UNITED STATES DISTRICT COURT
NORTHERN DISTRICT OF CALIFORNIA

IN RE: ROUNDUP	)	
PRODUCTS LIABILITY	)	MDL No. 2741
LITIGATION	)	
_____	)	Case No.
THIS DOCUMENT RELATES	)	16-md-02741-VC
TO ALL CASES	)	

SATURDAY, APRIL 8, 2017
CONFIDENTIAL - SUBJECT TO PROTECTIVE ORDER

- - -

Videotaped deposition of John Acquavella, Ph.D., Volume II, held at the offices of HUSCH BLACKWELL, L.L.C., 190 Carondelet Plaza, Suite 600, St. Louis, Missouri, commencing at 9:11 a.m., on the above date, before Carrie A. Campbell, Registered Diplomate Reporter, Certified Realtime Reporter, Illinois, California & Texas Certified Shorthand Reporter, Missouri & Kansas Certified Court Reporter.

- - -

MR. MILLER: Excuse me, Counsel. I don't have a copy yet. Thank you. All right. I have it now.

QUESTIONS BY MR. COPLE:

Q. Do you remember that exhibit, 10-5?

A. Yes.

Q. Now, do you remember yesterday with respect to Exhibit 10-5 counsel asking you questions regarding California's Proposition 65?

A. Yes.

Q. Now, as a nonlawyer, are you aware whether Prop 65 was triggered by a finding issued by IARC?

A. You know, I've heard that. It didn't occur to me yesterday when I was giving testimony, but I know that IARC decisions have an effect in lots of jurisdictions, and California is one of them.

Q. IARC determined, based on hazard identification, that glyphosate, in its view, is a probable carcinogen.

Is that a correct finding?

A. Right. So I say yes in the context that they don't consider, you know, feasibility, necessarily, or plausibility, first, based on the amount of likely exposure and the frequency of exposure that people who have contact with the chemical are likely to have.

So that's -- the shorthand for that is hazard identification, so, yes, in that context.

Q. Did IARC get the science correct?

A. We think science -- we think IARC got the science wrong, and we think they got the science wrong in many different areas, toxicology, genotoxicity, and also had a different interpretation of the epidemiology than the IARC epidemiology working group.

Q. Based on your scientific review for your expert epi panel as part of Intertek, did you find that there's evidence of carcinogenicity with exposure to glyphosate?

MR. MILLER: Expert.

Occupational Cancer Research Centre

An Detailed Evaluation of Glyphosate Use and the Risk of Non-Hodgkin Lymphoma in the North American Pooled Project (NAPP)

CSEB Conference | Mississauga, ON | June 3, 2015

Towards a cancer-free workplace

About NHL and Glyphosate

NHL is…

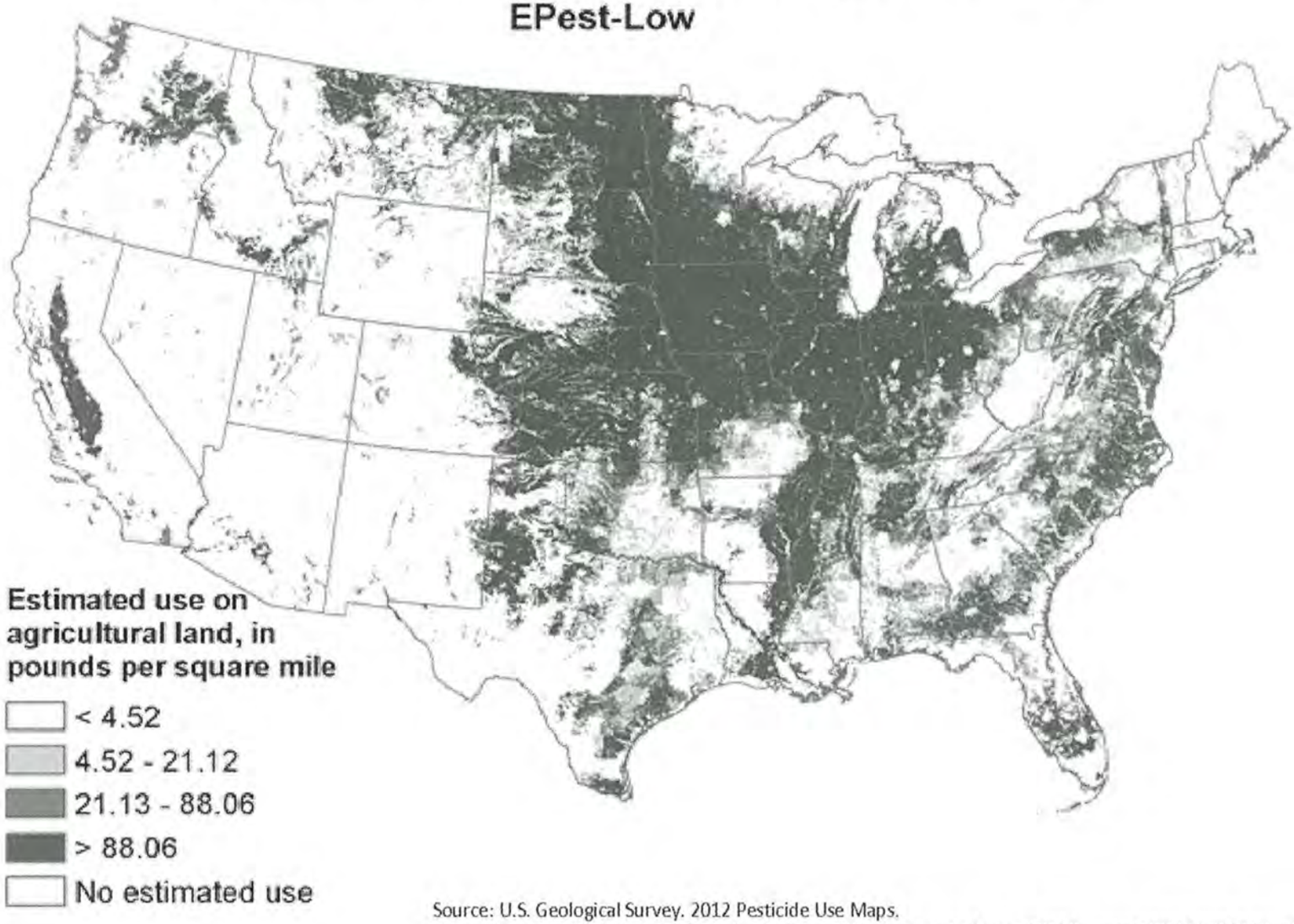
- A cancer that starts in the lymphocytes
- Heterogeneous, according to type of cell affected

