Occupational Cancer Research Centre

An Evaluation of Glyphosate Use and the Risk of Non-Hodgkin Lymphoma Major Histological Sub-Types in the North American Pooled Project

Manisha Pahwa, John J. Spinelli, Laura Beane Freeman, Paul A. Demers, Aaron Blair, Punam Pahwa, James A. Dosman, John R. McLaughlin, Shelia Hoar Zahm, Kenneth P. Cantor, Dennis D. Weisenburger, Shelley A. Harris

International Society for Environmental Epidemiology Conference | Sao Paulo, Brazil | August 31, 2015
#868 (Pesticides and Other POPs)

Towards a cancer-free workplace

Disclosure of Competing Financial Interests

None

Towards a cancer-free workplace

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

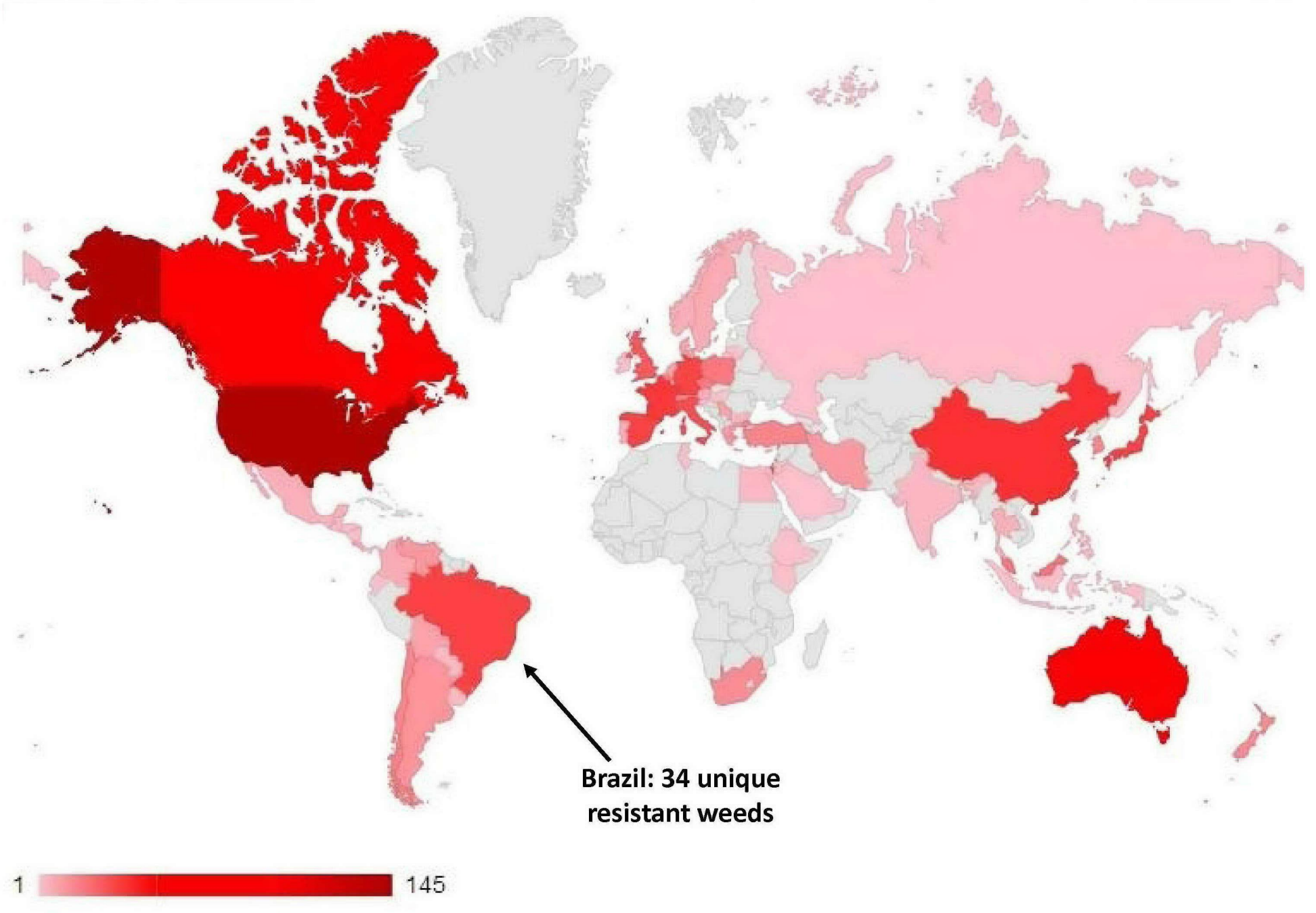
to the bioactive metabolite, paraoxon, is similar across species. Although bacterial mutagenesis tests were negative, parathion induced DNA and chromosomal damage in human cells in vitro. Parathion markedly increased rat mammary gland terminal end bud density.[4] Parathion use has been severely restricted 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

