 (ref)	22	1.0 (ref)	20	1.0 (ref)	34	
Low	1.0 (0.5–2.0)	11	xxx	2	1.2 (0.4–3.8)	4	0.4 (0.1–1.5)	3	2.1 (0.9–4.7)	8	
High	1.0 (0.5–2.0)	10	xxx	3	0.8 (0.3–2.5)	4	1.1 (0.3–3.9)	3	1.2 (0.5–3.2)	6	
	p trend = 0.70		p trend = xxx		p trend = 0.21		p trend = 0.67		p trend = 0.40		0.98
Chlordane											
None	1.0 (ref)	48	1.0 (ref)	42	1.0 (ref)	20	1.0 (ref)	21	1.0 (ref)	32	
Low	1.8 (1.0–3.1)	16	1.0 (0.5–2.2)	8	1.7 (0.7–4.3)	6	xxx	2	1.7 (0.9–3.3)	13	
High	1.5 (0.7–3.3)	8	1.4 (0.6–3.3)	7	1.3 (0.4–4.6)	3	xxx	2	0.7 (0.2–2.2)	3	
	p trend = 0.34		p trend = 0.69		p trend = 0.70		p trend = xxx		p trend = 0.57		0.85
DDT											
None	1.0 (ref)	42	1.0 (ref)	34	1.0 (ref)	17	1.0 (ref)	16	1.0 (ref)	28	
Low	1.0 (0.5–1.8)	16	1.6 (0.4–3.1)	2	3.3 (1.4–8.1)	9	0.4 (0.3–2.5))	5	1.2 (0.6–2.6)	10	
High	2.6 (1.3–4.8)	15	1.4 (0.6–3.5)	3	1.1 (0.3–3.6)	4	2.1 (0.7–6.5)	5	0.8 (0.4–1.8)	9	
	p trend = 0.04		P trend = 0.17		p trend = 0.80		p trend = 0.64		p trend = 0.37		0.44
Heptachlor											
None	1.0 (ref)	58	1.0 (ref)	47	1.0 (ref)	24	1.0 (ref)	21	1.0 (ref)	40	
Low	1.1 (0.5–2.3)	9	xxx	3	xxx	2	xxx	3	1.3 (0.4–3.8)	4	
High	1.4 (0.7–3.0)	9	xxx	1	xxx	1	xxx	2	1.2 (0.4–3.6)	4	
	p trend = 0.16		p trend = xxx		p trend = xxx		p trend = xxx		p trend = 0.91		0.68
Lindane											
None	1.0 (ref)	57	1.0 (ref)	49	1.0 (ref)	16	1.0 (ref)	21	1.0 (ref)	43	
Low	1.2 (0.6–2.5)	10	0.6 (0.2–1.7)	4	4.9 (1.9–12.6)	6	xxx	2	xxx	3	
High	2.6 (1.2–5.6)	9	2.0 (0.6–6.5)	3	3.6 (1.4–9.5)	6	xxx	1	xxx	2	
	p trend = 0.13		p trend = 0.96		**p trend = 0.04**		p trend = xxx		p trend = xxx		0.54
Toxaphene											
None	1.0 (ref)	68	1.0 (ref)	47	1 (ref)	23	1.0 (ref)	22	1.0 (ref)	40	

Table 4. Cont.

