Occupational Cancer Research Centre

An overview of results from the Cross-Canada Study of Pesticides and Health (CCSPH) and current state of the North American Pooled Project (NAPP)

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Towards a cancer-free workplace

Cancer Care Ontario

- Operational Service Agency for the Ontario government since 1997, governed by an act of legislation: The Cancer Act.

- Government's cancer advisor:
  - Directs and oversees more than $800 million in funding for hospitals and other cancer-care providers
  - Plans cancer services
  - Implements provincial cancer prevention and screening programs
  - Conducts and transfers research into improvements and innovations in clinical practice, cancer service delivery, and prevention

About the OCRC

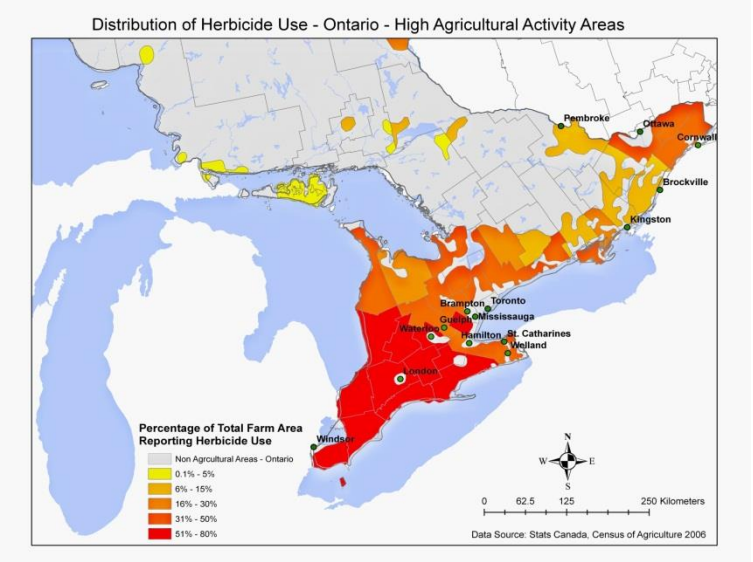
- “Towards a cancer-free workplace”
- Research on the causes, incidence, and prevention of workplace cancer
- Mostly funded by external grants and agencies

OCRC Research Agenda

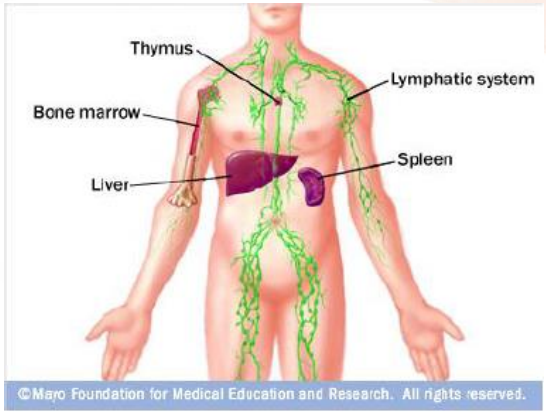
- The OCRC integrated research program consists of:
  - surveillance of occupational cancers and workplace exposures;
  - research into the causes of cancer in the workplace;
  - intervention research to develop and test prevention and exposure reduction strategies;
  - building capacity in applied occupational cancer research; and
  - knowledge transfer and exchange with stakeholders

Pesticides and human health

- **Are there links between pesticide exposures and certain types of cancer?**
  - Non-Hodgkin lymphoma
  - Hodgkin lymphoma
  - Multiple myeloma
  - Soft tissue sarcoma

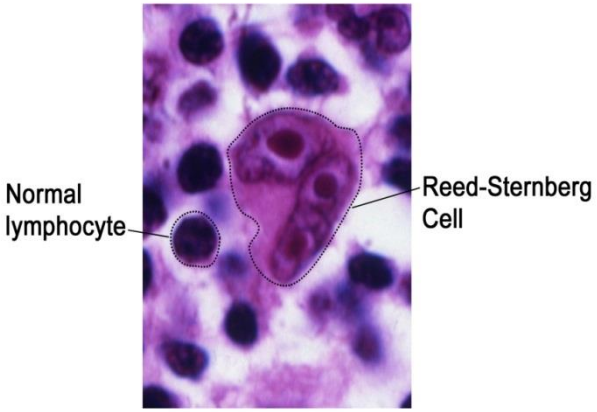


Non-Hodgkin lymphoma (NHL)



- The first most common hematological malignancy
- Large group of cancers of lymphocytes
- Generally, cancerous lymphocytes are found in lymph nodes but they can also spread to other parts of the lymphatic system
- Causes unknown, but immune suppression is a risk factor

Hodgkin lymphoma (HL)



- A cancer of the lymphatic system
- Most cases start in B lymphocytes (B cells)
  - Reed-Sternberg cells
- Causes unknown, but risk factors include age, family history of lymphoma, male gender, previous Epstein-Barr infection, immune suppression

U.S. National Cancer Institute. Non-Hodgkin lymphoma. http://www.cancer.gov/cancertopics/types/non-hodgkin
Mayo Clinic. Non-Hodgkin's lymphoma. http://www.mayoclinic.com/health/non-hodgkins-lymphoma/DS00350
Mayo Clinic. Hodgkin's lymphoma (Hodgkin's disease). http://www.mayoclinic.com/health/hodgkins-disease/DS00186/DSECTION=risk-factors

Multiple myeloma (MM)

- Second-most common hematological cancer worldwide
- Etiology poorly understood
  - Risk factors include older age, male gender, ethnicity

Soft tissue sarcoma (STS)

- A type of cancer that starts in the muscle, fat, fibrous tissue, blood vessels, nerves, joints, or other supporting tissue of the body (osteosarcomas develop in bone)
- Potential risk factors: certain inherited disorders, past treatment with radiation therapy

National Cancer Institute. Soft Tissue Sarcoma. http://www.cancer.gov/cancertopics/types/soft-tissue-sarcoma

Cross-Canada Study of Pesticides and Health (CCSPH)

