



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

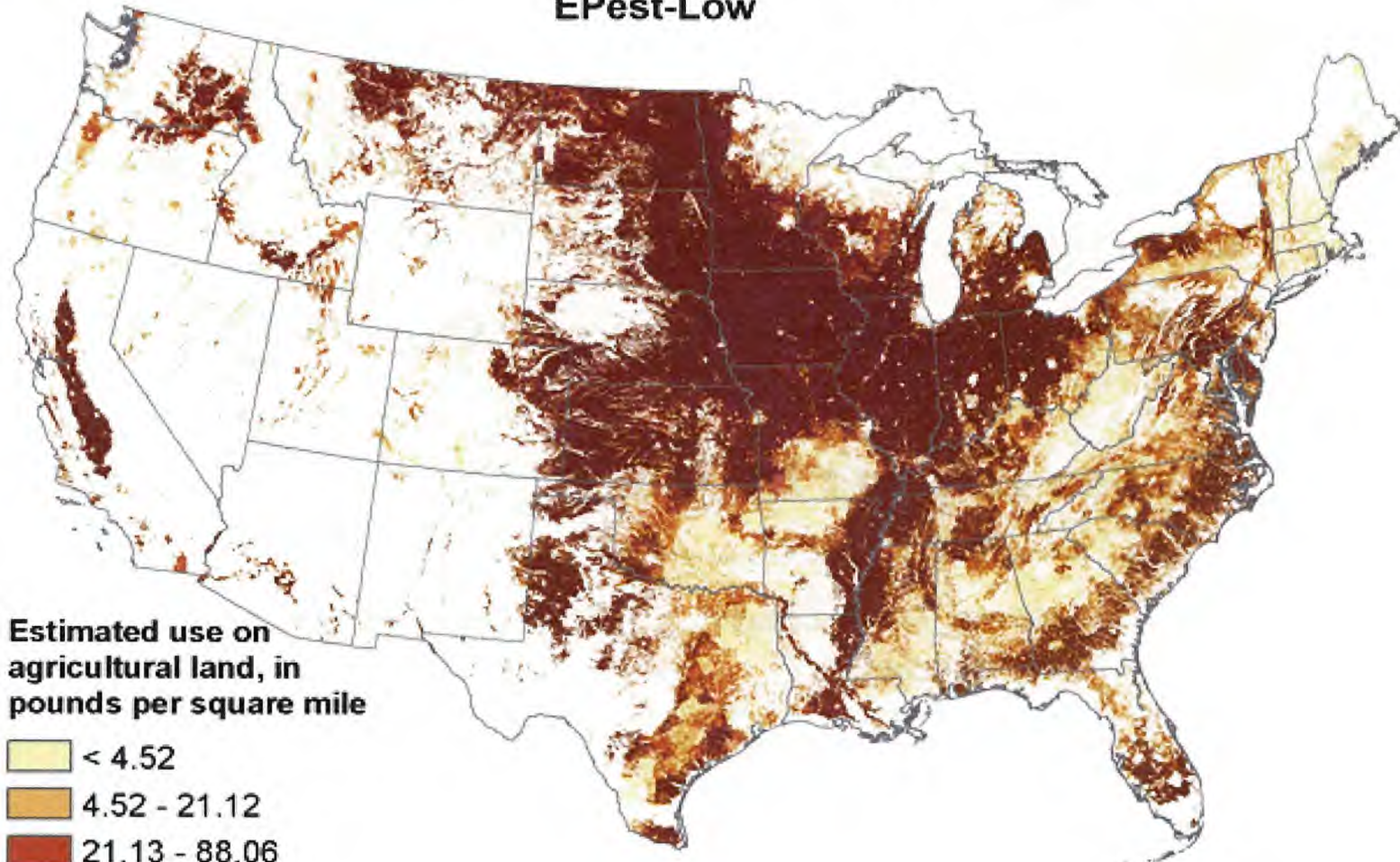
Glyphosate is...