Insecticides	SLL, CLL, MCL		Diffuse Large B-cell		Follicular B-cell		Other B-cell types		Multiple Myeloma		
	RR[3,4] (95% CI)	N[2]	RR[3,4] (95% CI)	N[2]	RR[3,4] (95% CI)	N[2]	RR[3,4] (95% CI)	N[2]	RR[3,4] (95% CI)	N[2]	NHL subtype Homogeneity Test (p-value)
Low	0.9 (0.4–2.3)	5	1.3 (0.5–3.3)	5	xxx	2	xxx	3	0.7 (0.2–2.0)	4	
High	0.4 (0.1–1.6)	2	0.9 (0.3–3.0)	3	xxx	2	xxx	2	0.7 (0.2–2.9)	2	
	p trend = 0.08		p trend = 0.77		p trend = xxx		p trend = xxx		p trend = 0.64		0.34
Fungicides											
Captan											
None	1.0 (ref)	118	1.0 (ref)	91	1.0 (ref)	52	1.0 (ref)	39	1.0 (ref)	76	
Low	0.9 (0.4–1.9)	7	1.1 (0.5–2.4)	7	xxx	2	xxx	3	1.4 (0.5–3.4)	5	
High	1.1 (0.5–2.6)	7	0.7 (0.1–3.1)	4	xxx	1	xxx	2	1.2 (0.5–2.9)	5	
	p trend = 0.78		p trend = 0.58		p trend = xxx		p trend = xxx		p trend = 0.75		0.92
Chlorothalonil											
None	1.0 (ref)	135	1.0 (ref)	107	1.0 (ref)	60	1.0 (ref)	50	1.0 (ref)	84	
Low	0.9 (0.4–2.3)	5	1.1 (0.4–3.1)	4	xxx	3	−xxx	1	1.1 (0.4–2.8)	5	
High	1.1 (0.4–3.3)	4	0.3 (0.1–1.2)	2	xxx	2	−xxx	1	0.7 (0.6–2.3)	3	
	p trend = 0.83		p trend = 0.09		p trend = xxx		p trend = xxx		p trend = 0.56		0.76
Metalaxyl											
None	1.0 (ref)	60	1.0 (ref)	45	1.0 (ref)	25	1.0 (ref)	23	1.0 (ref)	39	
Low	2.8 (1.4–5.8)	9	1.1 (0.4–2.6)	7	xxx	3	−xxx	2	0.4 (0.1–1.1)	4	
High	1.1 (0.4–2.8)	6	1.0 (0.4–2.7)	5	xxx	2	−xxx	1	1.1 (0.4–3.2)	4	
	p trend = 0.99		p trend = 0.97		p trend = xxx		p trend = xxx		p trend = 0.87		0.92
Maneb/ Mancozeb											
None	1.0 (ref)	69	1.0 (ref)	49	1.0 (ref)	25	1.0 (ref)	26	1.0 (ref)	41	
Low	2.1 (0.7–6.0)	4	4.0 (1.4–11.6)	4	xxx	2	−xxx	0	1.0 (0.4–2.5)	5	
High	1.2 (0.3–4.0)	3	0.9 (0.3–3.1)	3	−xxx	1	−xxx	0	2.2 (0.5–9.5)	2	
	p trend = 0.84		p trend = 0.74		p trend = xxx		p trend = xxx		p trend = 0.28		0.82
Fumigant											
Methyl Bromide											
None	1.0 (ref)	126	1.0 (ref)	86	1.0 (ref)	58	1.0 (ref)	44	1.0 (ref)	76	
Low	1.1 (0.5–2.2)	9	4.0 (2.2–7.4)	15	1.4 (0.5–4.2)	4	3.6 (1.3–9.8)	5	1.0 (0.5–2.1)	8	
High	0.8 (0.4–1.8)	8	1.0 (0.5–2.1)	11	0.3 (0.1–1.1)	3	1.3 (0.3–5.0)	3	0.8 (0.4–1.8)	8	
	p trend = 0.58		p trend = 0.67		p trend = 0.08		p trend = 0.56		p trend = 0.63		0.59

[1]During the period from enrollment (1993–1997) to December 31, 2010 in NC and December 31, 2011 in Iowa.
[2]Numbers of cases in columns do not sum to total number of NHL cases (n = 523) due to missing data. Ever/never use of all 26 pesticides (table 3) do not always match with exposure-response data in table 4 because of missing data to calculate lifetime-days of use.
[3]Adjusted for age (<45, 45–49, 50–54, 55–59, 60–64, 65–69, ≥70), State (NC vs. IA), Race (White vs. Black), AHS herbicides (in tertiles of total herbicide use-days). Significant RR and 95% confidence limits are bolded.
[4]RR was not calculated if the number of exposed cases for any NHL subtype was <6 and these cells are marked XXX. Four pesticides included in Table 2 (i.e., aldicarb, benomyl, dieldrin and parathion) were not included in Table 4 because no NHL subtype included≥6 cases of a specific cell types with lifetime-days of exposure.
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risk estimates (i.e., narrower confidence intervals) when we included phase 2 imputed data (n = 54,306) (data not shown). Lagging exposures by five years did not meaningfully change the association between lindane or DDT and total NHL (data not shown). The significant exposure-response trends linking use of a particular pesticide to NHL and certain NHL subtypes did not always correspond to a significant excess risk among those who ever used the same pesticide. For chemicals for which the detailed information was only asked about in the take-home questionnaire, we evaluated potential differences between the ever/never analyses based on the enrolment questionnaire and data from the same sub-set of participants who completed the exposure-