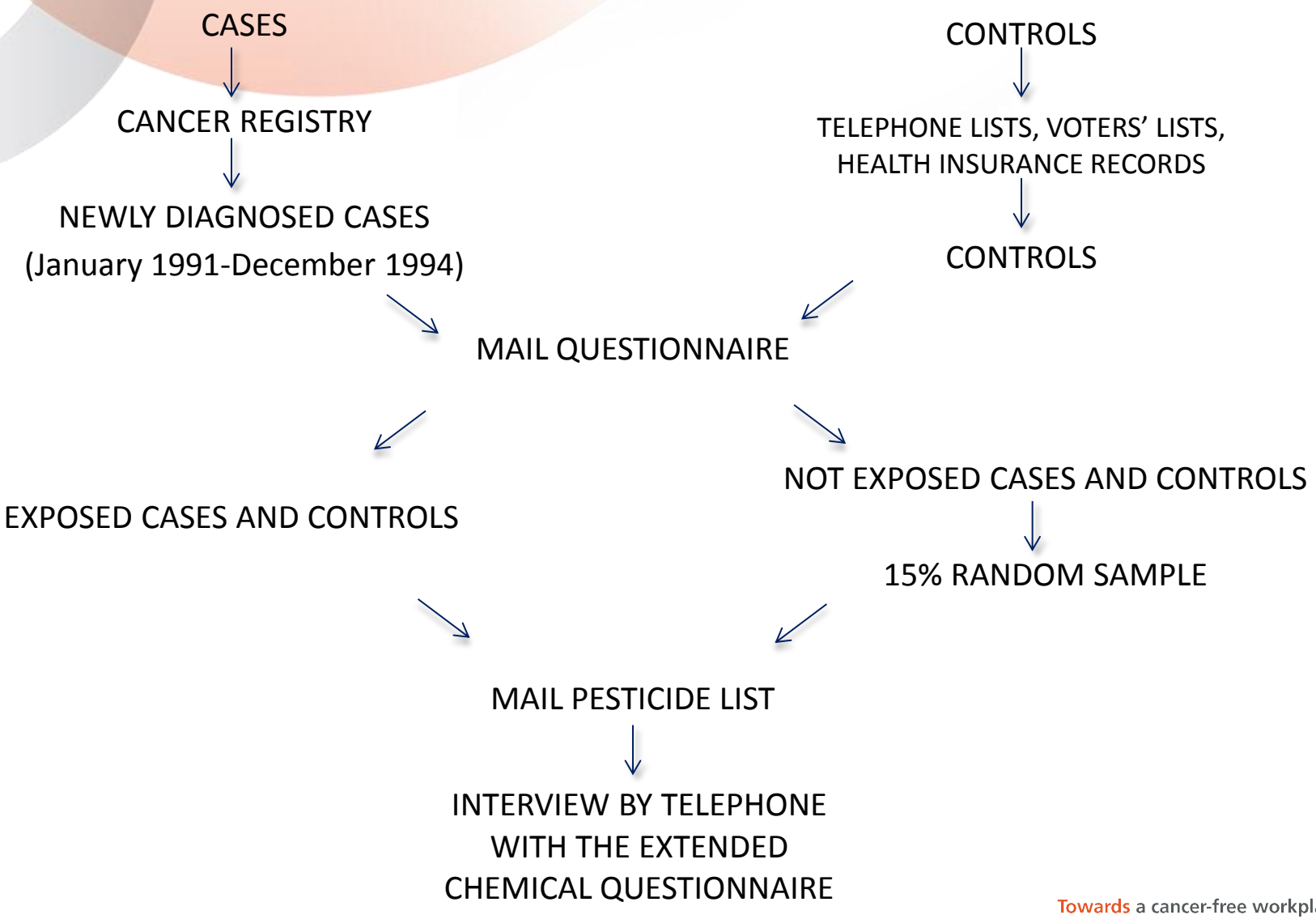
- Case-control study conducted on males aged 19 years and older in six provinces between 1991 and 1994

McDuffie et al. *Cancer Epidemiology, Biomarkers & Prevention* 2001;10:1155-1163

Goals of the CCSPH

- To assess specific agricultural factors that may be involved in cancer
- Modeled from similar studies completed by the U.S. National Cancer Institute in four states during the 1980s

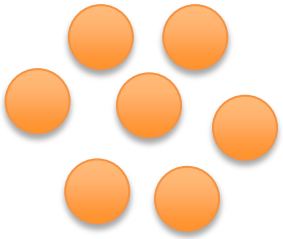
Overview of CCSPH study design



Study population

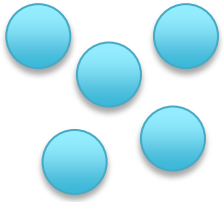
Cases

Non-Hodgkin lymphoma N=513

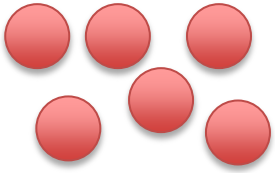


Follicular N=74
Diffuse N=132
Small lymphocytic N=26
Other N=281

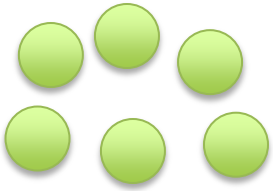
Hodgkin lymphoma N=316



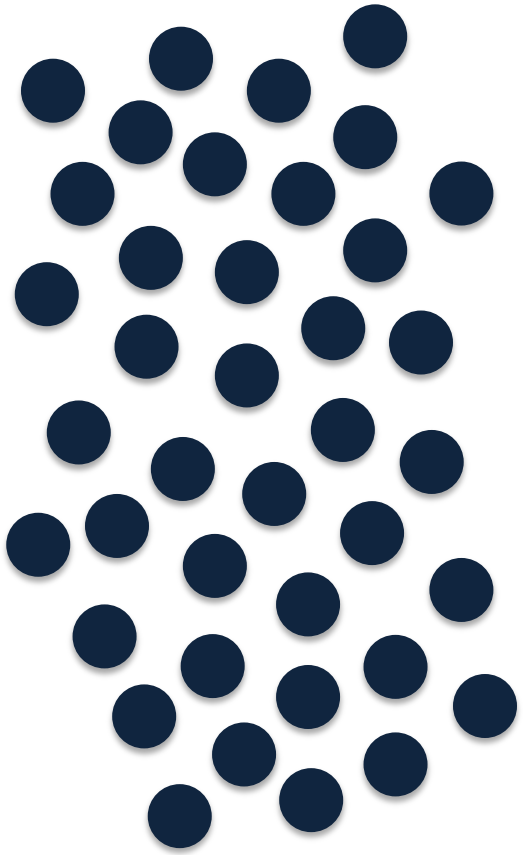
Multiple myeloma N=342



Soft tissue sarcoma N=357



Controls



N=1506

Photo credit: Environ Health Perspect. 2000 January; 108(1): A24–A26.

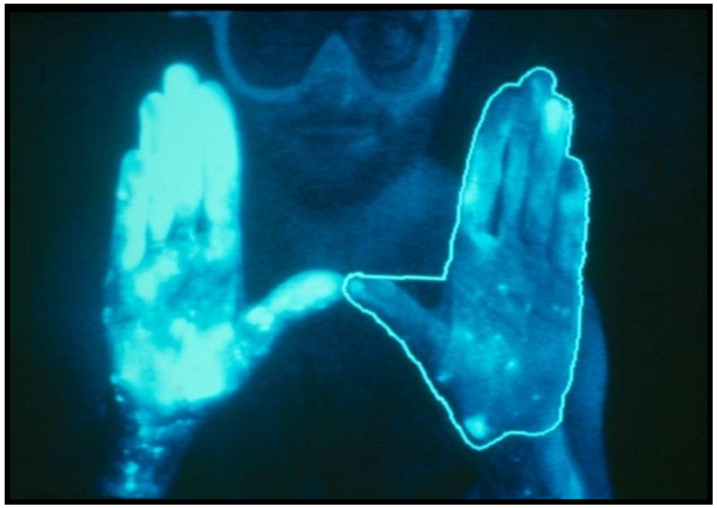
Assessing Pesticide Health Risks?