Glyphosate is…

- 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

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.[5] In mice, malathion increased hepatocellular adenoma or carcinoma (combined).[20] 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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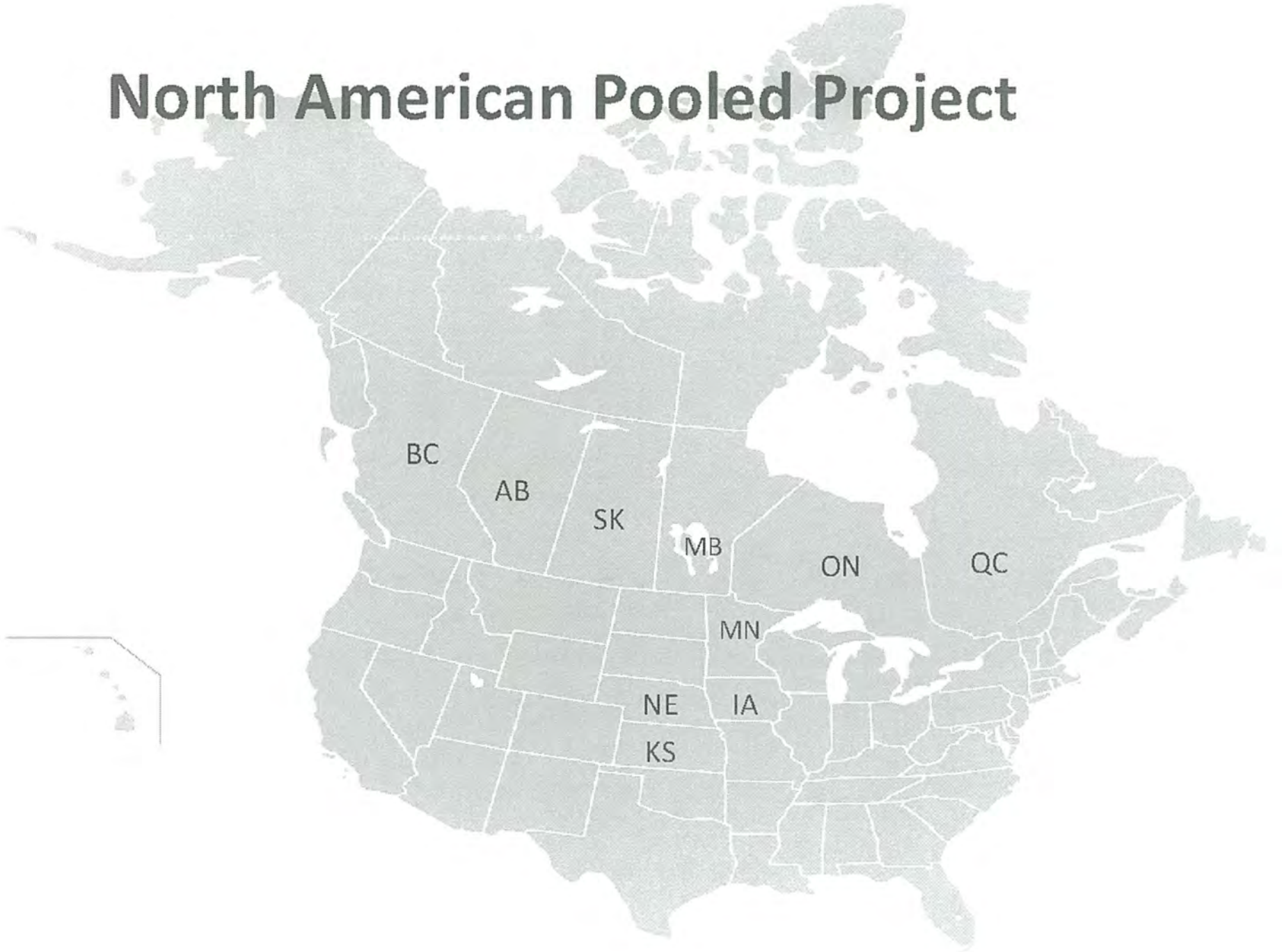
North American Pooled Project
BC
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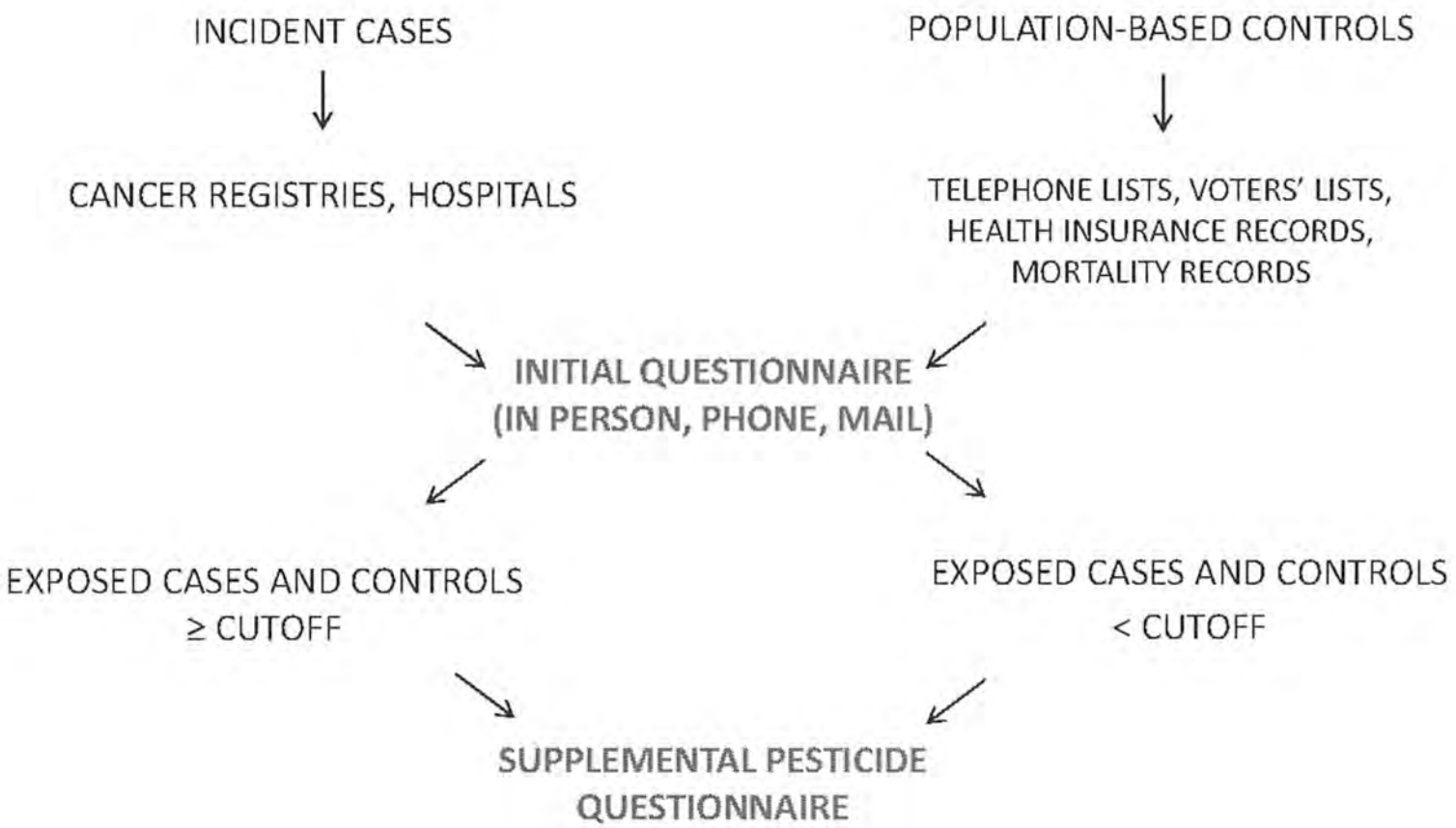
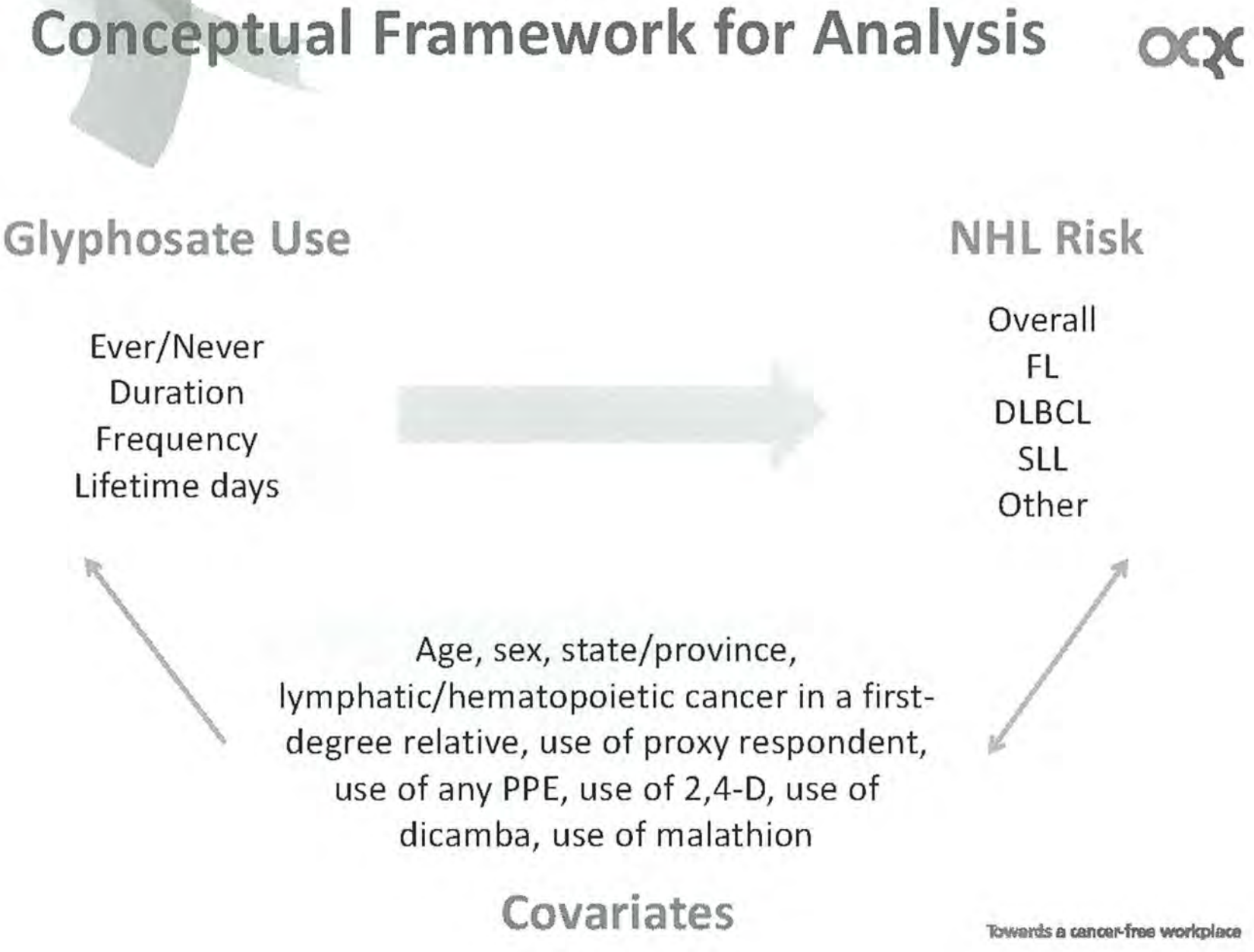
Design of Case-Control Studies



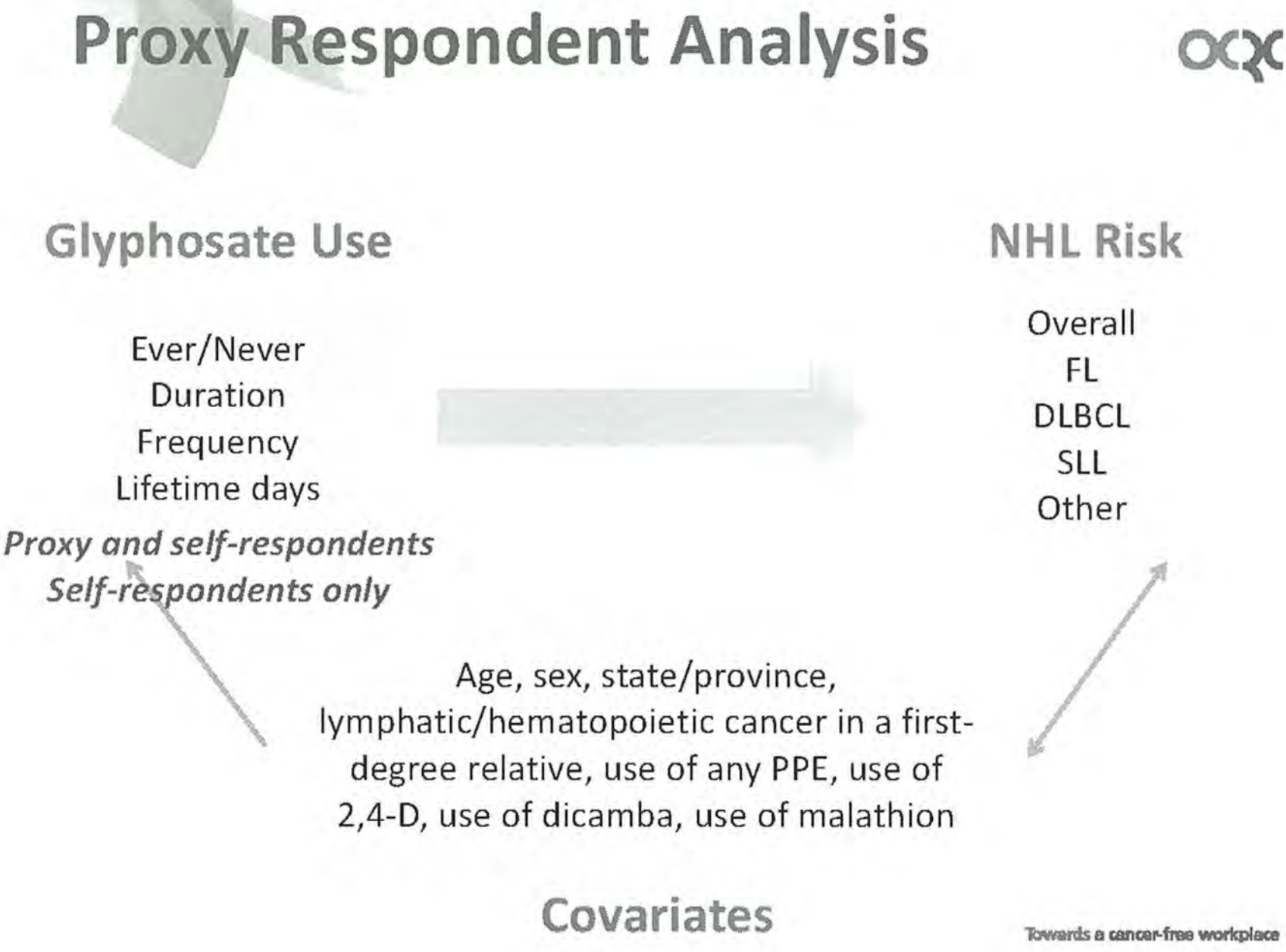
Glyphosate Use Information

Study	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



Proxy Respondent Analysis



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	400		
Location			
U.S.	1177	3625	
Canada	513	1506	
Respondent type			
Proxy	533	1692	1.05 (0.92, 1.19)
Self	1140	3372	1
Unknown/missing	17	67	

Selected Characteristics of NHL Cases and Controls (Continued)

Variable	Cases (N)	Controls (N)	OR (95% CI)
Lymphatic or hematopoietic cancer in a first-degree relative			
Yes	139	202	2.10 (1.67, 2.63)
No	1493	4790	1
Unknown/missing	58	139	
Ever lived or worked on a farm or ranch			
Yes	1102	3276	1.07 (0.94, 1.20)
No	577	1840	1
Unknown/missing	11	15	

Glyphosate Use and NHL Risks

NHL sub-type	Number of cases who reportedly ever used glyphosate	OR* (95% CI)
Overall	113	1.22 (0.91, 1.63)
FL	28	0.74 (0.44, 1.23)
DLBCL	45	1.32 (0.87, 2.02)
SLL	15	1.87 (0.91, 3.85)
Other	25	1.75 (1.01, 3.03)

*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, 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	1.40 (0.97, 2.04)	0.72 (0.37, 1.41)	1.77 (1.06, 2.96)	1.53 (0.59, 3.98)	2.23 (1.15, 4.32)
>3.5	1.02 (0.67, 1.54)	0.66 (0.32, 1.35)	1.03 (0.55, 1.93)	2.01 (0.82, 4.95)	1.31 (0.59, 2.90)
P-trend	0.19	0.40	0.09	0.28	0.06

*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, use of 2,4-D, use of dicamba, use of malathion

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	0.83 (0.51, 1.34)	0.53 (0.22, 1.29)	0.77 (0.37, 1.58)	1.40 (0.41, 4.74)	1.38 (0.58, 3.30)
>2	1.98 (1.16, 3.40)	1.52 (0.63, 3.67)	2.49 (1.23, 5.04)	2.48 (0.66, 9.37)	2.21 (0.78, 6.22)
P-trend	0.02	0.18	0.02	0.40	0.29

*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, use of 2,4-D, use of dicamba, use of malathion

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	1.00 (0.59, 1.68)	0.73 (0.29, 1.86)	0.92 (0.42, 2.01)	1.17 (0.25, 5.52)	1.85 (0.75, 4.60)
>7	1.19 (0.72, 1.97)	0.81 (0.34, 1.95)	1.25 (0.62, 2.52)	2.31 (0.74, 7.26)	1.56 (0.59, 4.18)
P-trend	0.79	0.76	0.79	0.35	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, use of 2,4-D, use of dicamba, use of malathion