response in the take-home questionnaire and found no meaningful differences in the results. We also evaluated the impact of using an updated definition of NHL; when using the original ICD-O-3 definition of NHL[19], lifetime-days of lindane use remained significantly associated with NHL risk (RR = 1.0 (ref), 1.3 (0.7–2.6), 1.2 (0.6–2.8), 2.7 (1.3–5.4), p trend = 0.006). The trend between total NHL and lifetime-days of DDT, however, was less clear and not statistically significant (RR = 1.0 (ref) 1.3 (0.9–1.8), 1.1 (0.5–2.1), 1.4 (0.8–2.6), p trend = 0.32) [Table S3 in File S1]. Carbaryl and diazinon showed non-significant trends with the older definition of NHL, but not with the newer definition used here.

Discussion

A significant exposure–response trend for total NHL was observed with increasing lifetime-days of use for two organochlorine insecticides, lindane and DDT, although RRs from ever/never comparisons were not elevated. On the other hand, terbufos use showed a significant excess risk with total NHL in ever vs. never exposed analysis, but displayed no clear exposure-response trend. Several pesticides showed significant exposure-response trends with specific NHL subtypes however, when polytomous models were used to test the difference in parametric estimates of trend among the five NHL subtypes, there was no evidence of heterogeneity in the sub-types for specific chemicals. The subtype relationships that looked particularly interesting were DDT and terbufos with the SLL/CLL/MCL subtype, lindane and diazinon with the follicular subtype, and permethrin with MM. These pesticide-NHL links should be evaluated in future studies.

Lindane (gamma-hexachlorocyclohexane) is a chlorinated hydrocarbon insecticide. Production of lindane was terminated in the United States in 1976, but imported lindane was used to treat scabies and lice infestation and for agricultural seed treatment [21] until its registration was cancelled in 2009 [22], the same year production was banned worldwide [23]. In our study, 3,410 people reporting ever using lindane (6%) prior to enrollment, 433 reported use at the phase 2 questionnaire (1%), indicating that use had dropped substantially. Oral administration of lindane has increased the incidence of liver tumors in mice and less clearly, thyroid tumors in rats [24]. Lindane produces free radicals and oxidative stress (reactive oxygen species [ROS]) [25] and has been linked with chromosomal aberrations in human peripheral lymphocytes in vitro [26].

Lindane has been linked with NHL in previous epidemiologic studies. A significant association between lindane use and NHL was observed in a pooled analysis of three population-based case-control studies conducted in the Midwestern US, with stronger relative risks observed for greater duration and intensity of use [27]. NHL was also associated with lindane use in a Canadian case-control study [28]. Lindane was significantly associated with NHL risk in an earlier report from the AHS [29]. We are not aware of any previous study that assessed the association between a NHL subtype and lindane use. The exposure-response pattern with total NHL and the follicular lymphoma subtype indicates a need for further evaluation of lindane and NHL.