Epidemiology

Toxicology

Photo credit: National Cancer Institute
Photo credit: http://www.nyas.org/publications

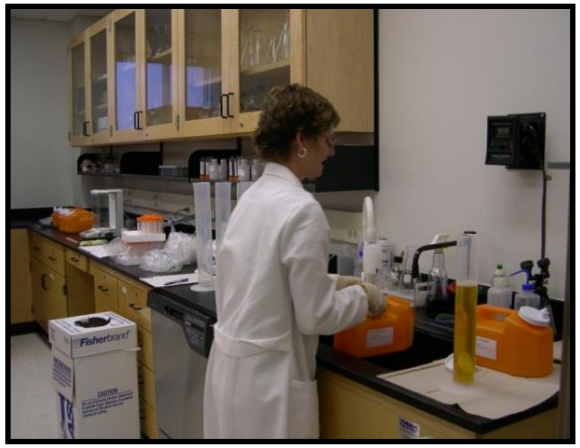
Exposure Assessment for Risk Assessment



Absorbed Dose - Biological Monitoring

- Blood/plasma
- Urine
- Adipose,
- Hair, Nails,
- Saliva
- Feces
- Placenta, Meconium
- Breast milk

…….etc.



Epidemiology – estimating human health risks?

	Cases	Controls	
Exposed	A	B	M_1
Not exposed	C	D	M_2
	N_1	N_2	N

Odds ratio (OR) = (A/B) / (C/D)

Assessing Human Health Risks?

Epidemiology

Toxicology

Photo credit: National Cancer Institute
Photo credit: http://www.nyas.org/publications/

Exposure Assessment for

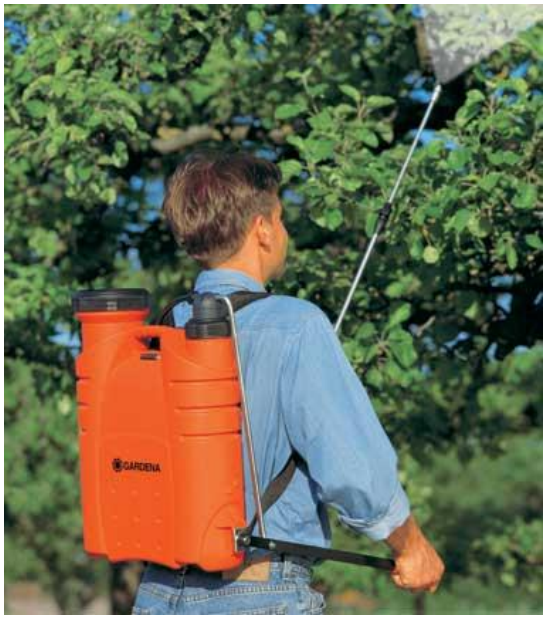
Table 2.2 Distribution of the main methods of exposure measurement (one selected from each study) in 564 studies of the aetiology of non-infectious disease published in the *American Journal of Epidemiology* between January 1980 and December 1989

Methods	Distribution (%)
Personal interview	49.1
Face to face	43.0
Telephone	4.1
Unclassifiable type	2.0
Self-administered questionnaire	14.0
By mail	6.4
Under supervision	7.6
Reference to records	22.3
Medical records	7.1
Other records	15.2
Physical or chemical measurements	13.3
On subject	10.8
On environment	2.5
Unclassifiable	1.2

Armstrong et al. Principles of Exposure Measurement in Epidemiology, Oxford Med. Pubs., 1992

Pesticide and other data collection

- **Postal questionnaires** were used to obtain information about demographics, medical and job history, and occupational exposure to pesticides etc.
- **Telephone interviews** were used to collect details about pesticide use from all participants who reported 10 or more hours per year of pesticide use during their lifetime and a 15% random sample of the remainder



Earlier findings from the CCSPH

- Some herbicides (dicamba , mecoprop) and insecticides (malathion, lindane, carbaryl, DDT, Aldrin) significantly increased the risk of **non-Hodgkin lymphoma**[1]
- Certain insecticides (diazinon, chlorpyrifos, and carbaryl) were found to increase the risk of **Hodgkin lymphoma**[2,3]
- The pesticides mecoprop, carbaryl and lindane were associated with higher odds of **multiple myeloma**[4]
- Insecticides (as a group) showed a link to **soft tissue sarcoma**[5]

[1]McDuffie et al. *Cancer Epidemiology, Biomarkers & Prevention* 2001;10:1155-1163; [2]Karunanayake et al. *Journal of Agromedicine* 2012;17:30-39; [3]Pahwa et al. *Journal of Occupational and Environmental Medicine* 2006;48:264-274; [4]Pahwa et al. *Journal of Agromedicine* 2012;17:40-50; [5]Pahwa et al. *Journal of Occupational and Environmental Medicine* 2011;53:1279-1286

Current analyses

- The CCSPH is a rich dataset and so far, over 15 articles have been published in peer-reviewed scientific journals
- The OCRC continues to use data from the CCSPH to explore questions about pesticide exposure and the development of cancer

ELECTRONIC PAPER

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

A J De Roos, S H Zahm, K P Cantor, D D Weisenburger, F F Holmes, L F Burmeister, A Blair

Occup Environ Med 2003;**60**:e11(http://www.occenvmed.com/cgi/content/full/60/9/e11)

See end of article for authors' affiliations

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Accepted 27 March 2003

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.

Recent OCRC Analyses

- Statistical analyses conducted based on:
  - Broad pesticide categories
  - Chemical class
  - Pesticide mode of action
  - Numbers of pesticides (multiple pesticides)
  - Pesticide combinations (concurrent or over a lifetime)
  - “Carcinogenic” classifications
  - Home versus work use
  - Days per year
  - Self versus proxy respondent
  - Pesticide exposures and immune conditions

Recent CCSPH manuscripts

Hohenadel K, Harris SA, McLaughlin JR, Spinelli JJ, Pahwa P, Dosman JA, Demers PA, Blair A. Exposure to multiple pesticides and risk of non-Hodgkin lymphoma in men from six Canadian provinces. *International Journal of Environmental Research and Public Health* 2011;8:2320-2330.

Pahwa M, Harris SA, Hohenadel K, McLaughlin JR, Spinelli JJ, Pahwa P, Dosman JA, Blair A. Pesticide use, immunologic conditions, and risk of non-Hodgkin lymphoma in Canadian men in six provinces. *International Journal of Cancer* 2012;131:2650-2659.

Navaranjan G, Hohenadel K, Blair A, Demers PA, Spinelli JJ, Pahwa P, McLaughlin JR, Dosman JA, Ritter L, Harris SA. Exposure to multiple pesticides and the risk of Hodgkin lymphoma in Canadian men. *Cancer Causes Control* 2013;24:1661-1673

Kachuri L, Demers PA. Blair A, Spinelli JJ, Pahwa M, McLaughlin JR, Pahwa P, Dosman JA and Harris SA. Multiple pesticide exposures and the risk of multiple myeloma in Canadian men. *International Journal of Cancer* 2013;133:1846-1858.