- A broad-spectrum herbicide
- Commonly known as “Roundup”
- The most frequently used herbicide in the world








Estimated Agricultural Use for Glyphosate, 2012

EPest-Low



**Estimated use on
agricultural land, in
pounds per square mile**

-  < 4.52
-  4.52 - 21.12
-  21.13 - 88.06
-  > 88.06
-  No estimated use

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

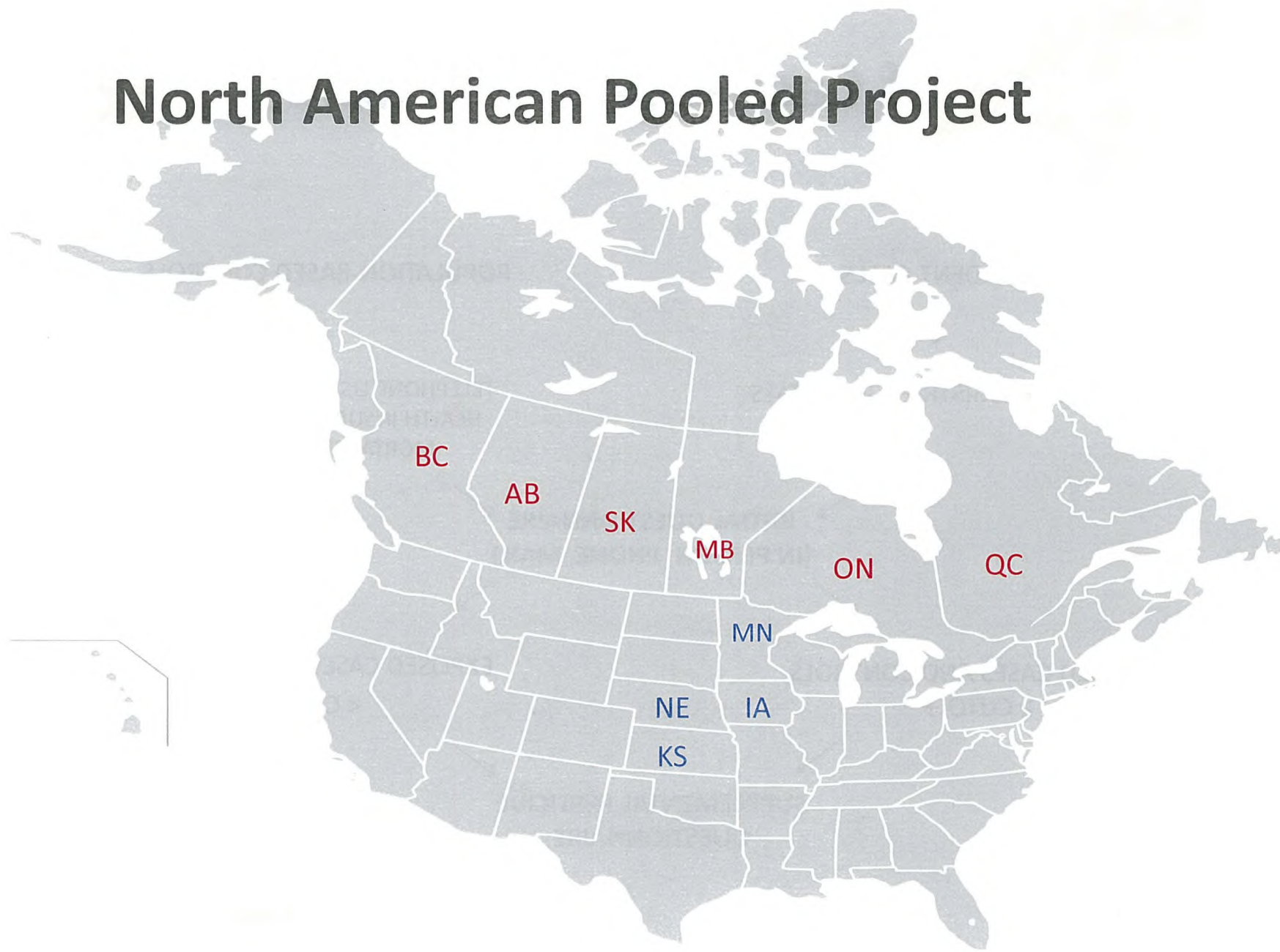
aggressive cancers after adjustment for other pesticides.⁹ In mice, malathion increased hepatocellular adenoma or carcinoma (combined).¹⁰ In rats, it increased thyroid carcinoma in males, hepatocellular adenoma or carcinoma (combined) in females, and mammary gland adenocarcinoma after subcutaneous injection in females.⁴ Malathion is rapidly absorbed and distributed. Metabolism to the