DDT is an organochlorine insecticide that was used with great success to control malaria and typhus during and after World War II [29] and was widely used for crop and livestock pest control in the United States from the mid-1940s to the 1960s [30]. Its registration for crop use was cancelled in the US in 1972 [30] and banned worldwide for agricultural use in 2009, but continues to be used for disease vector control in some parts of the world [23]. In our study, 12,471 participants (23%) reported ever using DDT prior to enrollment; 12%, 8.7% and 2.3% responding to the take-home questionnaire reported their first use occurred prior to the 1960s, during the 1960s, and during the 1970s, respectively. The National Toxicology Program classifies DDT as "reasonably anticipated to be a human carcinogen" [31] and IARC classifies DDT as a "possible human carcinogen (2B)" [12], both classifications were based on experimental studies in which excess liver tumors were observed in two rodent species. Epidemiology data on the carcinogenic risk of DDT is inconsistent. NHL was not associated with use of DDT in a pooled analysis of three case-control studies in the U.S. where information on exposure was obtained from farmers by questionnaire [32]. There also was no association between the use of DDT and NHL in our study when we used an earlier definition of NHL [18], suggesting some of the inconsistency may be due to disease definition. In the large Epilymph study, no meaningful links between DDT and the risk of NHL, or diffuse large B cell lymphoma were observed, and only limited support was found for a link to CLL [33], although a case-control study of farmers in Italy suggested increased risk of NHL and CLL with DDT exposure [34]. NHL was not associated with serum levels of DDT in a prospective cohort study from the U.S. [35], but NHL was associated with the DDT-metabolite p, p'-DDE, as well as chlordane and heptachlor-related compounds (oxychlordane, heptachlor epoxide) and dieldrin, in a study with exposure measured in human adipose tissue samples [36]. In a Danish cohort, a higher risk of NHL was associated with higher prediagnostic adipose levels of DDT, cis-nonachlor, and oxychlordane [37]. In a Canadian study, analytes from six insecticides/insecticide metabolites (beta-hexachlorocyclohexane, p, p'-dichloro-DDE, hexachlorobenzene (HCB), mirex, oxychlordane and transnonachlor) were linked with a significant increased risk with NHL [38]. However, in an analysis of plasma samples from a case-control study in France, Germany and Spain, the risk of NHL did not increase with plasma levels of hexachlorobenzene, beta-hexachlorobenzene or DDE [39]. In this analysis, NHL was significantly associated with reported use of DDT, but not with the other organochlorine insecticides studied (i.e., aldrin, chlordane, dieldrin, heptachlor, toxaphene). Our findings add further support for an association between DDT and total NHL and our results on SLL/CLL/MCL are novel and should be further explored.

Permethrin is a broad-spectrum synthetic pyrethroid pesticide widely used in agriculture and in home and garden use as an insecticide and acaricide, as an insect repellant, and as a treatment to eradicate parasites such as head lice or mites responsible for scabies [40]. This synthetic pyrethroid was first registered for use in the United States in 1979 [40]. The U.S. Environmental Protection Agency classified permethrin as "likely to be carcinogenic to humans" largely based on the observed increase incidence of benign lung tumors in female mice, liver tumors in rats and liver tumors in male and female mice [41]. Permethrin was not associated with NHL overall in our study, nor in pooled case-control studies of NHL from the U.S (the NHL definition in use at the time of the study did not include MM) [42]. In our analysis, however, the risk of MM increased significantly with lifetime-days of exposure to permethrin, as had been noted in an earlier analysis of AHS data [43]. We are unaware of other studies that have found this association.

Terbufos is an organophosphate insecticide and nematicide first registered in 1974 [44]. The EPA classifies terbufos as Group E, i.e., "Evidence of Non-Carcinogenicity for Humans" [44]. We found some evidence for an association between terbufos use and NHL, particularly for the SLL/CLL/MCL subtype. NHL was not associated with terbufos in the pooled case-control studies from the

U.S. [42] but there was a non-significant association between terbufos and small cell lymphocytic lymphoma [10].

Diazinon is an organophosphate insecticide registered for a variety of uses on plants and animals in agriculture [45]. It was commonly used in household insecticide products until the EPA phased out all residential product registrations for diazinon in December 2004 [45,46]. In an earlier evaluation of diazinon in the AHS, a significant exposure-response association was observed for leukemia risk with lifetime exposure-days [47]. While there was no link between diazinon and NHL overall in this analysis, there was a statistically significant exposure-response association between diazinon and the follicular lymphoma subtype and an association with the SLL/CLL/MCL subtype that was not statistically significant. Diazinon was previously associated with NHL in pooled case-control studies from the U.S. and particularly with SLL [10].