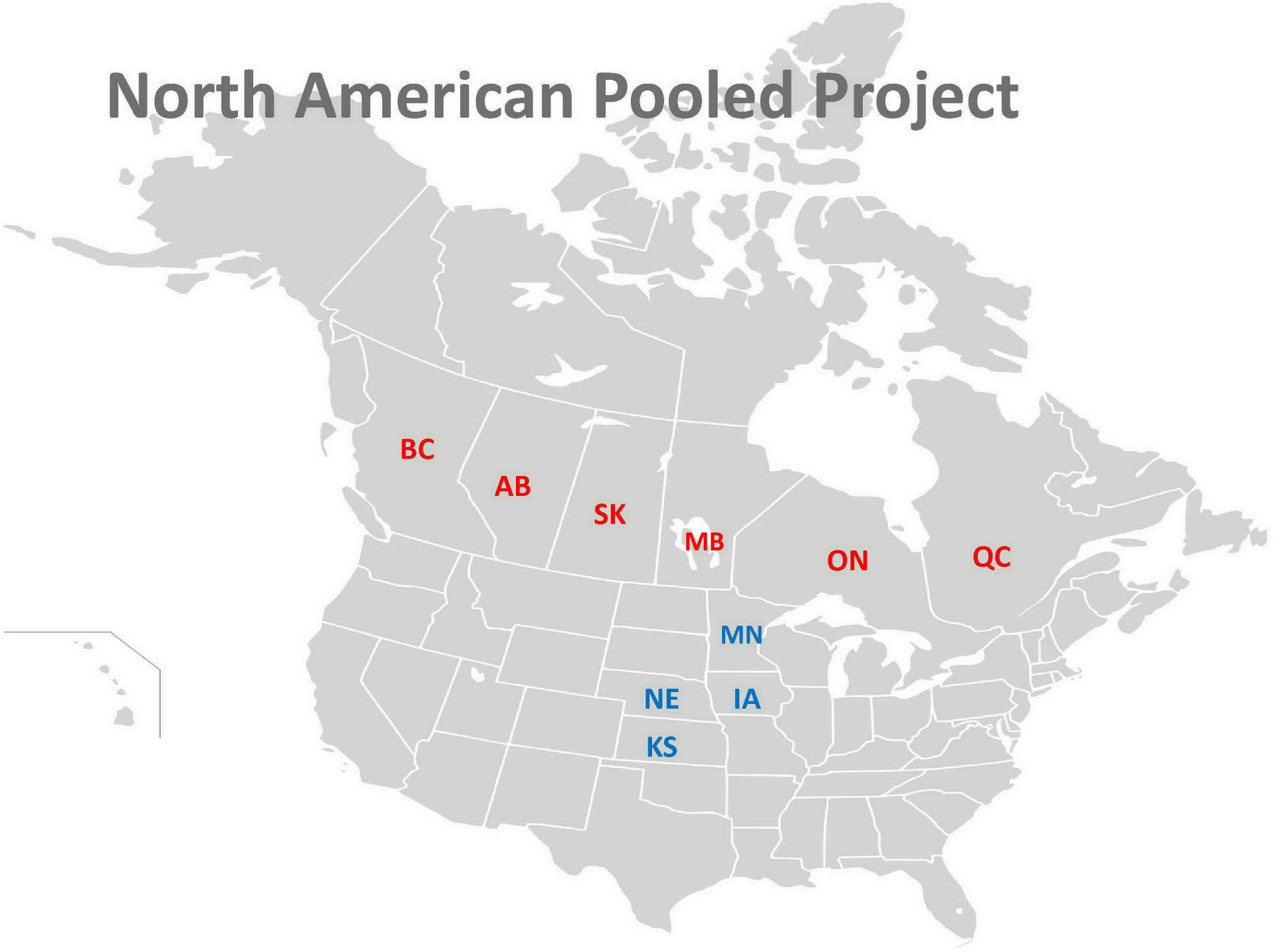
Lancet Oncol 2015
Published Online
March 20, 2015
http://dx.doi.org/10.1016/