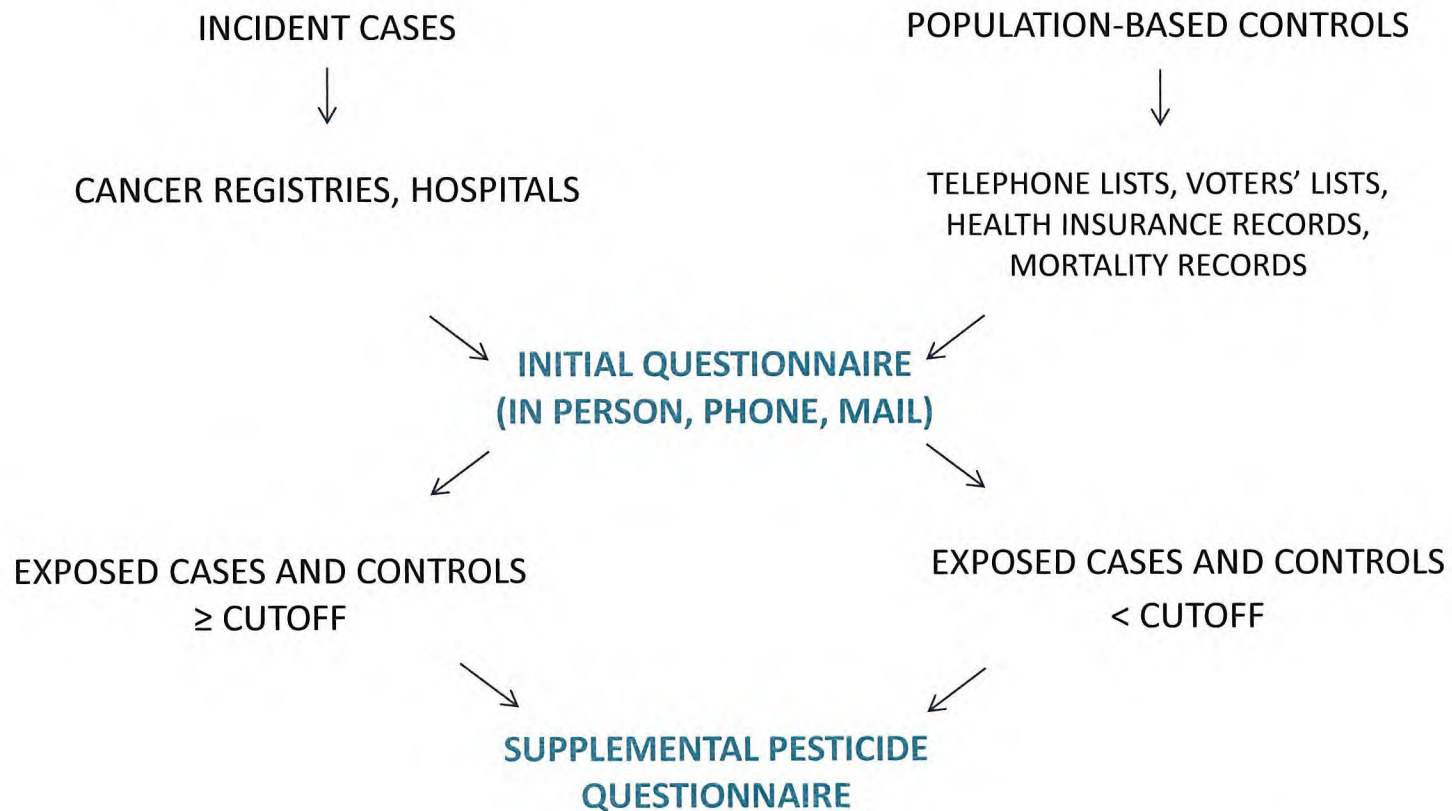
Lancet Oncol 2015
Published Online
March 20, 2015
<http://dx.doi.org/10.1016/>

Towards a cancer-free workplace

North American Pooled Project



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



Glyphosate Use

Ever/Never
Duration
Frequency
Lifetime days



NHL Risk

Overall
FL
DLBCL
SLL
Other

Age, sex, state/province,
lymphatic/hematopoietic cancer in a first-degree relative, use of proxy respondent, use of any PPE, use of 2,4-D, use of dicamba, use of malathion

Covariates



Proxy Respondent Analysis



Glyphosate Use

Ever/Never
Duration
Frequency
Lifetime days

Proxy and self-respondents
Self-respondents only



NHL Risk

Overall
FL
DLBCL
SLL
Other

Age, sex, state/province,
lymphatic/hematopoietic cancer in a first-
degree relative, use of any PPE, use of
2,4-D, use of dicamba, use of malathion

Covariates

Selected Characteristics of NHL Cases and Controls

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)
<i>Lymphatic or hematopoietic cancer in a first-degree relative</i>			
Yes	139	202	2.10 (1.67, 2.63)
No	1493	4790	1
Unknown/missing	58	139	
<i>Ever lived or worked on a farm or ranch</i>			
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



OR (95% CI) for NHL Overall

Glyphosate Use	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

Acknowledgements



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





Towards a cancer free workplace

www.occupationalcancer.ca