Evaluation of pesticides by the International Agency for Research on Cancer (IARC)

Pesticide name	IARC evaluation[1-7]
Formaldehyde, Arsenic	1 Definite
Ethylene dibromide	2A Probable
Chlordane; Heptachlor; Toxaphene; Chlorothalonil; Carbon tetrachloride; 1,2-Dibromo-3-chloropropane; 1,3-Dichloropropene; DDT; 2,4-D; Dicamba; Dichlorprop; MCPA; MCPB; Mecoprop; 2,4,5-T; Lindane	2B Possible

1. Volume 100F: A Review of Human Carcinogens: Chemical Agents and Related Occupations. Lyon: WHO Press, 2012. 2. Volume 100C: A Review of Human Carcinogens: Arsenic, Metals, Fibres, and Dusts. Lyon: WHO Press, 2012. 3. Volume 79: Some Thyrotropic Agents. Lyon: WHO Press, 2001. 4. Volume 73: Some Chemicals that Cause Tumours of the Kidney or Urinary Bladder in Rodents and Some Other Substances. Lyon: WHO Press, 1999. 5. Volume 71: Re-evaluation of Some Organic Chemicals, Hydrazine and Hydrogen Peroxide. Lyon: WHO Press, 1999. 6. Volume 53: Occupational Exposures in Insecticide Application, and Some Pesticides. Lyon: WHO Press, 1991. 7. Supplement 7: Overall Evaluations of Carcinogenicity: An Updating of IARC Monographs Volume 1 to 42. Lyon: WHO Press, 1987.

Pesticide classification for CCSPH - composite carcinogenicity score

	International Agency for Research on Cancer (IARC)	U.S. Environmental Protection Agency (U.S. EPA) Office of Pesticide Programs (OPP)[1]	U.S. EPA Integrated Risk Information Systems (IRIS)[2]
"Probably" carcinogenic	1, 2A	B and higher	B and higher
"Possibly" carcinogenic	1, 2A, 2B	C and higher	C and higher

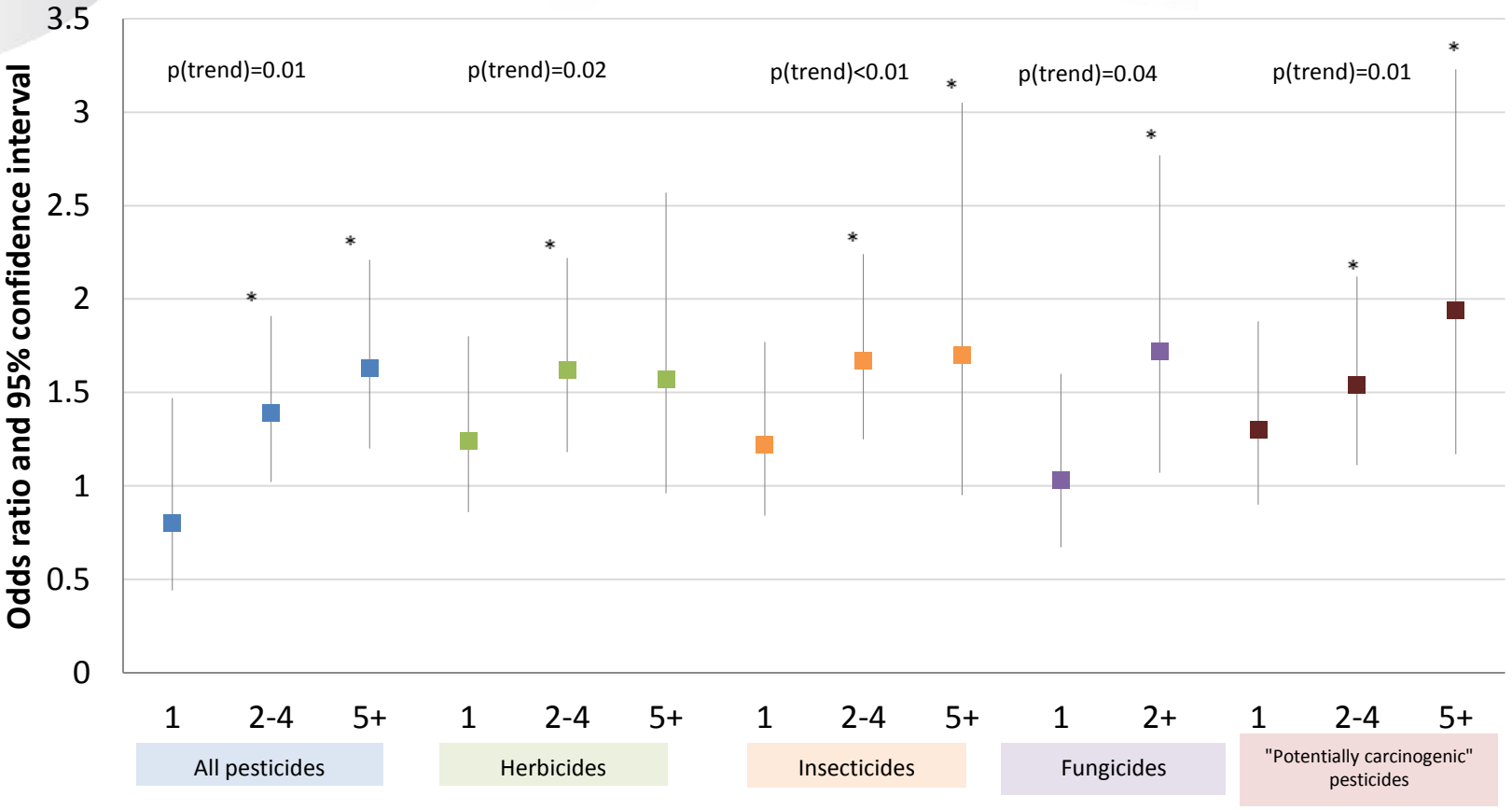
1. United States Environmental Protection Agency. Office of Pesticide Programs. http://www.epa.gov/pesticides/index.htm. 2. United States Environmental Protection Agency. Integrated Risk Information System. http://www.epa.gov/IRIS/.

Multiple pesticides and the risk of Non-Hodgkin lymphoma

Number of pesticides used	OR_{adj} (95% CI)
Herbicides	
0	1.00
1	1.24 (0.86, 1.80)
2-4	**1.62 (1.18, 2.22)**
5 or more	1.57 (0.96, 2.57)
	p_{trend}=0.02
Insecticides	
0	1.00
1	1.22 (0.84, 1.77)
2-4	**1.67 (1.25, 2.24)**
5 or more	1.70 (0.95, 3.05)
	p_{trend}<0.01
Fungicides	
0	1.00
1	1.03 (0.67, 1.60)
2 or more	**1.72 (1.07, 2.77)**
	p_{trend}=0.04

Hohenadel K et al. *International Journal of Environmental Research and Public Health* 2011;8:2320-2330.

Multiple pesticides and the risk of non-Hodgkin lymphoma



Hohenadel K et al. *International Journal of Environmental Research and Public Health* 2011;8:2320-2330.