Proxy vs. Self Respondents

Glyphosate Use	OR (95% CI) for NHL Overall	
	Proxy and Self Respondents[a]	Self Respondents Only[b]
Never used	1	1
Ever used	1.22 (0.91, 1.63)	1.04 (0.75, 1.45)
Duration (# years)		
>0 and ≤3.5	1.40 (0.97, 2.04)	1.32 (0.88, 1.97)
>3.5	1.02 (0.67, 1.54)	0.85 (0.53, 1.35)
Frequency (# days/year)		
>0 and ≤2	0.83 (0.51, 1.34)	0.76 (0.45, 1.31)
>2	1.98 (1.16, 3.40)	2.05 (1.13, 3.70)
Lifetime days (# years x # days/year)		
0 and ≤7	1.00 (0.59, 1.68)	0.98 (0.55, 1.74)
>7	1.19 (0.72, 1.97)	1.17 (0.68, 2.02)

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

Challenges

- Slight variations in study designs
- Missing information about intensity, duration, and frequency of glyphosate use
- Measurement error
- Small numbers for certain stratified analyses

Challenges

- Slight variations in study designs
- Missing information about intensity, duration, and frequency of glyphosate use
- Measurement error
- Small numbers for certain stratified analyses

Larger sample size = more statistical power

Conclusions

- Glyphosate use may be associated with ↑ NHL risk
- 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

Future Research Priorities

- Evaluation of other agricultural exposures, confounding, and interactions
- Non-occupational exposure
- Factors that modify exposure, e.g. immune conditions

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Canadian investigators

- Shelley A. Harris
- John J. Spinelli
- Punam Pahwa
- James A. Dosman
- John R. McLaughlin

US investigators

- Laura Beane Freeman
- Aaron Blair
- Shelia Hoar Zahm
- Kenneth P. Cantor
- Dennis D. Weisenburger

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Vol. 10, 1133–1163, November 2001

Non-Hodgkin's Lymphoma and Specific Pesticide Exposures in Men: Cross-Canada Study of Pesticides and Health[1]

Helen H. McDuffie,[2] Punam Pahwa, John R. McLaughlin, John J. Spinelli, Shirley Fincham, James A. Dosman, Diane Robson, Leo F. Skinnider, Norman W. Choi[3]

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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

[1] This research was funded by Health Canada Grant 6608-1258, the British Columbia Health Research Foundation, and the Centre for Agricultural Medicine, University of Saskatchewan.

[2] To whom requests for reprints should addressed, at Centre for Agricultural Medicine, 103 Hospital Drive, P. O. Box 120, Royal University Hospital, Saskatoon, S. K., S7N 0W8, Canada. Phone: (306) 966-6154; Fax: (306) 966-8799; E-mail: mcduffie@sask.usask.ca.

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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, 1993.

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, ranges, 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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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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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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(In final form 30 October 2001)

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	OR (CI) 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

	Time span, last exposure-diagnosis, years			
Agent	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

	Univariate		Multivariate	
Agent	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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ELECTRONIC PAPER

Integrative assessment of multiple pesticides as risk factors for non-Hodgkin's lymphoma among men

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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.[6 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[14] 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)[20] 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.[19 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.[19 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.[19 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 = $((\ln(10))/3.92)^2 \equiv 0.35$), 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,[12–30] and also corroborates findings of other studies.[5 38] OP insecticides are known to cause cytogenetic damage, and could thereby contribute to NHL aetiology.[39] There are data from in vitro, animal, and human studies that show effects of several OP insecticides on the immune system,[39–40] 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.[48] However, there is only very limited evidence for genotoxicity of atrazine, although there are no studies in humans.[49] 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.[47 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.[4] 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.[52]

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 10] 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.[12 53] Some recent studies have reported excess risk among

manufacturers[31] and farmers,[8] while others have not.[31] 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.[34] Furthermore, a study of professional 2,4-D applicators in Kansas observed an increase in the lymphocyte replication index following application.[35]

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.[36] 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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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.
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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, Orebro 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 posttransplantation 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.[8,15]

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

Agent	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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ORIGINAL ARTICLE

Lymphoma risk and occupational exposure to pesticides: results of the Epilymph study

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ABSTRACT

Objectives We investigated the role of occupational exposure to specific groups of agrochemicals in the aetiology of lymphoma overall, B cell lymphoma and its most prevalent subtypes.

Methods In 1998–2003, 2348 incident lymphoma cases and 2462 controls were recruited to the EPILYMPH case-control study in six European countries. A detailed occupational history was collected in cases and controls. Job modules were applied for farm work including specific questions on type of crop, farm size, pests being treated, type and schedule of pesticide use. In each study centre, industrial hygienists and occupational experts assessed exposure to specific groups of pesticides and individual compounds with the aid of agronomists. We calculated the OR and its 95% CI associated with lymphoma and the most prevalent lymphoma subtypes with unconditional logistic regression, adjusting for age, gender, education and centre.

Results Risk of lymphoma overall, and B cell lymphoma was not elevated, and risk of chronic lymphocytic leukaemia (CLL) was elevated amongst those ever exposed to inorganic (OR=1.6, 95% CI 1.0 to 2.5) and organic pesticides (OR=1.5, 95% CI 1.0 to 2.1). CLL risk was highest amongst those ever exposed to organophosphates (OR=2.7, 95% CI 1.2 to 6.0). Restricting the analysis to subjects most likely exposed, no association was observed between pesticide use and risk of B cell lymphoma.

Conclusions Our results provide limited support to the hypothesis of an increase in risk of specific lymphoma subtypes associated with exposure to pesticides.

What this paper adds

- Inconsistent opinions exist about the evidence linking occupational exposure to pesticides with lymphoma risk.
- The complex array of chemicals comprised in the pesticide definition and the heterogeneity of the pathological diagnoses included in the lymphoma or non-Hodgkin's lymphoma definitions might contribute to the controversy.
- We used the WHO classification of lymphoma to identify specific lymphoma entities, and state of the art retrospective exposure assessment for occupational exposure to chemical classes of pesticides and specific agrochemicals in a population-based case-control study.
- Our results provide limited evidence of an increase in risk of chronic lymphocytic leukaemia associated with exposure to organophosphates, and no association for other lymphoma subtypes.

INTRODUCTION

Among hundreds of agents and groups of agents examined in 85 years of International Agency for Research on Cancer (IARC) Monographs (volumes 1–99)[1] pesticides account for two dozens; only a few of those are still in use worldwide, some are obsolete but still in use in developing countries, and most have been banned or abandoned for some decades. Only arsenic and arsenical pesticides are group 1 human carcinogens, while occupational exposure in the spraying and application of non-arsenical insecticides overall is included in group 2A, because of limited evidence from epidemiological studies. Group 2A also includes two active ingredients, namely the fungicide captafol, which uses have been restricted in the USA and most world countries from 1999,[2] and ethylene dibromide, which is used as a grain fumigant. As for the rest, the insufficient evidence from human studies is coupled with the sufficient, limited or unavailable evidence from experimental animal studies. Nowadays, thousands of chemicals are available to farmers to treat plant diseases and protect their crops; their use changes year by year, across countries and within each country, and by type of crop and type of disease being treated: the difficulty of conducting epidemiological studies of the long term effects of agrochemicals is reflected in the poor information on their human carcinogenicity and the absence of evaluation by international scientific and regulatory agencies.

Reviews of the scientific literature reported inconsistent opinions about the association between occupational exposure to pesticides and non-Hodgkin's lymphoma (NHL).[3 4] In fact, while several meta-analyses have come to positive conclusions on NHL risk,[5–10] particularly for prolonged exposures,[11–13] or for exposure in the years

relatively close to the diagnosis,[14] risk has been shown to vary by gender,[15] or specific jobs,[16] and by specific chemicals.[17] Besides, the causal link is not always recognised,[18] and negative studies have also been published.[19–24] In some instances, interpretation of findings is limited by imprecise definition of either exposure or disease entity[22] or a small study size.[23] Geographical variation in NHL mortality has also been reported in relation to the prevalent type of crop, and therefore the pesticide used:[25–28] for instance, NHL mortality in the female population was elevated in an area of Minnesota where wheat, corn and soy crops were prevalent.[28]

METHODS

The EPILYMPH study, a multicentre case-control study on environmental exposures and lymphoid neoplasms, was conducted in Czech Republic, France, Germany, Italy, Ireland and Spain from 1998 to 2004. Details about the study have been described elsewhere.[29] Briefly, cases were all consecutive adult patients first diagnosed with lymphoma during the study period, resident in the referral area of the participating centres. The diagnosis was classified according to the 2001 WHO classification of lymphoma,[30] and slides of about 20% of cases from each centre were reviewed centrally by a panel of pathologists, coordinated by MM. Controls from Germany and Italy were randomly selected by sampling from the general population, matched to cases on gender, 5-year age-group, and residence area. The rest of the centres used matched hospital controls, with eligibility criteria limited to diagnoses other than cancer, infectious diseases and immunodeficient diseases. Approval by the relevant Ethics Committees was obtained in all centres. Informed consent was obtained for the 2348 lymphoma cases and 2462 controls who participated to the study. Overall, the participation rate was 88% in cases, 81% in hospital controls and 52% in population controls.

Trained interviewers conducted in person interviews with cases and controls, using the same structured questionnaire translated into the local language. Questions sought information on sociodemographic factors, lifestyle, health history and a list of all full time jobs held for 1 year or longer. Industrial hygienists in each participating centre coded the occupations and industries using the 5-digit 1968 International Labour Office International Standard Classification of Occupations[31] and the 4-digit codes of the 1996 European Statistical Classification of Economic Activities, revision 1 (NACE, rev. 1).[32] Study subjects who reported having worked in agriculture were given a job-specific module inquiring in detail into the following: detailed description of the tasks; kind of the crops and size of the cultivated area; type of pests being treated; pesticides used, and procedures of crop treatment; use of personal protective equipment; re-entry after treatment; frequency of the treatment in days/year.

Occupational exposure assessment

With the support of a local agronomist, and the support of a crop-exposure matrix, created by LM, to supplement the available information, industrial hygienists and occupational experts in each participating centre reviewed the general questionnaires and job modules to assess exposure to pesticides classified into inorganic (mainly sulphur and arsenic salts) and organic (carbamates, organophosphates, organochlorines, triazines and triazoles, phenoxyacids, and chlorophenols). Exposure was classified according to the following exposure metrics:

confidence, representing the industrial hygienist's degree of certainty that the worker had been truly exposed to the agent, based upon two criteria: 1. a summary evaluation of the probability of the given exposure (1= possible, but not probable; 2=probable; and 3=certain); and 2. the proportion of workers exposed in the given job (1≤40%; 2=40–90%; 3≥90%);

intensity of exposure, expressed in relation to the circumstances of use (personal preparation of the pesticide mixture, use of hand pump or tractor, size of the area being treated, re-entry after treatment) and use of personal protective equipment. Semiquantitative estimates of exposure were derived from the publicly available EUROPOEM programme,[33] and then categorised on a 4-point scale (0=unexposed; 1=low; 2=medium; 3=high);

frequency of exposure, expressed in annual days of pesticide use reported in the questionnaire or estimated based on the type of plant disease and the size of the crop or the livestock being treated (low≤50 days/year; medium 51–100 days/year; high≥101 days/year).

A cumulative exposure score was calculated for each pesticide group as follows: $C_i = S(y_j \times f_j/3)^{x_j}$ where C is the cumulative exposure score; i the study subject; j the jth job in the work history of study subject i; y the duration of exposure (in years); x the exposure intensity level f the exposure frequency level.

Cumulative exposure scores for each pesticide group were then categorised by tertiles of their distribution among the exposed (cases and controls combined).

Consistency in the occupational coding and exposure assessments was optimised through several meetings of the industrial hygienists.