Several other insecticides, fungicides and fumigants cited in recent reviews of the pesticide-cancer literature suggested etiological associations with total NHL [8,9], these include: oxychlordane, trans-nonachlor, and cis-nonachlor which are metabolites of chlordane; and dieldrin and toxaphene among NHL cases with t(14,18) translocations. We did not find a significant association between chlordane and total NHL nor with any NHL subtype, but we did not have information about chlordane metabolites to make a more direct comparison. Similarly we did not observe a significant association between dieldrin nor toxaphene and total NHL nor with any NHL subtypes. Mirex (1,3-cyclopentadiene), an insecticide, and hexachlorobenzene, a fungicide, were also associated with NHL risk [8,9] but we did not examine these compounds in the AHS.

This study has a number of strengths. It is a large population of farmers and commercial pesticide applicators who can provide reliable information regarding their pesticide use history [48]. Information on pesticide use and application practices was obtained prior to onset of cancer. An algorithm that incorporated several exposure determinants which predicted urinary pesticide levels was used to develop an intensity-weighted exposure metric in our study [20]. Exposure was ascertained prior to diagnosis of disease, which should eliminate the possibility of case-response bias [14]. Because of the detailed information available on pesticide use, we were able to assess the impact for the use of multiple pesticides. For example, we evaluated total pesticide use-days, and specific pesticides found to be associated with NHL or its subtypes in the AHS. We found no meaningful change in the associations with DDT, lindane, permethrin, diazinon and terbufos from such adjustments. Information on many potential NHL risk factors was available and could be controlled in the analysis.

Most epidemiological investigations of NHL prior to 2007 [17] did not include CLL and MM as part of the definition. These two subtypes made up 37% (193/523) of the NHL cases in this analysis. This is a strength of our study in that the definition of NHL used here is based on the most recent classification system [16,17] and will be relevant for comparisons with future studies. On the other hand, the inclusion of MM and CLL in the recent definition of NHL makes comparisons of our findings with earlier literature challenging, because the NHL subtypes may have different etiologies. For example, DDT was not significantly associated with NHL using the older definition, but was significantly associated with the NHL using the most recent definition of NHL because of its association with the SLL/CLL/MCL subtype (Table S1 in File S1). On the other hand, carbaryl and diazinon were associated with the old definition of NHL (although non-significantly) but not with the new definition. Lindane, however, was associated with both definitions of NHL. Lindane was significantly associated with the follicular lymphoma subtype and this subtype was included in the older and newer definition of NHL. No other pesticides were significantly associated with NHL under the old definition (Table S3 in File S1).

Although this is a large prospective study, limitations should be acknowledged. A small number of cases exposed to some specific pesticides could lead to false positive or negative findings. We also had reduced statistical power to evaluate some pesticides for total days of use and intensity-weighted days of use because some participants did not complete the phase one take-home questionnaire and the tests of homogeneity between specific pesticides and specific NHL subtypes were underpowered. Some chance associations could occur because of multiple testing, i.e., a number of pesticides, several NHL subtypes, and more than one exposure metric. Despite the generally high quality of the information on pesticide use provided by AHS participants [48,50], misclassification of pesticide exposures can occur and can have a sizeable impact on estimates of relative risk, which in a prospective cohort design would tend to produce false negative results [49].

Conclusion

Our results showed pesticides from different chemical and functional classes were associated with an excess risk of NHL and NHL subtypes, but not all members of any single class of pesticides were associated with an elevated risk of NHL or NHL subtypes, nor were all chemicals of a class included on our questionnaire. Significant pesticide associations were between total NHL and reported use of lindane and DDT. Links between DDT and terbufos and SLL/CLL/MCL, lindane and diazinon and follicular lymphoma, and permethrin and MM, although based on relatively small numbers of exposed cases, deserve further evaluation. The epidemiologic literature on NHL and these pesticides is inconsistent and although the findings from this large, prospective cohort add important information, additional studies that focus on NHL and its subtypes and specific pesticides are needed. The findings from this large, prospective cohort add important new information regarding the involvement of pesticides in the development of NHL. It provides additional information regarding specific pesticides and NHL overall and some new leads regarding possible links with NHL subtypes that deserve evaluation in future studies.