Towards a cancer-free workplace



International Survey of Herbicide Resistant Weeds: http://weedscience.org/graphs/geochart.aspx

North American Pooled Project



General Design of Case-Control Studies

INCIDENT CASES

Cancer registries, hospitals

POPULATION-BASED CONTROLS

Telephone lists, voters' lists, health insurance records, mortality records

QUESTIONNAIRE
(in person, phone, mail)

Towards a cancer-free workplace

Glyphosate Use Information

	EVER/NEVER	DURATION # Years	FREQUENCY # Days/Year	LIFETIME DAYS # Years x # Days/Year
Iowa/Minnesota	✓	✓	X	X
Kansas	✓	X	X	X
Nebraska	✓	✓	✓	✓
Canada	✓	✓	✓	✓

Conceptual Framework for Analysis

Glyphosate Use

Ever/Never
Duration
Frequency
Lifetime days

NHL Risk

Overall
FL
DLBCL
SLL
Other

Covariates

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

Selected Characteristics of NHL Cases and Controls

Variable	Cases (N)	Controls (N)	OR* (95% CI)
N	1690	5131	
Histological sub-type			
Follicular (FL)	468		
Diffuse (DLBCL)	647		
Small lymphocytic (SLL)	171		
Other	404		
Location			
U.S.	1177	3625	
Canada	513	1506	
Respondent type			
Self	1140	3372	1
Proxy	533	1692	1.01 (0.89, 1.15)
Unknown/missing	17	67	
Lymphatic or hematopoietic cancer in a first-degree relative			
No	1493	4790	1
Yes	139	202	2.13 (1.69, 2.67)
Unknown/missing	58	139	

*ORs adjusted for age and location

Glyphosate Use and NHL Risks

NHL sub-type	Number of cases who reportedly ever used glyphosate	OR[a] (95% CI)	OR[b] (95% CI)
Overall	113	1.43 (1.11, 1.83)	1.13 (0.84, 1.51)
FL	28	1.00 (0.65, 1.54)	0.69 (0.41, 1.15)
DLBCL	45	1.60 (1.12, 2.29)	1.23 (0.81, 1.88)
SLL	15	1.77 (0.98, 3.22)	1.79 (0.87, 3.69)
Other	25	1.66 (1.04, 2.63)	1.51 (0.87, 2.60)

a. ORs adjusted for age, sex, state/province, lymphatic or hematopoietic cancer in a first-degree relative, use of a proxy respondent, use of any personal protective equipment; b. ORs adjusted for all covariates in model (a) plus use of 2,4-D, use of dicamba, use of malathion

Duration (#Years) of Glyphosate Use and NHL Risks

# years	OR* (95% CI)				
	Overall	FL	DLBCL	SLL	Other
0	1	1	1	1	1
>0 and ≤3.5	1.59 (1.13, 2.22)	0.95 (0.52, 1.74)	2.02 (1.28, 3.21)	1.49 (0.63, 3.58)	2.08 (1.14, 3.78)
>3.5	1.20 (0.82, 1.75)	0.88 (0.46, 1.71)	1.19 (0.67, 2.12)	1.98 (0.89, 4.39)	1.32 (0.64, 2.71)
P-trend	0.03	0.96	0.03	0.08	0.14

*ORs adjusted for age, sex, state/province, lymphatic or hematopoietic cancer in a first-degree relative, use of a proxy respondent, use of any personal protective equipment

Frequency (#Days/Year) of Glyphosate Handling and NHL Risks

# days/year handled	OR* (95% CI)				
	Overall	**FL**	**DLBCL**	**SLL**	**Other**
0	1	1	1	1	1
>0 and ≤2	1.03 (0.67, 1.60)	0.81 (0.35, 1.84)	0.95 (0.49, 1.81)	1.27 (0.42, 3.89)	1.49 (0.66, 3.32)
>2	2.42 (1.48, 3.96)	2.21 (0.99, 4.93)	2.83 (1.48, 5.41)	2.29 (0.66, 7.98)	2.26 (0.85, 5.99)
P-trend	0.02	0.07	0.04	0.21	0.85