Statistical methods

We assessed risk of B cell lymphoma, and its most prevalent subtypes, diffuse large B cell lymphoma (DLBCL) and chronic lymphocytic leukaemia (CLL), associated with ever exposure to inorganic and organic pesticides (all types), and the organic pesticide groups listed in table 1. The analysis was led by PC, supported by GS, SD, MP and TN, both on all exposed subjects, and after restriction to subjects whose exposure was assessed with high confidence. Linear trends in all exposure metrics were also estimated. The OR was calculated using unconditional logistic regression, adjusted for age, gender, education and centre. Two-tailed 95% CI for the OR were estimated using the Wald statistics ($e^{\beta} \pm (z_{\alpha/2} \times se_{\beta})$). Subjects unexposed to any pesticide comprised the reference category used for all the analyses. Trends in the ORs were assessed using the Wald test for trend.

Role of the funding sources

The private and public institutions that sponsored this study did not influence or intervene in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

RESULTS

Details on the study size, number of cases and controls by participating centre, and their frequency distribution by selected variables of interest in the occupational analyses were reported elsewhere.[34] Table 1 shows the frequency distribution of exposure to pesticide groups for which exposure was assessed in the EPILYMPH study, by country. In a footnote, the active ingredients within each group are reported, selected among those reported by study subjects or suggested by the collaborating agronomists. Overall, the prevalence of exposure to pesticides in our study was low, with only 3.7% of participants exposed to inorganic pesticides and 6.4% exposed to organic pesticides,

Table 1 Prevalence of exposed to the individual pesticide groups by country in the EPILYMPH study

Pesticide groups*	Spain N=1222	France N=574	Germany N=1413	Italy N=598	Ireland N=409	Czech republic N=594	Total N=4810
Inorganic pesticides	88 (7.2)	14 (2.4)	28 (2.0)	31 (5.2)	14 (3.4)	6 (1.0)	181 (3.8)
Arsenicals	30 (2.4)	0 (0.0)	9 (0.6)	0 (0.0)	3 (0.7)	0 (0.0)	42 (0.9)
Organic pesticides	127 (10.4)	38 (6.7)	86 (6.1)	48 (8.2)	38 (9.4)	5 (0.8)	342 (7.1)
Carbamates	3 (0.2)	4 (0.7)	11 (0.8)	15 (2.5)	2 (0.5)	0 (0.0)	35 (0.7)
Organophosphates	7 (0.6)	4 (0.7)	11 (0.8)	16 (2.7)	14 (3.4)	1 (0.2)	53 (1.1)
Organochlorines	22 (1.8)	8 (1.4)	22 (1.6)	13 (2.2)	5 (1.0)	0 (0.0)	70 (1.5)
Triazines and triazoles	0 (0.0)	3 (0.6)	2 (0.1)	13 (2.2)	0 (0.0)	2 (0.3)	20 (0.4)
Phenoxyacids	2 (0.2)	4 (0.7)	10 (0.7)	5 (0.8)	4 (1.0)	0 (0.0)	25 (0.5)
Chlorophenols	46 (3.7)	9 (0.9)	31 (2.0)	19 (3.0)	10 (2.0)	0 (0.0)	115 (2.4)

For each country, the total number of participants is provided upon which the percentage of exposed (in brackets) is calculated.
*Note: Inorganic pesticides include: sulphur, arsenic, fluorine, zinc, mercury derivatives and other; arsenicals include: ammonium, calcium, sodium and potassium arsenate; organic pesticides include carbamates (aldicarb, carbaryl, mancozeb, methomyl, propoxur and other), organophosphates (acephate, diazinon, dimethoate, glyphosate, malathion, parathion and other), organochlorines (aldrin, DDT, chlordane, endrin, lindane, metoxychlor, endosulfan and other), triazines and triazoles (atrazine, propazine, terbutryn and other), phenoxyacids (2,4 dichlorophenoxyacetic acid, 2,4,5 T, methylchloro-phenoxyacetic acid, mecoprop and other), chlorophenols (2 chlorophenol, pentachlorofenol and other).

and it was lowest for triazines and triazoles and phenoxy acids. The prevalence of exposed was highest in Spain and lowest in the Czech Republic. The prevalence of exposure to the specific groups of pesticides varied by country. Use of inorganic pesticides was widespread, but it mainly consisted of copper sulphide or other sulphur compounds as reported by study subjects, indicated by the agronomist or by the crop-exposure matrix. Arsenicals were mainly used in Spain and, to a smaller extent, in Ireland. Among organic pesticides, chlorophenols were most frequently represented, and their prevalence was highest in Spain, Italy and Germany. Organophosphates were the most prevalent group of organic pesticides in Ireland. The most variegate pattern of pesticide use was described in Italy.

Table 2 shows risk of lymphoma overall, B cell lymphoma, DLBCL and CLL, amongst those ever exposed to each type of pesticide considered in this study. No excess risk of lymphoma (all types), B cell lymphoma and DLBCL was observed in association with ever exposure to inorganic or organic pesticide, nor to any of the organic pesticide groups assessed in this study. Risk of CLL was significantly associated with ever exposure to

Table 2 Risk of lymphoma and major subtypes associated with ever exposure to pesticide groups in the Epilymph study

	Lymphoma (all types)			B cell lymphoma			Diffuse large B cell lymphoma			Chronic lymphocytic leukaemia		
Pesticide group	Cas/cont	OR	95% CI	Cai/cont	OR	95% CI	Cas/cont	OR	95% CI	Cas/cont	OR	95% CI
Inorganic pesticides												
Any confidence level	100/81	1.3	0.9 to 1.7	81/81	1.2	0.8 to 1.6	13/81	0.7	0.4 to 1.3	28/81	1.6	1.0 to 2.5
High confidence	57/46	1.3	0.9 to 2.0	42/46	1.1	0.7 to 1.8	7/46	0.7	0.3 to 1.6	15/46	1.6	0.8 to 2.9
Arsenicals												
Any confidence level	18/24	0.8	0.4 to 1.4	14/24	0.7	0.4 to 1.3	2/24	0.4	0.1 to 1.6	6/24	1.1	0.4 to 2.7
High confidence	4/5	0.8	0.2 to 3.1	2/5	0.5	0.1 to 2.6	0/5	0.0	–	0/5	0.0	–
Organic pesticides												
Any confidence level	180/162	1.2	0.9 to 1.4	148/162	1.2	0.9 to 1.5	28/162	0.8	0.5 to 1.2	45/162	1.5	1.0 to 2.1
High confidence	101/91	1.1	0.8 to 1.5	79/91	1.1	0.8 to 1.5	13/91	0.7	0.4 to 1.2	23/91	1.4	0.8 to 2.2
Carbamates and thiocarbamates												
Any confidence level	16/19	0.9	0.5 to 1.7	9/19	0.7	0.3 to 1.5	1/19	0.2	0.0 to 1.8	3/19	1.1	0.3 to 3.8
High confidence	4/8	0.5	0.2 to 1.7	3/8	0.5	0.1 to 2.0	0/8	0.0	–	1/8	0.9	0.1 to 7.2
Organophosphates												
Any confidence level	32/21	1.6	0.9 to 2.8	23/21	1.4	0.8 to 2.6	5/21	1.1	0.4 to 2.9	9/21	2.7	1.2 to 6.0
High confidence	11/7	1.6	0.6 to 4.2	7/7	1.4	0.5 to 3.9	1/7	0.6	0.1 to 5.3	1/7	0.9	0.1 to 7.7
Organochlorines												
Any confidence level	33/37	0.9	0.6 to 1.5	27/37	0.9	0.5 to 1.4	5/37	0.6	0.2 to 1.6	10/37	1.2	0.6 to 2.5
High confidence	12/12	1.0	0.5 to 2.3	11/12	1.1	0.5 to 2.6	2/12	0.7	0.2 to 3.3	5/12	1.9	0.6 to 5.6
Triazines and triazoles												
Any confidence level	8/12	0.7	0.3 to 1.7	6/12	0.7	0.2 to 1.7	2/12	0.8	0.2 to 3.4	2/12	0.9	0.2 to 4.1
High confidence	5/6	0.9	0.3 to 2.8	3/6	0.6	0.2 to 2.5	1/6	0.8	0.1 to 6.4	1/6	0.8	0.1 to 6.9
Phenoxy acids												
Any confidence level	14/11	1.3	0.6 to 2.9	12/11	1.4	0.6 to 3.1	4/11	1.7	0.5 to 5.2	2/11	0.9	0.2 to 4.1
High confidence	5/5	1.0	0.3 to 3.6	4/5	1.1	0.3 to 4.1	2/5	1.9	0.4 to 9.9	0/5	0.0	–
Chlorophenols												
Any confidence level	59/56	1.1	0.8 to 1.6	49/56	1.1	0.7 to 1.6	13/56	1.1	0.6 to 2.0	13/56	1.1	0.6 to 2.2
High confidence	32/27	1.2	0.7 to 2.1	25/27	1.1	0.6 to 2.0	6/27	1.0	0.4 to 2.5	5/27	1.0	0.4 to 2.6

Results are presented for all confidence levels combined and limited to study subjects with high confidence of exposure.

Table 3 Chronic lymphocytic leukaemia risk and intensity of exposure to pesticide groups (all levels of confidence)

	Unexposed			Low			Medium			High		
Pesticide groups	Ca/co	OR	95% CI	Ca/co	OR	95% CI	Ca/co	OR	95% CI	Ca/co	OR	95% CI
Inorganic pesticides	362/2262	1.0	–	14/33	2.2	1.1 to 4.2	10/34	1.2	0.6 to 2.5	3/11	1.2	0.3 to 4.3
Organic pesticides	362/2262	1.0	–	21/81	1.4	0.8 to 2.3	18/55	1.6	0.9 to 2.8	6/26	1.2	0.5 to 3.0
Carbamates*	362/2262	1.0	–	0/10	–	–	3/9	1.8	0.5 to 6.9			
Organophosphates*	362/2262	1.0	–	5/13	2.7	0.9 to 7.8	4/8	2.6	0.7 to 9.2			
Organochlorines*	362/2262	1.0	–	5/15	1.8	0.6 to 5.0	5/20	1.0	0.4 to 2.8			
Phenoxy acids*	362/2262	1.0	–	0/7	–	–	2/4	2.4	0.4 to 13.8			
Chlorophenols	362/2262	1.0	–	7/27	1.2	0.5 to 2.6	5/18	1.4	0.4 to 3.9	1/11	0.5	0.1 to 4.2

*Medium and high intensity categories combined.

organic pesticides and particularly to organophosphates (OR=2.6, 95% CI 1.2 to 6.0). An elevated risk of CLL was also associated with ever exposure to inorganic pesticides (OR=1.6, 95% CI 1.0 to 2.5), but not with arsenical pesticides. Because of the a priori hypothesis of an association, we cite the moderate excess risk of B cell lymphoma associated with ever exposure to phenoxyacids (OR=1.4, 95% CI 0.6 to 3.1). No excess risk was observed in association with ever exposure to the other pesticide groups. The results did not change when exploring risk for NHL, thus excluding CLL and multiple myeloma, but including T-cell lymphomas. Further adjustment for ever exposure to solvents or contact with livestock did not virtually change the risk estimates.

Table 3 shows risk of CLL by intensity of exposure. The excess risk associated with ever exposure to inorganic pesticides was limited to the lowest category of intensity of exposure. Risk for medium-high intensity of exposure to organophosphates showed a 2.6-fold excess (CI 95% 0.7 to 9.2), matching that observed for the low intensity category; however, the CI was wide at either level, and there was no trend in risk (Wald test for trend=0.14; p=0.44).

Risk of B cell lymphoma associated with ever exposure to organophosphates did not vary according to whether exposure started before 1980 or from 1980 onwards and it did not increase by cumulative exposure tertiles (Wald test for trend p=0.09). Instead, CLL risk was highest when exposure started from 1980 onwards (OR=4.0, 95% CI 0.9 to 16.6), and it increased significantly by increasing cumulative exposure tertile (Wald test for trend p=0.02).

Only a few individual agrochemicals were represented by a sizable number of study subjects, and the exposed cases of DLBCL, CLL and even B cell lymphoma overall were too few for any meaningful inference to be drawn. Exposure to the three most frequently identified individual organophosphate pesticides, namely dimethoate and parathion, among the most commonly used agricultural insecticides, and glyphosate, an organophosphorous herbicide, was more prevalent among B cell lymphoma cases, while exposure to 2,4 dichlorophenoxyacetic acid (2,4 D) was not (table 4). Four cases and no controls had been exposed to methylchloro-phenoxyacetic acid (MCPA) (p=0.13); these were one case of diffuse large B cell lymphoma, one case of follicular lymphoma and two cases of unspecified non-Hodgkin's lymphoma. Three cases and one control to other phenoxy herbicides (p=0.28) not shown in the tables.