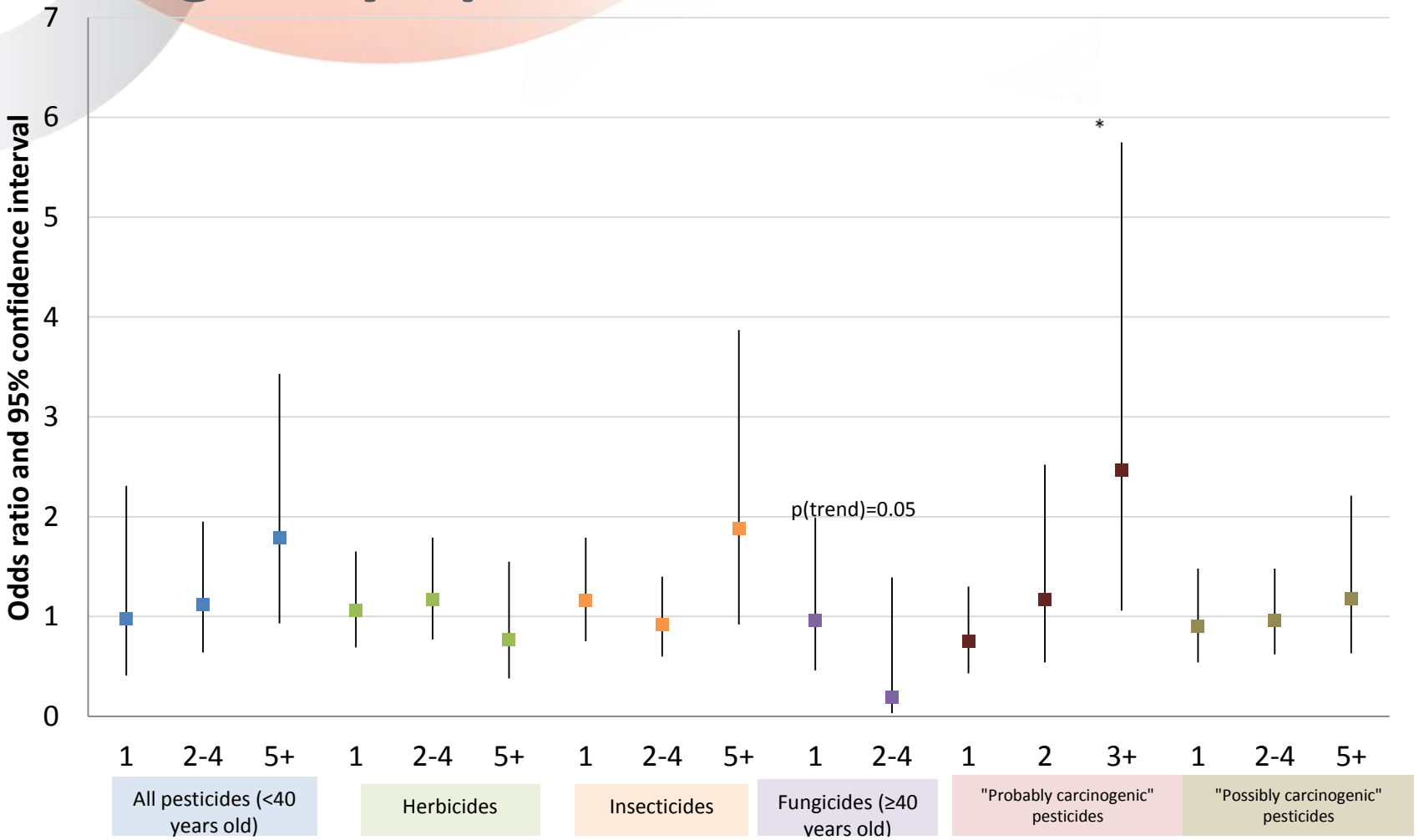
Multiple pesticides and the risk of Hodgkin lymphoma

Number of pesticides used	OR_{adj} (95% CI)
Insecticides	
0	1.00
1	1.16 (0.75, 1.79)
2-4	0.92 (0.60, 1.40)
5 or more	1.88 (0.92, 3.87)
	p_{trend}=0.35
Herbicides	
0	1.00
1	1.06 (0.69, 1.65)
2-4	1.17 (0.77, 1.79)
5 or more	0.77 (0.38, 1.55)
	p_{trend}=0.40
Phenoxy herbicides	
0	1.00
1	0.94 (0.63, 1.41)
2	1.01 (0.57, 1.78)
3 or more	1.01 (0.48, 2.11)
	p_{trend}=0.43

Navaranjan G et al. *Cancer Causes & Control* 2013;24:1661-1673.

ORs adjusted for age and province.

Multiple pesticides and the risk of Hodgkin lymphoma



Navaranjan G et al. *Cancer Causes & Control* 2013;24:1661-1673.

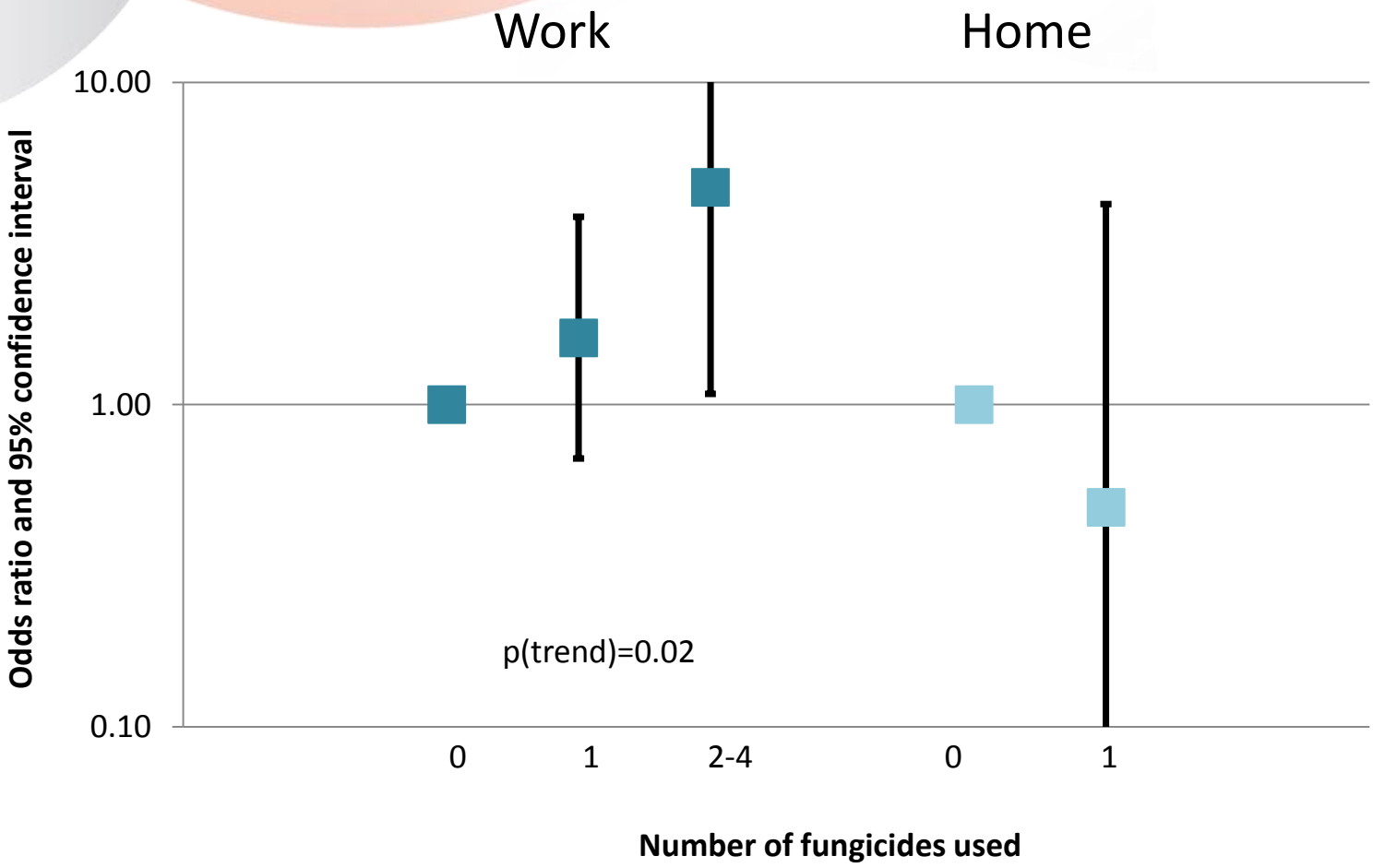
ORs adjusted for age and province.