*ORs adjusted for age, sex, state/province, lymphatic or hematopoietic cancer in a first-degree relative, use of a proxy respondent, use of any personal protective equipment

Lifetime Days (#Years x #Days/Year) of Glyphosate Use and NHL Risks

Lifetime days	OR* (95% CI)				
	Overall	**FL**	**DLBCL**	**SLL**	**Other**
0	1	1	1	1	1
>0 and ≤7	1.20 (0.74, 1.95)	1.03 (0.43, 2.48)	1.14 (0.56, 2.30)	1.04 (0.24, 4.58)	1.93 (0.82, 4.51)
>7	1.55 (0.99, 2.44)	1.33 (0.60, 2.94)	1.51 (0.79, 2.88)	2.13 (0.76, 5.96)	1.69 (0.68, 4.15)
P-trend	0.02	0.02	0.10	0.01	0.33

*ORs adjusted for age, sex, state/province, lymphatic or hematopoietic cancer in a first-degree relative, use of a proxy respondent, use of any personal protective equipment

Challenges

- Uncollected information about duration and frequency of glyphosate use in some locations
- Small numbers for certain stratified analyses
- Measurement error
- Potential recall bias and unmeasured confounding

Strengths

- Larger sample size = more statistical power to incorporate evaluations of NHL sub-types with detailed glyphosate use metrics
- Risk estimates adjusted for other pesticide uses *(results not presented)*
- Evaluated ORs based on data from self-respondents only and assessed effect modification of PPE use on glyphosate-NHL associations *(results not presented)*

Conclusions

- Glyphosate use may be associated with ↑ risk of NHL
- Some differences in risk by sub-type, but not consistent across different glyphosate use metrics
- Large sample size yielded more precise results than possible in previous smaller studies

Further Considerations

- Glyphosate use is projected to increase worldwide, especially in emerging large-scale agricultural economies in Latin America, Asia, and South Africa
- Use of glyphosate is important for global food supply

BUT…

- Glyphosate-resistant weeds are a concern and threat to its prolonged and isolated use
- The human (and environmental) health effects of newer herbicide formulations that contain glyphosate with ≥1 other active ingredient are largely unknown

Acknowledgements

- **Canadian investigators:** Drs. Shelley A. Harris, John J. Spinelli, Paul A. Demers, Punam Pahwa, James A. Dosman, John R. McLaughlin
- **U.S. investigators:** Drs. Laura Beane Freeman, Aaron Blair, Shelia Hoar Zahm, Kenneth P. Cantor, Dennis D. Weisenburger
- **NAPP Executive Committee:** Drs. Shelley A. Harris, Laura Beane Freeman, John J. Spinelli
- **Data pooling:** Mr. Joe Barker (IMS Inc.)

This analysis was funded by the Canadian Cancer Society Research Institute (Prevention Research Grant #703055)