When limiting the analysis to the only study subjects whose exposure was assessed with a high degree of confidence, numbers became smaller and CIs wider. The excess risk of CLL associated with exposure to organophosphates and that of B cell lymphoma associated with exposure to phenoxyacids were no longer observed. Risk was not significantly elevated for the B cell lymphomas overall among study subjects with high confidence of exposure to organophosphates, and CLL risk was moderately increased among study subjects with high confidence of exposure to organochlorines . Overall, these results were not interpretable because of the small number of cases and the rarity of the exposed.

Table 4 Risk of B cell lymphoma and occupational exposure to selected specific active ingredients of pesticides

	B cell Lymphoma		
Pesticide	Ca/Co	OR	95% CI
Mancozeb	2/4	0.6	0.1 to 3.5
Methomyl	0/4	–	
Dimethoate	3/2	1.8	0.3 to 10.6
Glyphosate	4/2	3.1	0.6 to 17.1
DDT	3/3	1.2	0.2 to 5.9
Endosulfan	0/4	–	
2,4-dicholorophenol	2/4	0.6	0.1 to 3.5
Methylchloro phenoxyacetic acid	4/0	∞	

DDT, dichloro-diphenyl-trichloro-ethane.

DISCUSSION

Our results provide limited support to the hypothesis of an association between occupational exposure to organophosphorous pesticides and risk of CLL. We did not find evidence of an association with lymphoma overall, B cell lymphoma as a group of different subtype entities and DLBCL. The low prevalence of exposed in our community based study did not allow to explore the association with other less prevalent lymphoma subgroups, nor to detect unquestionable associations with specific agrochemicals. Also, we were unable to confirm the repeatedly reported association between exposure to phenoxyacids and lymphoma. It is worth reporting, however, that while we did not observe any indication of a higher prevalence of exposure to 2,4 D among cases in respect to controls, four B cell lymphoma cases and no controls were identified as exposed to MCPA.

Organophosphate insecticides were introduced for agricultural use in Europe mainly in the early 1970s, when insect resistance to organochlorines became manifest. Their use was associated with an almost twofold increase in risk of NHL in a Nebraska case-control study;[35] women appeared to be at greater risk.[15] Similar findings were reported in Italy and China.[36 37] An increase in NHL risk was also reported in Australia for exposures defined as substantial, although no increasing trend in risk was observed with frequency, intensity level, probability, duration and period of exposure.[38] Specific organophosphates were investigated in several studies. Malathion, one the most frequently used organophosphorous insecticide, showed an association in a Canadian case-control study,[39] and in another study conducted

in Iowa and Minnesota.[40] Diazinon and dichlorvos also showed an association in the Minnesota study.[40] The positive association with exposure to diazinon was confirmed, but limited to lymphocytic lymphoma, in one study,[41] while results of the US Agricultural Health Study were negative for malathion.[42] Studies were negative for phorate,[43] and positive for terbufos, scoring the fourth in the US sales of organophosphates, although again no trend was observed by exposure metrics.[44] Selected lymphoma subtypes, such as multiple myeloma[45] and hairy cell leukaemia[46] were reported in association with exposure to glyphosate. The four B cell lymphoma cases exposed to glyphosate in our study included one case each of DLBCL, CLL, multiple myeloma and unspecified B cell lymphoma.

2,4 D is the best known phenoxy acid. Its association with NHL risk was first reported in Sweden[47] and thereafter confirmed in the US,[48] with a sixfold increase among farmers using it for more than 20 days/year, and significant increases in risk for direct use and lack of use of personal protective equipment. Further positive results were reported in case-control studies,[35 49 50] while a Danish follow-up study[51] was negative for an association, and a multicentre mortality study of 19 000 European workers exposed to phenoxy acids and chlorophenols[52–54] confirmed the association in presence of concurrent exposure to 2,2,4,4 tetrachlorodibenzodioxin, a frequent contaminant of phenoxy herbicides and chlorophenols, but not when tetrachlorodibenzodioxin exposure was excluded. Recent updates of historical cohorts of phenoxyacids manufacturers and trichlorophenol manufacturers provided negative or conflicting findings.[55–57] On the other hand, a dose-related increase in NHL mortality by semiquantitative indicators of exposure to pentachlorophenol was observed in a cohort of woodworkers in British Columbia, Canada[58] and two out of three NHL cases in a small cohort of Swedish woodworkers exposed to phenoxyacid herbicides belonged to the highest exposure subgroup.[59] Although the most recent case-control studies, with a more accurate exposure assessment, tend to confirm the association of NHL risk with phenoxy herbicides, and particularly 2,4D, 4-chlor-2-MCPA, and 4-chlor-2-methyl phenoxypropionic acid (MCPP or meclorpop),[14 38 44–46 60 61] reviews still underline the uncertainties and inconsistency in the results.[62] A specific effect of 2,4D on the haemolymphopoietic tissue was supported by the observation of an increase of the lymphocyte proliferation index in workers exposed to the herbicide.[63]

Our results did not find an association with phenoxyacid herbicides and chlorophenols, and provide only limited support to an increase in risk associated with exposure to organophosphate insecticides and herbicides. We did not observe an association with exposure to carbamates and thiocarbamates, organochlorines, and triazines and triazoles.

Use of carbamates in general, and carbaryl in particular, was associated with an increase in NHL risk in Italy,[36] Canada[39] and the USA[40] and the association was inconsistent by exposure metric in the US Agricultural Health Study,[64] while, in this large survey, NHL risk showed an increasing trend with increasing exposure to butilate, a thiocarbamate,[65] and sevin was the only carbamate associated with a dose-related increase in NHL risk in a Chinese study.[66] We did not find an association between exposure to carbamates and risk of lymphoma or its most prevalent subtypes.

A first suggestion of an increasing NHL risk among exposed to organochlorine insecticides, namely chlordane, toxafene, aldrin, lindane and DDT, came from several international case-control studies, where concurrent exposure to numerous other pesticides also occurred.[36 39 40] Multiple myeloma,[67] CLL[39] and hairy cell leukaemia[60] were more frequently associated. However, detailed analyses of US case-control studies found out that the positive association with exposure to DDT or lindane disappeared after adjusting for exposure to organophosphates and phenoxyacids.[69 70] Positive findings have been more recently published on lindane,[71 72] but they keep being inconclusive for the entire class of organochlorines.[73]

Suggestions of a positive association between triazine herbicides and NHL risk provided limited evidence because of multiple concurrent exposures and the small study size;[68 75] besides, the pooled analysis of three case-control studies[74] and the analysis of the repeatedly cited US Agricultural Health Study[75 76] did not support the hypothesis of a role of atrazine and cyanazine. Less relevant in this regard seems to be the increased risk associated with exposure to metribuzin in one study, as all lymphopoietic malignancies were considered altogether and the CI included unity.[77]

Our study presented the advantage of a very detailed exposure assessment, coupled with an up-to-date pathological definition of disease entities. Such conditions represent substantial improvements in the assessment of occupational exposures and in lessening exposure and disease misclassification in population-based studies, which would help in revealing true associations. While this differentiates our effort from most previous population-based case-control studies, loss of statistical power is the unavoidable consequence of the gain in specificity. In fact, the overall prevalence of exposed was small, with 3.8% participants exposed to inorganic pesticides and 7.1% exposed to organic pesticides, and when restricting the analysis to study subject with high confidence exposure to pesticides in general, or when investigating individual chemicals, numbers were further reduced and the CI of the risk estimates widened. For the same reason, no analysis on the effects of specific combined pesticide exposures was conducted. On the other hand, since biological effects are likely to vary by individual chemicals in a chemical class or functional class, when exploring associations with such classes results may be diluted, thereby missing true effects related to individual chemicals.

The use of hospital controls in several centres contributing to this multinational effort, and the low response rate in the two centres where controls were population-based, may have introduced selection bias, further limiting the interpretation of our study results.

We included age, gender, education, and centre as covariates in our regression models to adjust our risk estimates, as a set of core factors potentially relevant in subgroup analyses. We selected education as a surrogate for lifestyle factors potentially acting as confounders of the association between pesticide exposure and risk of B cell lymphoma. In turn, lifestyle might surrogate exposure to endotoxin, a component of the outer membrane of Gram-negative bacteria, a common contaminant associated with poverty, crowding, pets, household cleanliness and the rural environment.[78 79] However, the endotoxin role in lymphomagenesis remains to be investigated. Other potential confounders would include occupational exposure to solvents and livestock, and household use of insecticides. We did not observe any change in the risk estimates for B cell lymphoma and CLL associated with ever exposure to organophosphates after adjusting by ever exposure to solvents or contact with livestock. Information on household insecticide use was self-reported by the study subjects; however, the low prevalence of occupationally exposed in our population based study, and the poor ability of study subjects to identify the chemical class of

the household insecticides, did not allow the use of such information. We cannot exclude that bias might have resulted, although it seems unlikely that it would have acted only on the specific association between occupational exposure to organophosphates and CLL.

Caution is therefore required in interpreting our findings. Among pesticides considered in the IARC Monographs for their potential human carcinogenicity,[1] subjects in our study mentioned having used arsenicals, DDT, chlorophenols and phenoxyacids. In most instances, the use of these chemicals date to early periods in the work histories of study subjects, while the limited evidence of an association with CLL risk was related to still popular organophosphorous insecticides and phenoxy herbicides that did not undergo specific IARC evaluations thus far. The lack of consistent dose response trends with all the exposure metrics might support chance as the explanation for the observed associations, or it might imply some mechanism different from a direct intervention in the carcinogenic process. For instance, dimethoate was shown to have the lowest cytotoxic and genotoxic potential in cultured cells, compared to other three organophosphates and the organochlorine endosulfan;[81] however, its administration in experimental female mice caused a decrease in total immunoglobulins and IgM and in the number of plaque forming cells;[83] the same effects were observed over three generations following repeated administration of low doses dimethoate in outbred Wistar rats.[82] Functional activity of Th1 lymphocytes, immune reactions associated with these cells, and interferon-γ production were impaired after subacute malathion intoxication in albino rats,[83] while thymic atrophy and reduction in splenic germinal centres followed methylparathion administration in rabbits.[84] Such immunosuppressive effects do not seem related to acetylcholinesterase inhibition, the typical toxicological mechanism of organophosphate poisoning, and cover a large number of pesticides, including organochlorines, organophosphates, carbamates and pyrethroids.[85 86] It is unclear whether the typically toxicological criterion of dose-response in establishing causal association would apply also in mechanisms involving the immune system.

In conclusion, our analysis of a large European data set provides no support to a role of occupational exposure to several specific agrochemicals in the aetiology of B cell lymphoma, and limited support in the aetiology of CLL. Further multicentre studies in international settings coupling state of the art exposure assessment in farm work and availability of detailed pathological diagnoses with a larger study size might provide the proper setting to further test the hypothesis.