Hodgkin lymphoma: Residential versus occupational pesticide use

- Use and exposure to pesticides in home and garden may be different from occupational settings

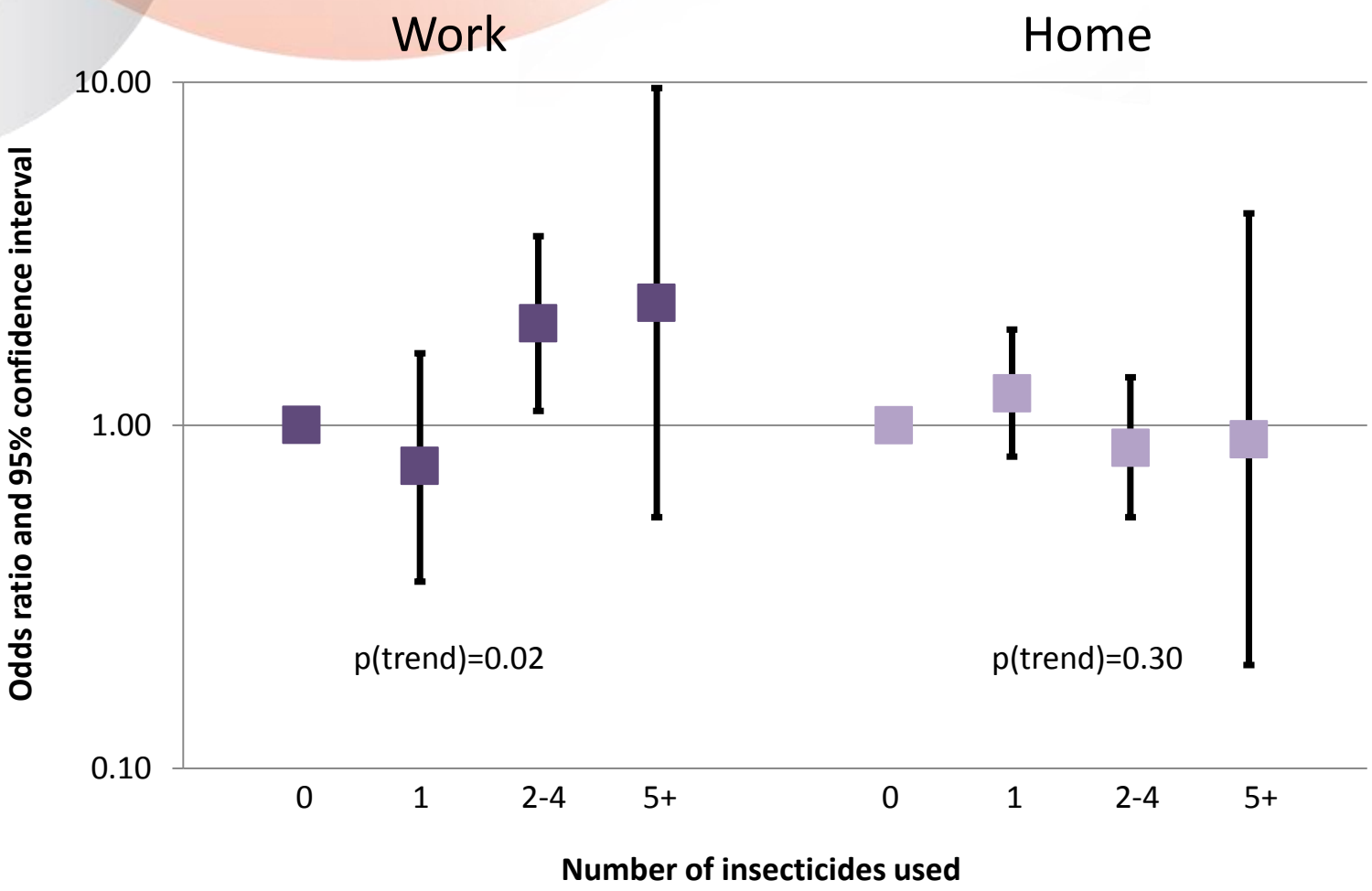
Navaranjan G et al. *Cancer Causes & Control* 2013;24:1661-1673.

HL - Fungicides among subjects <40 years



Navaranjan G et al. *Cancer Causes & Control* 2013;24:1661-1673.
ORs adjusted for age and province.