Supporting Information

File S1 This file contains Table S1, Table S2, and Table S3. Table S1, Frequency of NHL in Agricultural Health Study applicators using New (Interlymph hierarchical classification of lymphoid neoplasms) and Older Definitions (ICD-O-3). Table S2, Pesticides included in the Agricultural Health Study questionnaires by Chemical/Functional Class. Table S3, Pesticide exposure (lifetime-days) and adjusted risks of total NHL incidence (Older definition [ICD-O-3]).
(DOC)

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References

1. Milham S (1971) Leukemia and multiple myeloma in farmers. Am J Epidemiol 94: 507–510.
2. Cantor KP (1982) Farming and mortality from non-Hodgkin's lymphoma: a case-control study. Int J Cancer 29: 239–247.
3. Blair A, Malker H, Cantor KP, Burmeister L, Wiklund K (1985) Cancer among farmers: A review. Scand J Work Environ Health 11: 397–407.
4. Pearce NE, Smith AH, Fischer DO (1985) Malignant lymphoma and multiple myeloma linked with agricultural occupation in a New Zealand cancer registration-base-study. Am J Epidemiol 121: 235–237.
5. Baris D, Silverman DT, Brown LM, Swanson GM, Hayes RB, et al. (2004) Occupation, pesticide exposure and risk of multiple myeloma. Scand J Work Environ Health 30(3): 215–222.
6. Beane Freeman LE, DeRoos AJ, Koutros S, Blair A, Ward MH, et al. (2012) Poultry and livestock exposure and cancer risk among farmers in the agricultural health study. Cancer Causes Control 23: 663–670.
7. Cordes DH, Rea DF (1991) Farming: A Hazardous Occupation. In: Health Hazards of Farming. Occupational Medicine: State of the Art Reviews. Vol6(3). Hanley & Belfus, Inc., Philadelphia, PA.
8. Alavanja M, Bonner M (2012) Occupational pesticide exposure and cancer risk. A Review. J. Toxicol Environ Health B Critic Review. 1594: 238–263.
9. Alavanja MCR, Ross MK, Bonner MR (2013) Increased cancer burden among pesticide applicators and others due to pesticide exposure. CA, Cancer J Clin; 63(2): 120–142.
10. Waddell BL, Zahm SH, Baris D, Weisenburger DD, Holmes F, et al. (2001). Agricultural use of organophosphate pesticides and the risk of non-Hodgkin's lymphoma among male farmers (United States). Cancer Causes and Control 12: 509–517.
11. Merhi M, Raynal H, Cahuzac E, Vinson F, Cravedi JP, et al. (2007) Occupational exposure to pesticides and risk of hematopoietic cancers: meta-analysis of case-control studies. Cancer Causes Control. 18: 1209–1226.
12. IARC (1991) International Agency for Research on Cancer (IARC). Occupational Exposures in Insecticide applications and some pesticides. Lyon, France: IARC, 1991. Monographs on the Evaluation of Carcinogenic Risk to Humans, volume 53.
13. Morton LM, Slager SL, Cerhan JR, Wang SS, Vajdic CM, et al. (2014) Etiologic Heterogeneity Among NHL Subtypes: The InterLymph NHL Subtypes Project. J Natl Cancer Institute 48: 130–144.
14. Alavanja MCR, Sandler DP, McMaster SB, Zahm SH, McDonnell CJ, et al. (1996) The Agricultural Health Study. Environ Health Perspect 104: 362–369.
15. Alavanja MC, Samanic C, Dosemeci M, Lubin J, Tarone R, et al. (2003) Use of agricultural pesticides and prostate cancer risk in the Agricultural Health Study Cohort. Am J Epidemiol 157(9): 800–814.
16. SEER Program, National Cancer Institute. Available: http://seer.cancer.gov/lymphomarecode Accessed September 15, 2013.
17. Morton LM, Turner JJ, Cerhan JR, Linet MS, Treseler PA, et al. (2007) Proposed classification of lymphoid neoplasms for epidemiologic research from the Pathology Working Group of the International Lymphoma Epidemiology Consortium (InterLymph). Blood 110(2): 695–708.
18. Percy C, Fritz A, Ries L (2001) Conversion of neoplasms by topography and morphology from the International Classification of Disease for Oncology, second edition, to International Classification of Diseases for Oncology, 3rd ed. Cancer Statistics Branch, DCCPS, SEER Program, National Cancer Institute; 2001.
19. Heltshe SL, Lubin JH, Koutros S, Coble JB, Ji B-T, et al. (2012) Using multiple imputation to assign pesticide use for non-respondents in the follow-up questionnaire in the Agricultural Health Study J. Exp Sci Environ Epidemiol 22(4): 409–416.
20. Coble J, Thomas KW, Hines CJ, Hoppin JA, Dosemeci M, et al. (2011) An updated algorithm for estimation of pesticide exposure intensity in the Agricultural Health Study. Int J Environ Res Public Health. 8(12): 4608–4622.
21. ATSDR (2005) Agency for Toxic Substances and Disease Registry. Toxicological profile for Alpha-, Beta-, Gamma- and Delta- Hexachlorcyclohexane, August, 2005. Available: http://www.atsdr.cdc.gov/Toxprofiles/tp43.pdf. Accessed 2013 Sep 15.
22. EPA (2006a) US Environmental Protection Agency (2006). Lindane; Cancellation Order December 13, 2006. Federal Register/Vol 71, number 239, page 74905.