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Lymphoma risk and occupational exposure to pesticides: results of the Epilymph study

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Supplementary Information

Non–Hodgkin Lymphoma and Occupational Exposure to Agricultural Pesticide Chemical Groups and Active Ingredients: A Systematic Review and Meta–Analysis

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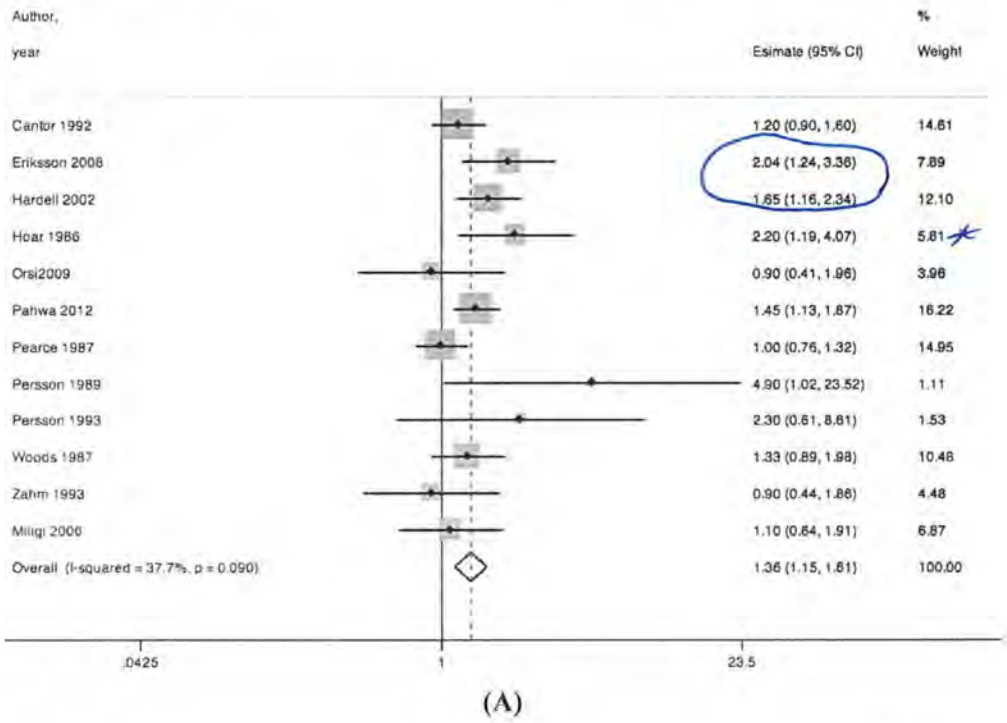
S1. List of terms included in the PubMed literature search.

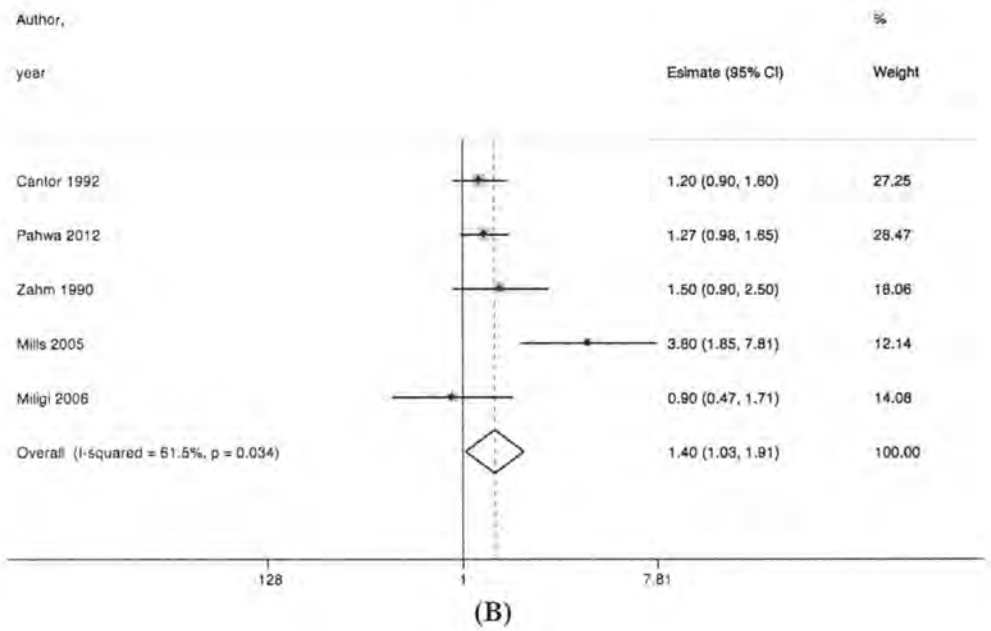
((((((((("agricultural workers' diseases/chemically induced"[MAJR] AND "neoplasms"[MeSH Major Topic] AND ("1980/01/01"[PDAT] : "2013/06/31"[PDAT]) AND "humans"[MeSH Terms]) OR ((((("occupational exposure"[MeSH Terms] OR occupational exposure[Title/Abstract]) OR "occupational exposure"[MeSH Terms]) OR occupational exposures[Title/Abstract]) AND ("1980/01/01"[PDAT] : "2013/06/31"[PDAT]) AND "humans"[MeSH Terms])) AND (((((((("lymphoma, non–hodgkin"[MeSH Terms] AND "humans"[MeSH Terms] AND english[la]) OR (non–hodgkin[tiab] OR non–hodgkins[tiab]) AND (lymphoma[tiab] OR lymphomas[tiab])) AND ("1980/01/01"[PDAT] : "2013/06/31"[PDAT]) AND "humans"[MeSH Terms]) OR "neoplasms"[MeSH Terms]) OR neoplasm[Title/Abstract]) OR cancer morbidity[Title/Abstract]) OR cancer mortality[Title/Abstract]) AND ("1980/01/01"[PDAT] : "2013/06/31"[PDAT]) AND "humans"[MeSH Terms])) AND (((pesticid[tiab] OR pesticidal[tiab] OR pesticidal'[tiab] OR pesticidally[tiab] OR pesticidas[tiab] OR pesticide[tiab] OR pesticide/albumin[tiab] OR pesticide/animal[tiab] OR pesticide/biocide[tiab] OR pesticide/commodity[tiab] OR pesticide/crop[tiab] OR pesticide/environmental[tiab] OR pesticide/fertilizer[tiab] OR pesticide/food[tiab] OR pesticide/fruit[tiab] OR pesticide/fungicide[tiab] OR pesticide/ha[tiab] OR pesticide/heavy[tiab] OR pesticide/herbicide[tiab] OR pesticide/humic[tiab] OR pesticide/m2[tiab] OR pesticide/matrix[tiab] OR pesticide/metabolite[tiab] OR pesticide/metabolites[tiab] OR pesticide/metal[tiab] OR pesticide/mmt[tiab] OR pesticide/neurotoxin/free[tiab] OR pesticide/nitrate[tiab] OR pesticide/oxidation[tiab] OR pesticide/pathogen[tiab] OR pesticide/petroleum[tiab] OR pesticide/polymer[tiab] OR pesticide/product[tiab] OR pesticide/seed[tiab] OR pesticide/soil[tiab] OR pesticide/solvent[tiab] OR pesticide'[tiab] OR pesticide's[tiab] OR pesticideformulating[tiab] OR pesticiderelated[tiab] OR pesticides[tiab] OR pesticides/biocides[tiab] OR pesticides/chemicals[tiab] OR pesticides/commodities[tiab] OR pesticides/consumption[tiab] OR pesticides/contaminants[tiab] OR pesticides/fertilisers[tiab] OR pesticides/fertilizer[tiab] OR pesticides/fertilizers[tiab] OR pesticides/fruit[tiab] OR pesticides/fungicides[tiab] OR pesticides/herbicide[tiab] OR pesticides/herbicides[tiab] OR pesticides/insecticides[tiab] OR pesticides/metabolites[tiab] OR pesticides/metals[tiab] OR pesticides/pesticide[tiab] OR pesticides/petroleum[tiab] OR pesticides/polycyclic[tiab] OR pesticides/sample[tiab] OR pesticides/vasectomy/occupational[tiab] OR pesticides/weedicides[tiab] OR pesticides'[tiab] OR pesticidesatlas[tiab] OR pesticidestargeted[tiab] OR pesticidic[tiab] OR pesticids[tiab])

OR "pesticides"[MeSH Terms] OR pesticides[nm] OR (insecticid[tiab] OR insecticidal[tiab] OR insecticidal/acaricidal[tiab] OR insecticidal/anthelmintic[tiab] OR insecticidal/antifeedant[tiab] OR insecticidal/irritant[tiab] OR insecticidal/larvicidal[tiab] OR insecticidal/narcotic[tiab] OR insecticidal'[tiab] OR insecticidal'b[tiab] OR insecticidally[tiab] OR insecticidation[tiab] OR insecticide[tiab] OR insecticide/acaricide[tiab] OR insecticide/antifeedant[tiab] OR insecticide/ascaricide[tiab] OR insecticide/atrazine[tiab] OR insecticide/fumigant[tiab] OR insecticide/fungicide[tiab] OR insecticide/herbicide[tiab] OR insecticide/kg[tiab] OR insecticide/lipid[tiab] OR insecticide/liter[tiab] OR insecticide/miticide[tiab] OR insecticide/mosquito[tiab] OR insecticide/nematicide[tiab] OR insecticide/nematocide[tiab] OR insecticide/organophosphrus[tiab] OR insecticide/pesticide/herbicide[tiab] OR insecticide/repellant[tiab] OR insecticide/repellent[tiab] OR insecticide'[tiab] OR insecticide's[tiab] OR insecticided[tiab] OR insecticideresistance[tiab] OR insecticideresistant[tiab] OR insecticides[tiab] OR insecticides/acaricides[tiab] OR insecticides/attract[tiab] OR insecticides/larvicides[tiab] OR insecticides/mn[tiab] OR insecticides/pesticides[tiab] OR insecticides/repellents[tiab] OR insecticides'[tiab] OR insecticidetreated[tiab] OR insecticidewise[tiab] OR insecticidial[tiab] OR insecticidic[tiab] OR insecticiding[tiab] OR insecticidity[tiab] OR insecticido[tiab]) OR "insecticides"[MeSH Terms] OR insecticides[nm] OR (herbicidal[tiab] OR herbicidally[tiab] OR herbicide[tiab] OR herbicide/binding[tiab] OR herbicide/dessicant[tiab] OR herbicide/fungicide[tiab] OR herbicide/g[tiab] OR herbicide/humic[tiab] OR herbicide/insect[tiab] OR herbicide/kg[tiab] OR herbicide/micelle[tiab] OR herbicide/ml[tiab] OR herbicide/mutation[tiab] OR herbicide/nematicide[tiab] OR herbicide/outcome[tiab] OR herbicide/pesticide[tiab] OR herbicide/substrate[tiab] OR herbicide/therapeutic[tiab] OR herbicide/tio2[tiab] OR herbicide's[tiab] OR herbicided[tiab] OR herbicideh[tiab] OR herbicideh/phytocide[tiab] OR herbicideinduced[tiab] OR herbicides[tiab] OR herbicides/chlorophenols[tiab] OR herbicides/desiccants[tiab] OR herbicides/fungicides[tiab] OR herbicides/pesticides[tiab] OR herbicides'[tiab] OR herbicidetolerant[tiab] OR herbicidies[tiab] OR herbicidin[tiab] OR herbicidins[tiab] OR herbicidovorans[tiab] OR herbicids[tiab]) OR (herbicides[nm] OR herbicidins[nm]) OR (fungicid[tiab] OR fungicidal[tiab] OR fungicidal/bactericidal[tiab] OR fungicidal/fungistatic[tiab] OR fungicidal/parasiticidal[tiab] OR fungicidally[tiab] OR fungicidals[tiab] OR fungicide[tiab] OR fungicide/algicide[tiab] OR fungicide/antioxidant[tiab] OR fungicide/bactericide[tiab] OR fungicide/disinfectant[tiab] OR fungicide/oomyceticide[tiab] OR fungicide/slimicide[tiab] OR fungicide's[tiab] OR fungicideal[tiab] OR fungicideinsensitive[tiab] OR fungicides[tiab] OR fungicides/herbicides[tiab] OR fungicides'[tiab] OR fungicidial[tiab] OR fungicidic[tiab] OR fungicidicus[tiab] OR fungicidin[tiab] OR fungicidine[tiab] OR fungicidity[tiab] OR fungicido[tiab] OR fungicidy[tiab])) AND ("1980/01/01"[PDAT] : "2013/06/31"[PDAT]) AND "humans"[MeSH Terms])) NOT News[Publication Type]) NOT Congresses[Publication Type]) NOT Review[Publication Type]) AND ("1980/01/01"[PDAT] : "2013/06/31"[PDAT]) AND "humans"[MeSH Terms]) NOT "child"[MeSH Terms] AND (("1980/01/01"[PDAT] : "2013/12/31"[PDAT]) AND "humans"[MeSH Terms]))

Figure S1. Forest plots showing estimates of association between non–Hodgkin lymphoma and occupational, agricultural exposures to (**A**) phenoxy herbicides, (**B**) 2,4–D, (C) MCPA, (**D**) glyphosate, (**E**) organochlorine insecticides, and (**F**) DDT.