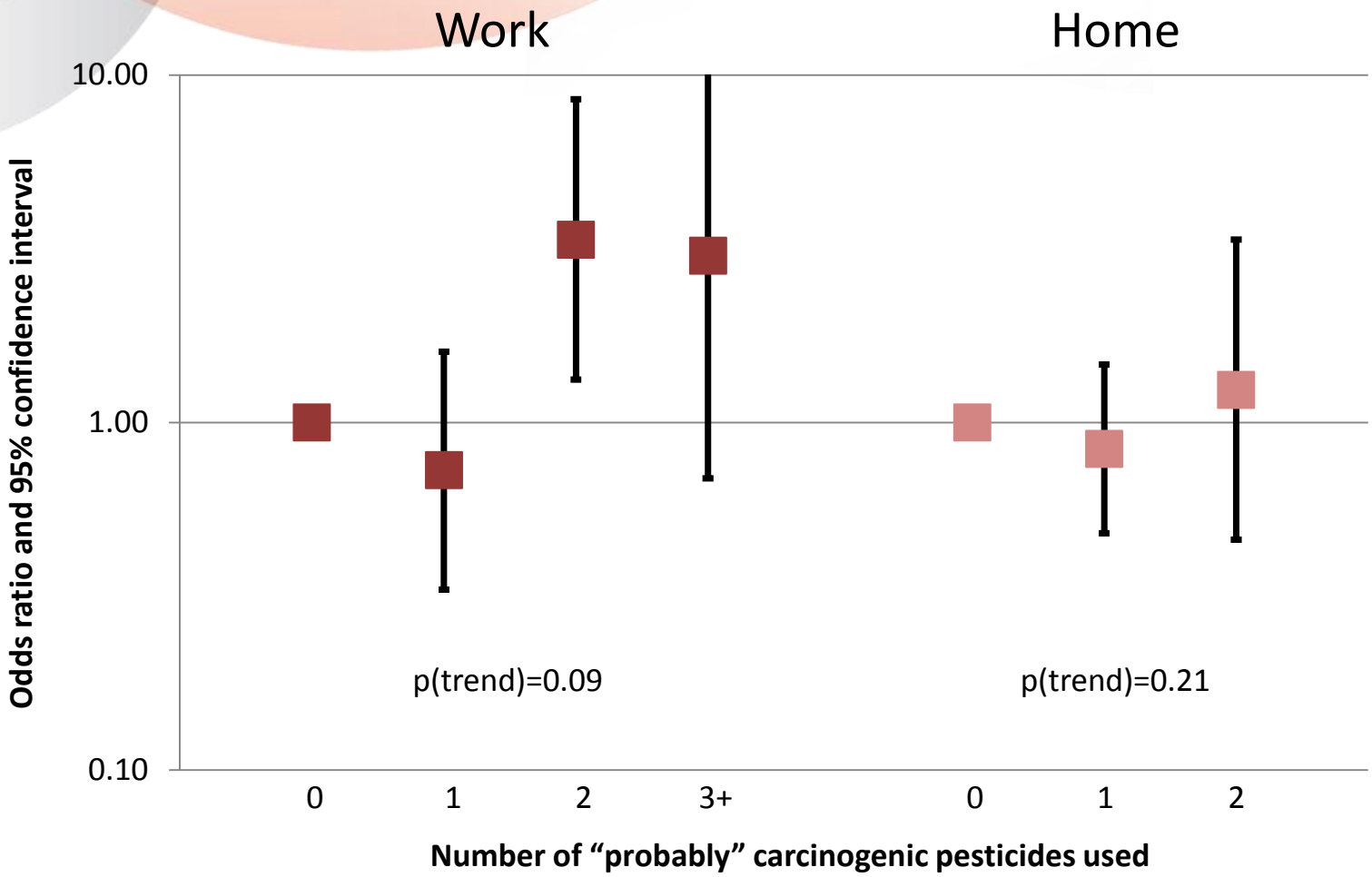
HL- Insecticides



Navaranjan G et al. *Cancer Causes & Control* 2013;24:1661-1673.

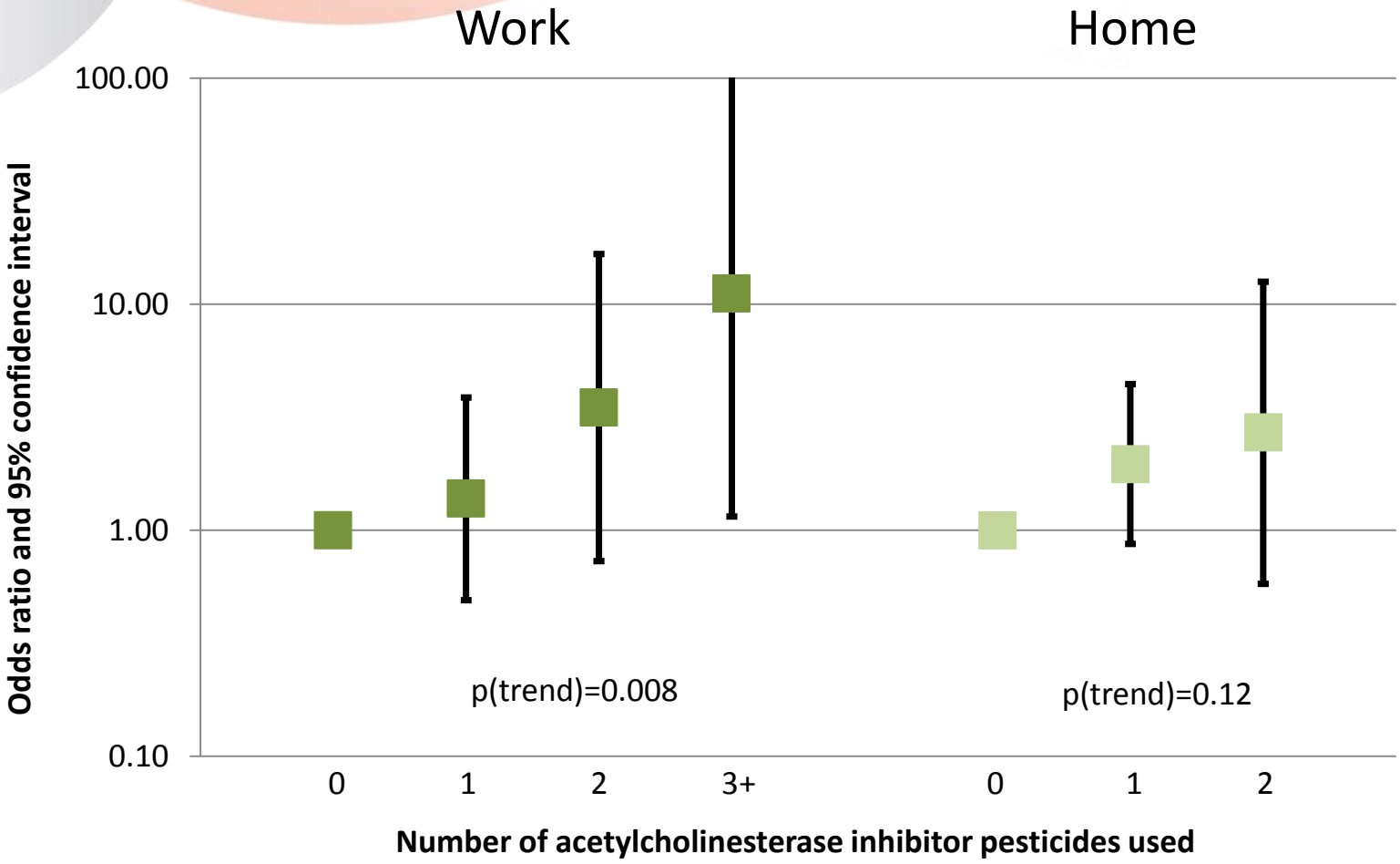
ORs adjusted for age and province.

HL - "Probably" carcinogenic pesticides



Navaranjan G et al. *Cancer Causes & Control* 2013;24:1661-1673.
ORs adjusted for age and province.