Contact

Manisha Pahwa, Research Associate

Occupational Cancer Research Centre, Cancer Care Ontario

620 University Avenue, Toronto, Ontario, M5G 2L7

manisha.pahwa@occupationalcancer.ca

www.occupationalcancer.ca

Towards a cancer free workplace

www.occupationalcancer.ca

About NHL and Glyphosate

NHL

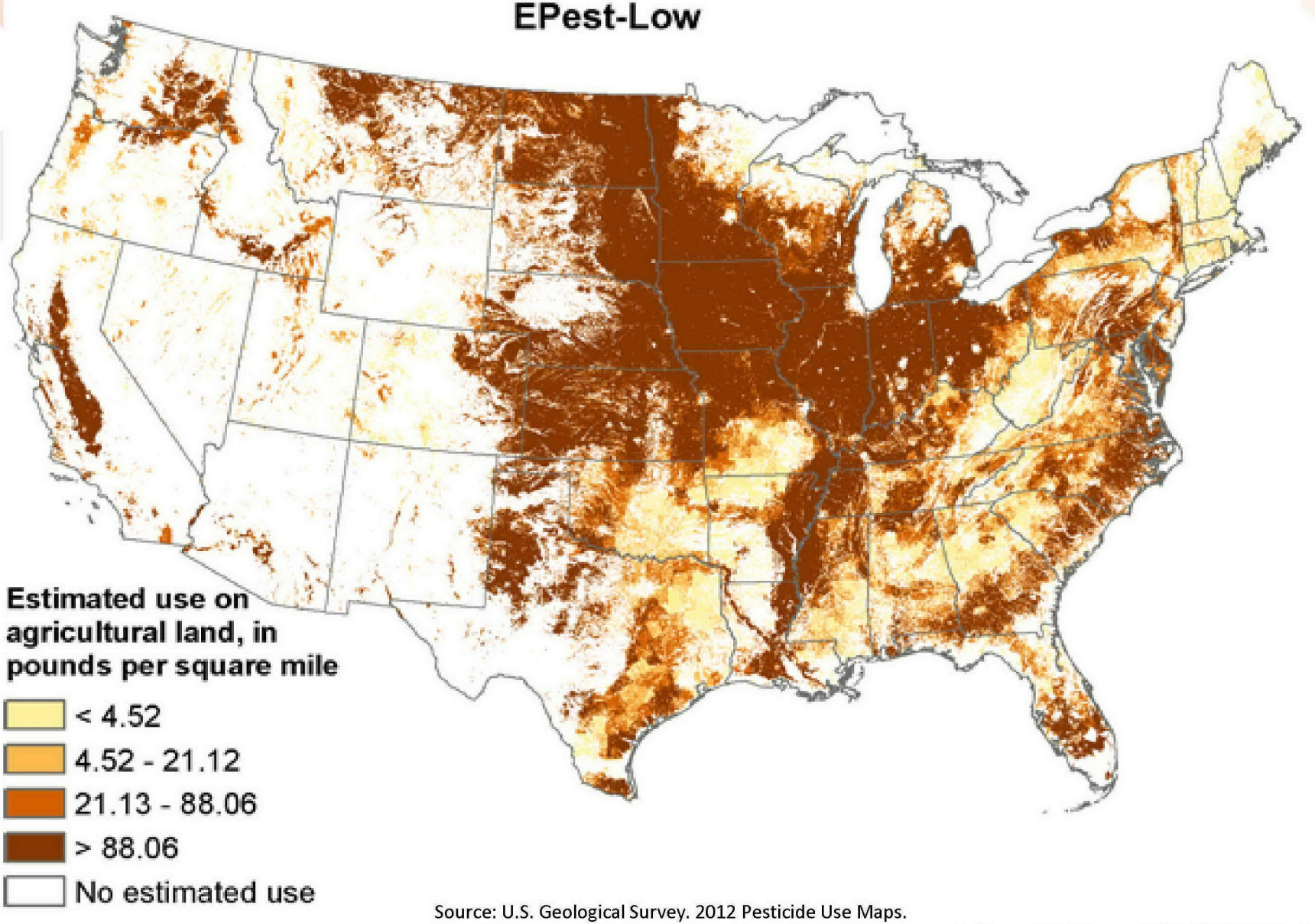
- A cancer that starts in the lymphocytes
- Heterogeneous, according to type of cell affected