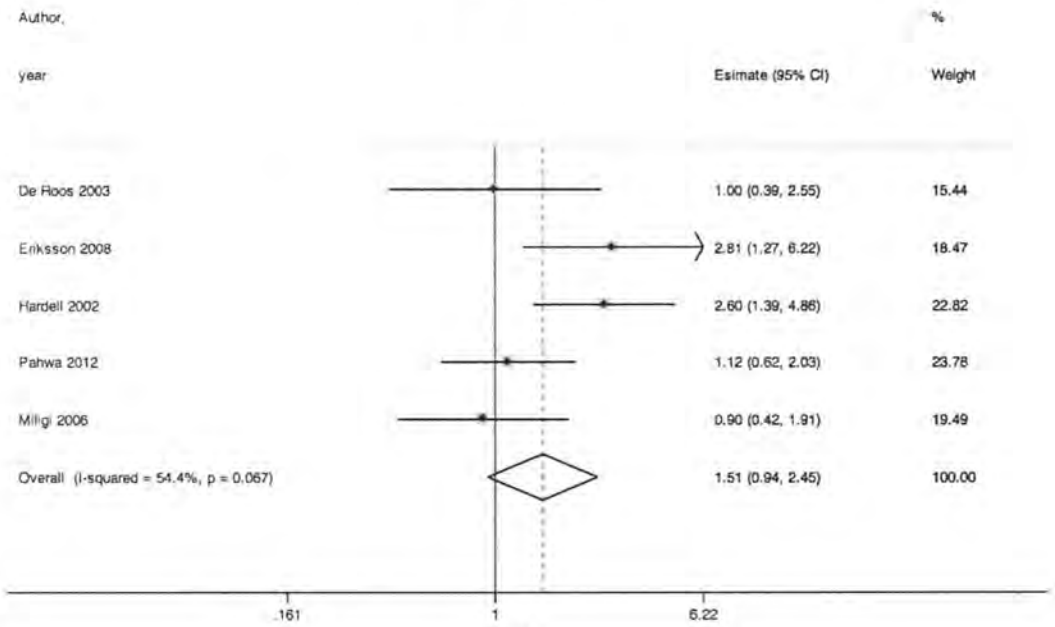


(A)

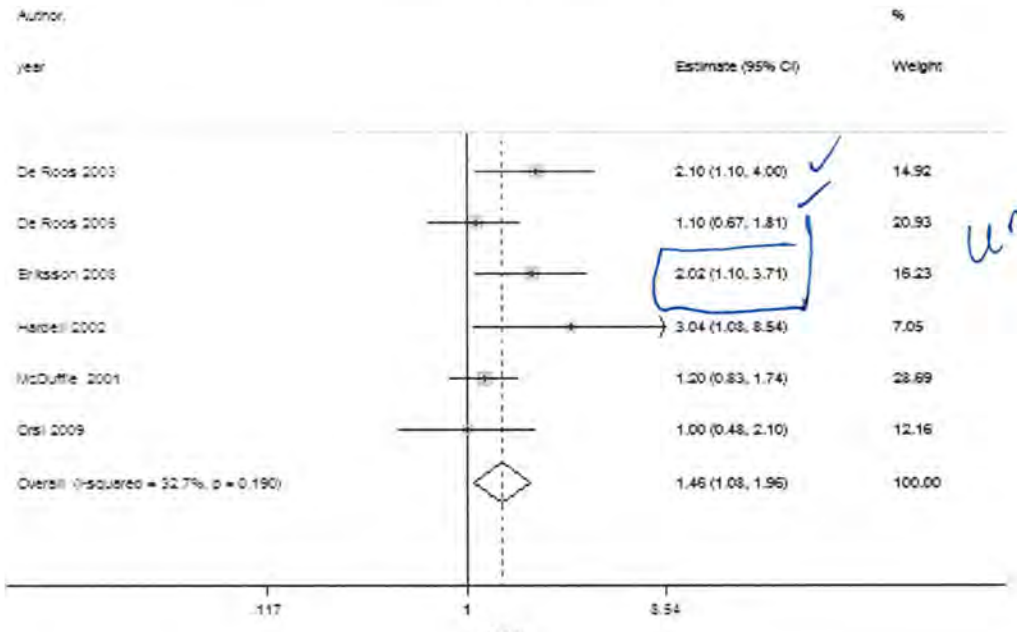


(B)

Figure S1. *Cont.*

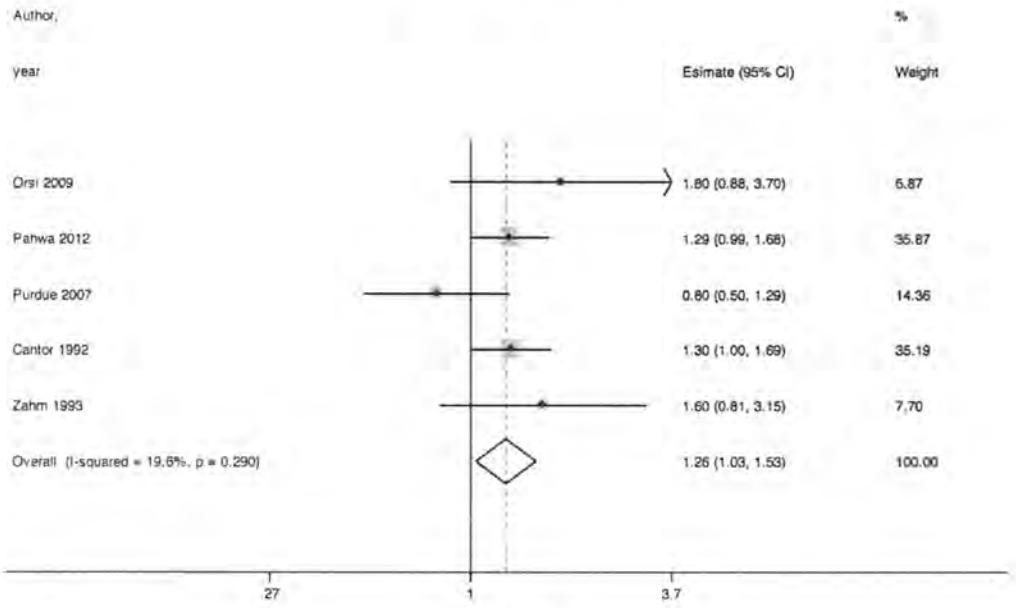


(C)

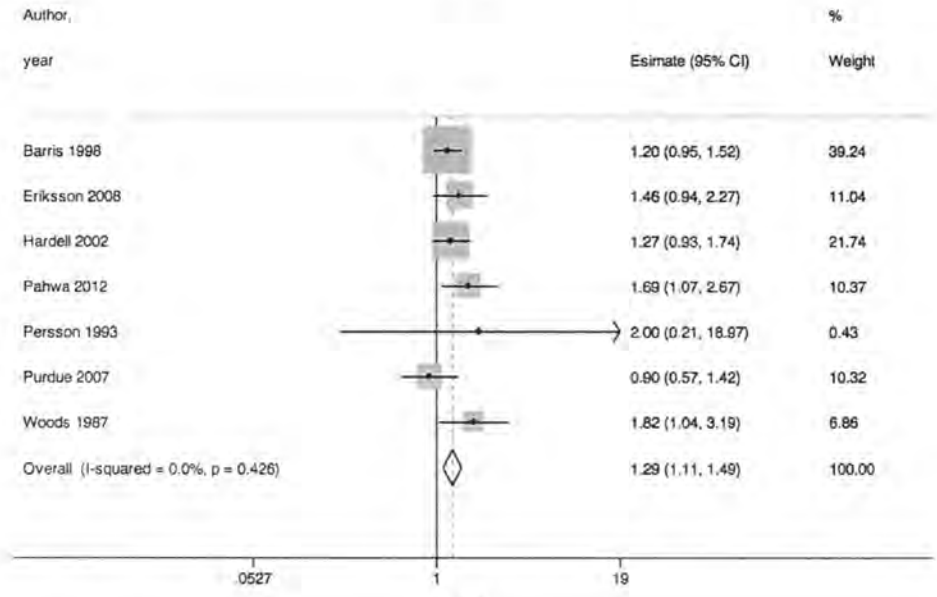


(D)

Figure S1. *Cont.*



(E)



(F)

Notes: 2,4–D, 2,4–Dichlorophenoxyacetic acid; 2,4,5–T, 2,4,5–Trichlorophenoxyacetic acid; DDT, dichlorodiphenyltrichloroethane; MCPA, 2–methyl–4–chlorophenoxyacetic acid.

Table S1. Results of the sensitivity analysis of the effects of gender on the meta– analytic relative risk estimates of association between non–Hodgkin lymphoma and occupational exposure to agricultural pesticides

Chemical	Meta relative risk, 95% CI	I^2	Papers contributing
Male only population			
Amide herbicides	1.7, 0.7–3.8	64.0%	[1,2]
Glyphosate	1.7, 1.0–2.9	52.7%	[3–5]
Phenoxy herbicides	1.4, 1.1–1.6	44.1%	[1,2,4,6–8]
2,4–D	1.3, 1.2–1.5	0.0%	[1,6,9]
MCPA	1.5, 0.8–2.7	56.6%	[3,4,6]
Benzoic acid herbicides	1.3, 0.9–1.9	0.0%	[1,2]
Trifluralin	1.0, 0.6–1.5	0.0%	[3,5]
Triazine herbicides	1.5, 0.70–3.4	73.5%	[1,2]
OP insecticides	1.7, 1.3–2.1	39.2%	[6,10]
Diazinon	1.7, 1.2–2.3	0.0%	[5,10]
Malathion	1.8, 1.4–2.2	0.0%	[6,10]
Carbamate insecticides	1.8, 1.3–2.4	0.0%	[5,11]
OC insecticides	1.3, 1.1–1. 6	0.0%	[1,6]
DDT	1.3, 1.1–1.5	27.3%	[4,6,8,12]
Aldrin	1.4, 0.2–11.1	92.0%	[3,5]
Chlordane	1.3, 0.9–1.7	0.0%	[3,5,8]
Lindane	1.9, 1.2–2.9	38.0%	[5,13,14]
Male and female population			
Phenoxy herbicides	1.6, 1.0–2.5	42.2%	[15–19]
2,4–D	1.8, 0.5–7.5	88.3%	[19,20]
MCPA	1.6, 0.5–4.8	76.0%	[15,19]
OC insecticides	1.2, 0.5–2.5	70.4%	[16,21]
DDT	1.2, 0.8–1.7	18.0%	[15,18,21]

Notes: 2,4–D, 2,4–Dichlorophenoxyacetic acid; DDT, dichlorodiphenyltrichloroethane; MCPA, 2–methyl–4–chlorophenoxyacetic acid; NHL, OC, Organochlorine; OP; Organophosphorus.

Table S2. Results of the sensitivity analysis of the effects of study design on the meta–analytic relative risk estimates of association between non–Hodgkin lymphoma and occupational exposure to agricultural pesticides, with contributing estimates restricted to case–control studies.

Chemical	Meta relative risk, 95% CI	I^2	Paper contributing
Glyphosate	1.6, 1.1–2.2	36.6%	[3–5,15,16]
Organochlorine insecticides	1.3, 1.1–1.6	0.0%	[1,6,16,22]
Aldrin	1.4, 0.2–11.1	92.0%	[3,5]
Chlordane	1.3, 0.9–1.7	0.0%	[3,5,8]
DDT	1.3, 1.1–1.6	0.0%	[4,6,8,12,15,18]
Lindane	1.9, 1.2–2.9	38.0%	[5,13,14]

Notes: DDT; dichlorodiphenyltrichloroethane.