23. Stockholm Convention Report (2009) Report of the conference of the Parties of the Stockholm Convention on Persistent Organic Pollutants on the work of its fourth meeting. Convention on Persistent Organic Pollutants. Fourth Meeting, Geneva, 4–8 May 2009. Available: http://chm.pops.int/Portals/0/Repository/COP4/UNEP-POPS-COP.4–38.English.pdf.
24. IARC (1987) International Agency for Research on Cancer (IARC). Overall evaluation of carcinogenicity: an updating of IARC monographs volume 1 to 42. Lyon, France: IARC, 1987. Monographs on the Evaluation of Carcinogenic Risk to Humans, Supplement 7.
25. Piskac-Collier AL, Smith MA (2009) Lindane-induced generation of reactive oxygen species and depletion of glutathione do not result in necrosis in renal distal tube cells. J Toxicol and Environ Health, Part A. 72: 1160–1167.
26. Rupa DS, Reddy PP, Reddi OS (1989). Genotoxic effect of benzene hexachloride in cultured human lymphocytes. Hum Genet 83: 271–273.
27. Blair A, Cantor KP, Zahm SH (1998) Non-Hodgkin's lymphoma and agricultural use of the insecticide lindane. Am J Ind Med 33: 82–87.
28. McDuffie HH, Pahwa P, Mclaughlin JR, Spinelli JJ, Fincham S, et al. (2001) Non-Hodgkin's lymphoma and specific pesticide exposures in Men: Cross-Canada Study of Pesticides and Health. Cancer, Epidemiology, Biomarkers & Prevention 10: 1155–1163.
29. Purdue MP, Hoppin JA, Blair A, Dosemeci M, Alavanja MCR (2007) Occupational exposure to organochlorine insecticides and cancer incidence in the Agricultural Health Study. Int J Cancer. 120(3): 642–649.
30. EPA (2012) US Environmental Protection Agency 2012. DDT-A Brief History and Status. Available: http://www.epa.gov/pesticides/factsheets/chemicals/ddt-brief-history-status.htm. Accessed 2013 Sep 15.
31. NTP (2011) National Toxicology Program, Report on Carcinogen- Twelfth Edition. Available: http://ntp.niehs.nih.gov/go/roc12. Accessed 2013 Sep 15.
32. Baris D, Zahm SH, Cantor KP, Blair A (1998). Agricultural use of DDT and the risk of non-Hodgkin's lymphoma: pooled analysis of three case-control studies in the United States, Occup Environ Med 55: 522–527.
33. Cocco P, Satta G, Dubois S, Pilli C, Pillieri M, et al. (2013) Lymphoma risk and occupational exposure to pesticides: results of the Epilymph study. Occupational Environ Med 70(2): 91–98.
34. Nanni O, Amadori D, Lugaresi C, Falcini F, Scarpi E, et al. (1996) Chronic lymphocytic leukaemia and non-Hodgkin's lymphomas by histological type in farming-animal breeding workers: a population case-control study based on a priori exposure matrics Occup Environ Med 53(10): 652–657.
35. Rothman N, Cantor KP, Blair A, Bush D, Brock JW, et al. (1997) A nested case-control study of non-Hodgkin lymphoma and serum organochlorine residues. The Lancet 350: 240–244.
36. Quintana PJE, Delfino RJ, Korrick S, Ziogas A, Kutz FW, et al. (2004) Adipose tissue levels of organochlorine pesticides and chlorinated biphenyls and the risk of non-Hodgkin's lymphoma. Environ Health Perspect 112: 854–861.
37. Brauner EV, Sorensen MA, Gaudreau E, LeBlanc A, Erikson KT, et al. (2012) A prospective study of organochlorines in adipose tissue and risk of non-Hodgkin lymphoma. Environ Health Perspect. 120(1): 105–111.
38. Spinelli JJ, Ng CH, Weber JP, Connors JM, Gascoyne RD, et al. (2007) Organochlorines and risk of non-Hodgkin lymphoma. Int J Cancer. 121(12): 2767–2775.
39. Cocco P, Brennan P, Ibba A, de Sanjose Llongueras S (2008) Plasma polychlorobiphenyl and organochlorine pesticide level and risk of major lymphoma subtypes. Occup Environ Med 65: 132–140.
40. EPA 2006(b). U.S. Environmental Protection Agency. 2006. Re-registration Eligibility Decision for Permethrin: Available: http://www.epa.gov/oppsrrd1/REDs/permethrin_red.pdf. Accessed 2013 Sep 15.
41. NPIC (2012). National Pesticide Information Center. Chemicals Evaluated for Carcinogenic Potential. Office of Pesticide Programs. U.S. Environmental Protection Agency. November 2012. Available: http://npic.orst.edu/chemicals_evaluated.pdf. Accessed 2013 Sep 15.
42. De Roos AJ, Zahm SH, Cantor KP, Weisenburger DD, Holmes FF, t al. (2003) Integrative assessment of multiple pesticides as risk factors for non-Hodgkin's lymphoma among men Occup Environ Med 60: E11.
43. Rusiecki JA, Patel R, Koutros S, Beane Freeman LE, Landgren O, et al. (2009) Cancer incidence among pesticide applicators exposed to permethrin in the Agricultural Health Study. Environ Health Perspect 117: 582–586.
44. EPA 2006(b). U.S. Environmental Protection Agency. 2006. Re-registration Eligibility Decision for Terbufos: Available: http://www.epa.gov/pesticides/reregistration/REDs/terbufos_red.pdf Accessed 2013 Nov 18.
45. Environmental Protection Agency, 2004. Interim registration eligibility decision: diazinon. Available: http://www.epa.gov/pesticides/reregistration/REDs/diazinon_red.pdf. Accessed 2013 Nov 18.
46. Donaison D, Kieley T, Grube A (2002) Pesticide industry sales and usage: 1998 and 1999 market estimates. Washington, DC.: US Environmental Protection Agency, 2002 (EPA-733-R-02–001).