Glyphosate

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

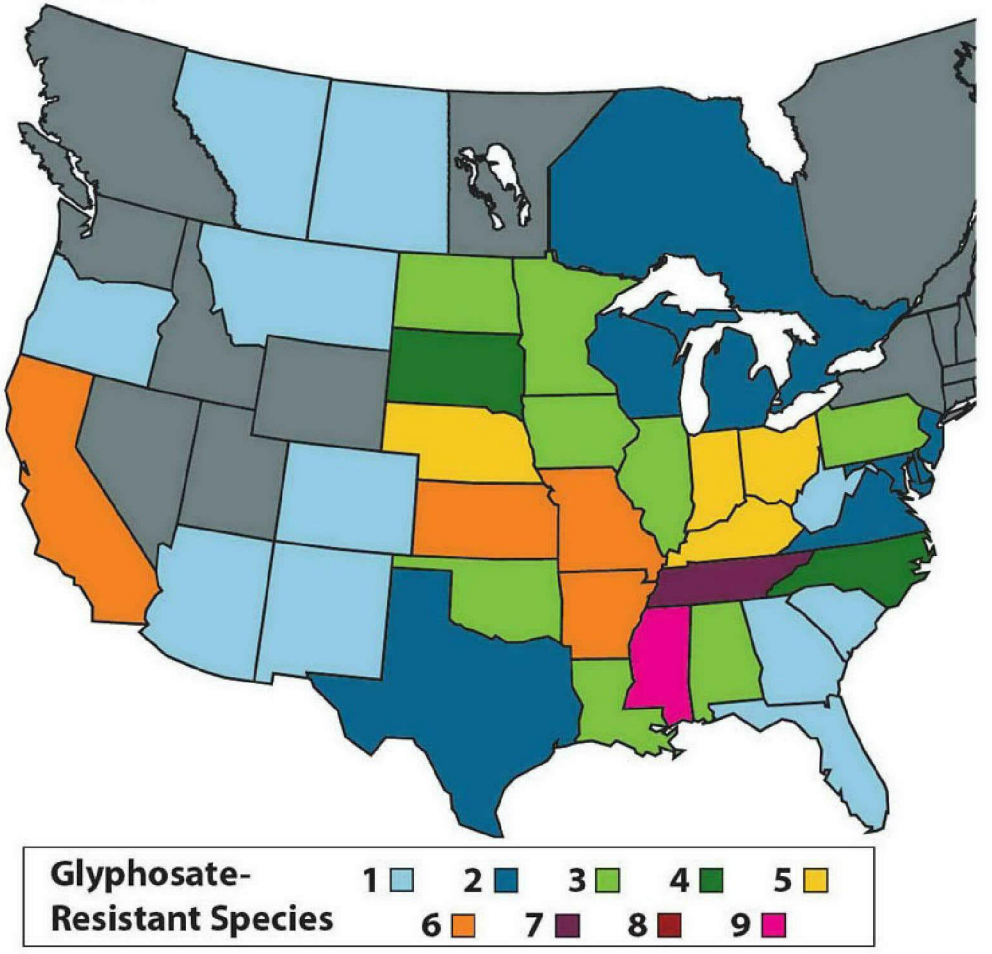
Estimated Agricultural Use for Glyphosate, 2012