Table S3. Results of the sensitivity analysis of the effects of diagnosis period on the meta– analytic relative risk estimates of association between non–Hodgkin lymphoma and occupational exposure to agricultural pesticides

Chemical	Meta relative risk, 95% CI	I^2	Papers contributing
Diagnosis period 1975–1989			
2,4–D	1.8, 1.0–3.1	76.6%	[1,9,20]
Amide herbicides	1.4, 0.8–2.3	43.2%	[1,2,22]
Glyphosate	2.3, 1.4–4.0	0.0%	[3,4]
MCPA	1.7, 0.7–4.4	63.8%	[3,4]
Phenoxy herbicides	1.4, 1.1–1.7	44.9%	[1,2,4,7,8,17,18,22]
Triazine herbicides	1.4, 0.9–2.2	47.3%	[1,2,23]
Carbamate insecticides	1.6, 1.1–2.4	0.0%	[11,22]
OC insecticides	1.3, 1.0–1.7	0.0%	[1,22]
OP insecticides	1.5, 1.2–1.8	0.0%	[10,22]
Diazinon	1.6, 1.2–2.2	0.0%	[10,20]
Chlordane	1.5, 1.0–2.5	0.0%	[3,8]
Trifluralin	0.9, 0.6–1.3	0.0%	[3,20,22]
Malathion	1.6, 1.3–2.1	0.0%	[10,20]
DDT	1.3, 1.1–1.5	0.0%	[4,8,12,18]
Lindane	2.0, 0.9–4.4	65.0%	[13,14]
Diagnosis period in the 1990s			
2,4–D	1.6, 0.8–3.1	79.3%	[6,19,20]
Glyphosate	1. 5, 1.0–2.1	41.1%	[4,5,15,24]
MCPA	1.6, 0.9–2.9	61.9%	[4,6,15,19]
Phenoxy herbicides	1.5, 1.3–1.8	0.5%	[4,6,15,19]
Trifluralin	1.0, 0.6–1.6	0.0%	[5,20]
Aldrin	1.5, 0.2–10.1	90.0%	[5,21]
Chlordane	0.9, 0.6–1.4	42.2%	[5,21]
Diazinon	1.5, 1.0–2.4	0.0%	[5,20]
DDT	1.3, 1.0–1.6	25.4%	[4,6,15,21]
Lindane	1.9, 1.1–3.2	46.6%	[5,14,21]
Malathion	1.9, 1.5–2.5	0.0%	[6,20]
OC insecticides	1.1, 0.7–1.7	66.2%	[6,21]
Diagnosis period in the 2000s			
Glyphosate	1.3, 0.9–2.0	31.8%	[15,16,24]
Phenoxy herbicides	1.4, 0.7–3.2	66.7%	[15,16]
Lindane	2.0, 0.8–5.0	70.6%	[14, 21]
OC insecticides	1.2, 0.5–2.5	70.4%	[16,21]

Notes: 2,4–D, 2,4–Dichlorophenoxyacetic acid; DDT, dichlorodiphenyltrichloroethane; MCPA, 2–methyl–4–chlorophenoxyacetic acid; NHL, OC, Organochlorine; OP; Organophosphorus; [1] The first, second, and third editions of the International classification of diseases for oncology were introduced in 1976, 1990, and 2000, respectively.

Table S4. Results of the sensitivity analysis of the effects of geographic region on the meta-analytic relative risk estimates of association between non Hodgkin lymphoma and occupational exposure to agricultural pesticides

Chemical	Meta risk ratio estimate, 95% CI	I^2	Papers contributing
Only papers that report results from studies conducted in North America			
Glyphosate	1.3, 1.0–1.8	26.7%	[3,5,24]
Phenoxy herbicides	1.4, 1.1–1.6	12.9%	[1,2,6,8,22]
2,4–D	1.5, 1.1–2.1	66.5%	[1,6,9,20]
MCPA	1.1, 0.7–1.8	0.0%	[3,6]
DDT	1.3, 1.0–1.7	45.1%	[6,8,12,21]
OC insecticides	1.2, 1.0–1.5	24.7%	[1,6,21,22]
OP insecticides	1.6, 1.3–2.0	15.1%	[6,10,22]
Lindane	1.5, 1.2–1.9	0.0%	[5,13,21]
Only papers that report results from studies conducted in the United States			
2,4–D	1.8, 1.0–3.1	76.6%	[1,6,9,20]
Amide herbicides	1.4, 0.8–2.3	43.2%	[1,2,22]
Glyphosate	1.5, 0.8–2.8	58.5%	[3,24]
Phenoxy herbicides	1.3, 1.0–1.7	27.1%	[1,2,8,22]
Trifluralin	0.9, 0.6–1.3	0.0%	[3,20,22]
Triazine herbicides	1.4, 0.9–2.2	47.3%	[1,2,22]
Aldrin	0.5, 0.4–0.8	0.0%	[3,21]
Carbamate insecticides	1.6, 1.1–2.4	0.0%	[22,23]
Chlordane	1.1, 0.7–2.0	55.0%	[3,8,21]
DDT	1.2, 0.9–1.7	44.8%	[8,12,21]

Table S4. *Cont.*

Chemical	Meta risk ratio estimate, 95% CI	I^2	Papers contributing
Only papers that report results from studies conducted in the United States			
Diazinon	1.6, 1.2–2.2	0.0%	[10,20]
Lindane	1.4, 1.1–1.9	0.0%	[13,21]
Malathion	1.6, 1.3–2.1	0.0%	[10,20]
OC insecticides	1.2, 0.8–1.7	47.5%	[1,21,22]
OP insecticides	1.5, 1.2–1.8	0.0%	[10,22]
Only papers that report results from studies conducted in European countries			
Glyphosate	1.7, 1.0–3.1	42.8%	[4,15,16]
Phenoxy herbicides	1.6, 1.2–2.1	29.1%	[4,15–19]
MCPA	1.9, 0.9–3.8	64.8%	[4,15,19]
Only papers that report results from studies conducted in Sweden			
Glyphosate	2.2, 1.3–3.8	0.0%	[4,15]
MCPA	2.7, 1.6–4.4	0.0%	[4,15]
Phenoxy herbicides	1.9, 1.4–2.4	0.0%	[4,15,17,18]
DDT	1.3, 1.0–1.7	0.0%	[4,15,18]

Notes: 2,4–D, 2,4–Dichlorophenoxyacetic acid; DDT, dichlorodiphenyltrichloroethane; MCPA, 2–methyl–4–chlorophenoxyacetic acid; NHL, OC, Organochlorine; OP; Organophosphorus

Table S5. Results of the sensitivity analysis of the effects of control source on the meta– analytic relative risk estimates of association between non–Hodgkin lymphoma and occupational exposure to agricultural pesticides, with contributing estimates restricted to those from population–based case–control studies.

Chemical	Meta risk ratio estimate, 95% CI	I^2	Papers contributing
HERBICIDES			
Amide herbicides	1.4, 0.8–2.3	43.2%	[1,2,22]
Glyphosate	1.7, 1.2–2.6	39.0%	[3,4,5,15]
Phenoxy herbicides	1.5, 1.2–1.7	20.7%	[1,2,4,6,8,15,17–19,22]
Triazine herbicides	1.4, 0.9–2.2	47.3%	[1,2,22]
INSECTICIDES			
Organochlorine insecticides	1.2, 1.0–1.5	24.7%	[1,6,21,22]
Organophosphate insecticides	1.6, 1.4–1.8	0.0%	[1,6,10,22]

Table S6. Results of the sensitivity analysis of the effects of paper contributing on the meta– analytic relative risk estimates of association between non–Hodgkin lymphoma and occupational exposure to agricultural pesticides.

Chemical	Meta estimate, 95% CI	I^2	Change	Papers contributing
HERBICIDES				
Alachlor	0.9, 0.6–1.5	69.7%	Use Cantor 1992 [1] instead of De Roos 2003 [3]	[1,25]
Glyphosate	1.3, 1.0–1.7	18.2%	Use Cantor 1992 [1] instead of De Roos 2003 [3]	[1,24]
2,4–D	1.3, 0.8–2.1	82.5%	Use De Roos 2003 [3] instead of Cantor 1992 [1] and Zahm 1990 [9]	[3,6,19,20]
Carbamate herbicides	1.2, 0.5–2.6	24.8%	Use Cantor 1992 [1] and Hoar 1986 [2] instead of Zheng 2001 [11]	[1,2,16,22]
Trifluralin	1.1, 0.7–1.8	40.0%	Use Cantor 1992 [1] and Hoar 1986 [2] instead of De Roos 2003[3]	[1,2,5,20,22]
INSECTICIDES				
OP insecticides	1.7, 1.4–2.0	0.0%	Use Cantor 1992 [1] instead of Waddell 2001 [10]	[1,6,16,22]
Diazinon	1.5, 1.1–2.1	0.0%	Use Cantor 1992 [1] instead of Waddell 2001 [10]	[1,3,5,20]
Diazinon	1.7, 1.2–2.4	0.0%	Use De Roos 2003 [3] instead of Cantor 1992 [1] and instead of Waddell 2001 [10]	[3,5,20]
Dimethoate	1.2, 0.7–2.0	0.0%	Use De Roos 2003 [3] instead of Waddell 2001 [10]	[3,5]
Malathion	1.7, 1.3–2.2	13.5%	Use Cantor 1992 [1] (use of malathion on animals) instead of Waddell 2001 [10] or De Roos 2003 [3]	[1,6,20]
Malathion	1.8, 1.4–2.4	0.0%	Use Cantor 1992 [1] (use of malathion on crops) instead of Waddell 2001 [10] or De Roos 2003 [3]	[1,6,20]
Malathion	1.6, 1.2–2.3	37.2%	Use De Roos 2003 [3] instead of Waddell 2001 [10] and Cantor 1992 [1]	[3,6,20]
Carbaryl	1.9, 1.3–2.9	0.0%	Use Cantor 1992 [1] instead of Zheng 2001 [11]	[1,5]
Carbaryl	1.5, 0.7–3.1	64.7%	Use De Roos 2003 [3] instead of Cantor 1992 [1] or Zheng 2001 [11]	[3,5]
Carbofuran	1.1, 0.7–1.8	0.0%	Use Cantor 1992 [1] instead of Zheng 2001 [11]	[1,5]

Table S6. *Cont.*

Chemical	Meta estimate, 95% CI	I^2	Change	Papers contributing
Carbofuran	1.1, 0.6–2.0	23.0%	Use De Roos 2003 [3] instead of Cantor 1992 [1] or Zheng 2001 [11]	[3,5]
DDT	1.3, 1.1–1. 5	0.0%	Use Cantor 1992 [1] (use of DDT on animals) instead of Baris 1998 [12]	[1,4,6,8,15,18,21]
DDT	1.3, 1.2–1. 6	9.1%	Use Cantor 1992 [1] (use of DDT on crops) instead of Baris 1998 [12]	[1,4,6,8,15,18,21]
Methoxychlor	1.0, 0.8–1.4	0.0%	Use Cantor 1992 [1] instead of De Roos 2003 [3]	[1,5]
Aldrin	1.3, 0.5–2.9	80.2%	Use Cantor 1992 [1] instead of De Roos 2003 [3]	[1,5,21]
Chlordane	1.2, 0.8–1.7	48.7%	Use Cantor 1992 [1] (Use of chlordane on animals) instead of De Roos 2003 [3]	[1,5,8,21]
Chlordane	1.1, 0.8–1.7	42.1%	Use Cantor 1992 [1] (Use of chlordane on crops) instead of De Roos 2003 [3]	[1,5,8,21]
Dieldrin	1.0, 0.4–2.2	50.8%	Use Cantor 1992 [1] instead of De Roos 2003[3]	[1,21]
Heptachlor	1.0, 0.7–1.7	20.5%	Use Cantor 1992 [1] instead of De Roos 2003[3]	[1,21]
Lindane	1.62, 1.16–2.27	30.6%	Use Cantor 1992 [1] (use of lindane on animals) instead of Blair 1998 [13] and De Roos 2003 [3]	[1,5,14,21]
Lindane	1.85, 1.27–2.69	23.30 %	Use Cantor 1992 [1] (use of lindane on crops) instead of Blair 1998 [13]and De Roos 2003 [3]	[1,5,14,21]
Lindane	1.62, 1.08–2.41	39.20 %	Use De Roos 2003 [3] instead of Cantor 1992 [1] or Blair 1998 [13]	[3,5,14,21]
Toxaphene	1.25, 0.72–2.19	23.50 %	Use Cantor 1992 [1] (use of toxaphene on animals) instead of De Roos 2003 [3]	[1,20,21]
Toxaphene	1.50, 0.96–2.33	0.00%	Use Cantor 1992 [1] (use of toxaphene on crops) instead of De Roos 2003 [3]	[1,20,21]

Notes: 2,4–D, 2,4–Dichlorophenoxyacetic acid; DDT, dichlorodiphenyltrichloroethane; MCPA, 2–methyl–4–chlorophenoxyacetic acid; NHL, OC, Organochlorine; OP; Organophosphorus.

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