Author Contributions

Conceived and designed the experiments: MCA DPS AB. Performed the experiments: MCA CFL KT CJH. Analyzed the data: MCA JNH CFL CJH KHB JB DWB KT DPS JAH SK GA JHL AB LEB. Contributed reagents/materials/analysis tools: MCA JB DWB CFL. Wrote the paper: MCA LEBF JNH CFL CJH KT AB DWB JHL. Designed the software: JB DWB.

47. Beane Freeman LE, Bonner MR, Blair A, Hoppin JA, Sandler DP, et al. (2005). Cancer incidence among male pesticide applicators in the Agricultural Health Study cohort exposed to diazinon. Am J Epidemiol. 162: 1070–1079.
48. Blair A. Tarone R, Sandler D, Lynch CF, Rowland A, et al. (2002) Reliability of reporting on life-style and agricultural factors by a sample of participants in the Agricultural Health Study from Iowa. Epidemiology 13(1): 94–99.
49. Blair A, Thomas HT, Coble J, Sandler DP, Hines CJ, et al. (2011). Impact of pesticide exposure on misclassification on estimates of relative risks in the Agricultural Health Study. Occup Environ Med 68: 537–541.
50. Thomas KW, Dosemeci M, Coble JB, Hoppin JA, Sheldon LS, et al. (2010) Assessment of a pesticide exposure intensity algorithm in the Agricultural Health Study. J Expo Sci Environ Epidemiol 20(6): 559–569.