EPest-Low



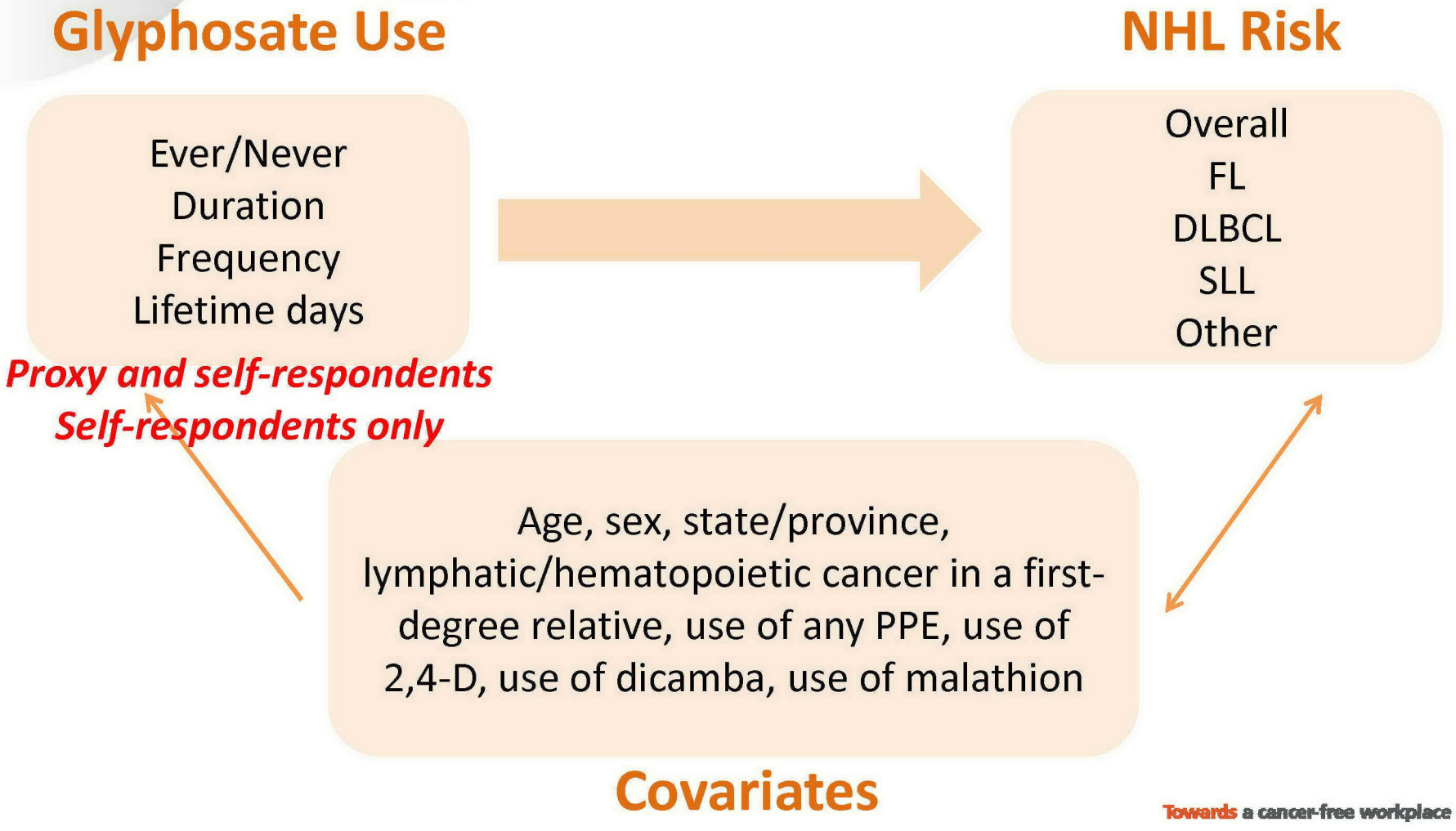
Source: U.S. Geological Survey. 2012 Pesticide Use Maps.
https://water.usgs.gov/nawqa/pnsp/usage/maps/show_map.php?year=2012&map=GLYPHOSATE&hilo=L

Glyphosate-Resistant Weed Species in North America



https://www.pioneer.com/home/site/mobile/plan/soybeans/weed-mgmt/

Proxy Respondent Analysis



Towards a cancer-free workplace

Selected Characteristics of NHL Cases and Controls (Continued)

Variable	Cases (N)	Controls (N)	OR (95% CI)
Ever lived or worked on a farm or ranch			
No	577	1840	1
Yes	1102	3276	1.06 (0.94, 1.20)
Unknown/missing	11	15	
Ever used any type of PPE			
No	374	1127	1
Yes	105	310	1.12 (0.86, 1.45)
Unknown/missing	1211	3694	

Proxy vs. Self Respondents

	OR (95% CI) for NHL Overall	
Glyphosate Use	**Proxy and Self Respondents[a]**	**Self Respondents Only[b]**
Never used	1	1
Ever used	1.13 (0.84, 1.51)	0.95 (0.69, 1.32)
Duration (# years)		
>0 and ≤3.5	1.28 (0.88, 1.84)	1.17 (0.79, 1.74)
>3.5	0.94 (0.62, 1.42)	0.78 (0.49, 1.24)
Frequency (# days/year)		
>0 and ≤2	0.74 (0.46, 1.19)	0.66 (0.39, 1.12)
>2	1.73 (1.02, 2.94)	1.77 (0.99, 3.17)
Lifetime days (# years x # days/year)		
0 and ≤7	0.87 (0.52, 1.45)	0.82 (0.46, 1.44)
>7	1.08 (0.66, 1.77)	1.06 (0.62, 1.81)

a. ORs adjusted for age, sex, state/province, lymphatic or hematopoietic cancer in a first-degree relative, use of a proxy respondent, use of any PPE, use of 2,4-D, use of dicamba, use of malathion; b. ORs adjusted for age, sex, state/province, lymphatic or hematopoietic cancer in a first-degree relative, use of any PPE, use of 2,4-D, use of dicamba, use of malathion

Future Research Priorities

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

Acknowledgements

Canadian investigators

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

U.S. investigators

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