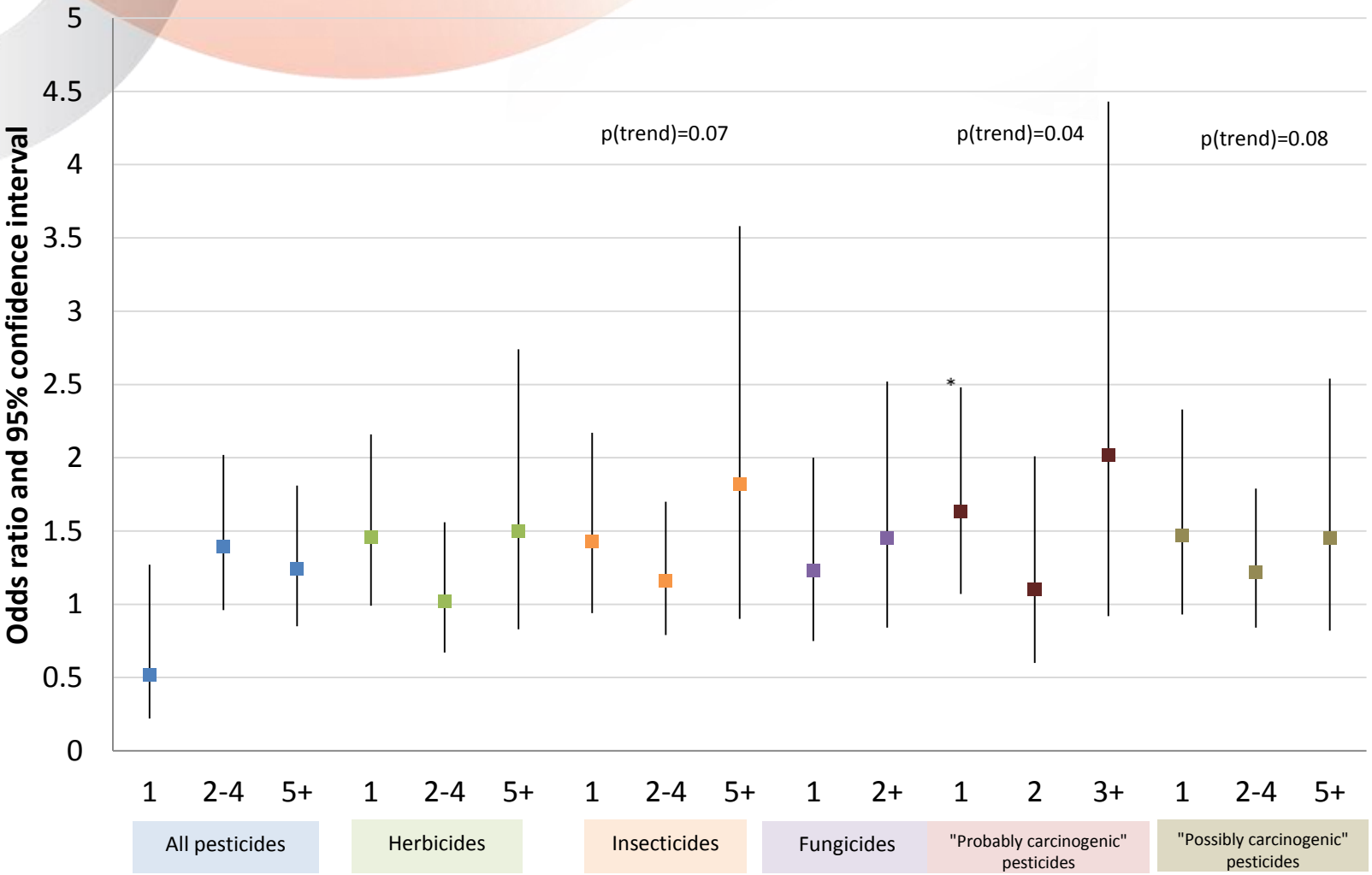
HL - Acetylcholinesterase inhibitors among subjects <40 years



Navaranjan G et al. *Cancer Causes & Control* 2013;24:1661-1673.

ORs adjusted for age and province.

Multiple pesticides and the risk of multiple myeloma



Kachuri L et al. *International Journal of Cancer* 2013;133:1846-1858.

ORs adjusted for age, province of residence, use of a proxy respondent, smoking status, selected medical conditions (rheumatoid arthritis, allergies, measles, shingles, cancer) and family history of cancer

Number of pesticides by chemical class and the risk of multiple myeloma

Number of pesticides used	Cases	Controls	OR_{adj} (95% CI)
Phenoxy herbicides			
0	255	1058	1.00
1	56	170	**1.56 (1.09, 2.25)**
2-4	16	80	0.90 (0.50, 1.64)
≥5	15	49	1.50 (0.78, 2.87)
			p_{trend}=0.16
Organochlorine insecticides			
0	274	1098	1.00
1	41	158	1.17 (0.79, 1.74)
2	15	74	0.96 (0.52, 1.78)
≥3	12	27	**2.21 (1.05, 4.66)**
			p_{trend}=0.13
Carbamate insecticides			
0	315	1298	1.00
≥1	27	59	**1.94 (1.16, 3.25)**

Kachuri L et al. *International Journal of Cancer* 2013;133:1846-1858.

ORs adjusted for age, province of residence, use of a proxy respondent, smoking status, selected medical conditions (rheumatoid arthritis, allergies, measles, shingles, cancer) and family history of cancer

Use of individual pesticides by days/year and the risk of multiple myeloma

Individual pesticide		Number exposed		OR_{adj} (95% CI)
	Days/year	Cases	Controls	
2,4-D	>0 and ≤2	35	144	1.13 (0.74, 1.74)
	>2 and ≤5	23	77	1.36 (0.80, 2.31)
	>5	17	49	1.46 (0.79, 2.70)
Mecoprop	>0 and ≤2	14	40	1.87 (0.96, 3.61)
	>2	12	31	**2.15 (1.03, 4.48)**
DDT	>0 and ≤2	9	17	**2.53 (1.05, 6.06)**
	>2	10	27	1.16 (0.52, 2.59)
Carbaryl	>0 and ≤2	11	18	**2.61 (1.13, 6.01)**
	>2	9	14	**2.74 (1.10, 6.83)**
Captan	>0 and ≤2	8	9	**4.50 (1.60, 12.63)**
	>2	5	12	2.00 (0.60, 6.67)

Kachuri L et al. *International Journal of Cancer* 2013;133:1846-1858.

ORs adjusted for age, province of residence, use of a proxy respondent, smoking status, selected medical conditions (rheumatoid arthritis, allergies, measles, shingles, cancer) and family history of cancer

Summary of findings from current OCRC analyses

- IARC and U.S. EPA classifications reflective of probable and possible carcinogenicity are predictive of cancer risk
- The risk of non-Hodgkin lymphoma increased with the use of multiple pesticides and these trends were significant
- Certain pesticides may risk factors for Hodgkin lymphoma and multiple myeloma, but results are inconsistent

Strengths and limitations of CCSPH data

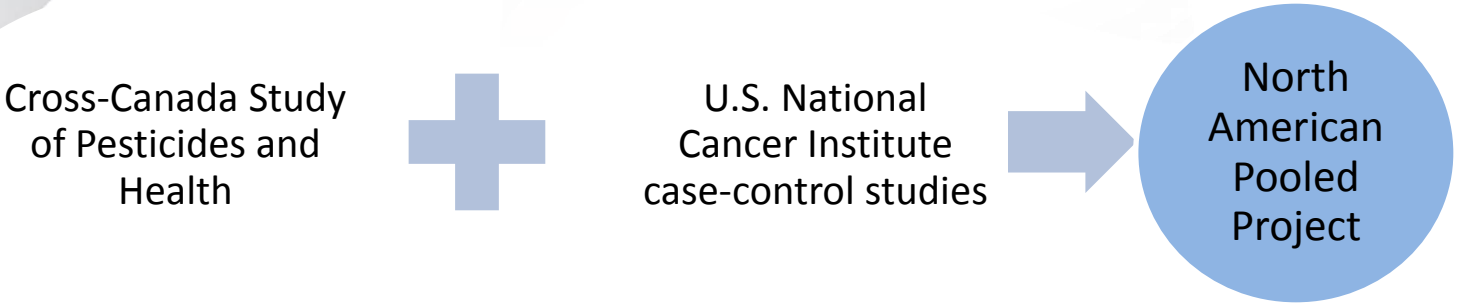
Strengths

- Population-based study of a large number of incident cases
- Information on a large number of pesticides and variety of potential confounding variables
- Considerable variation in pesticide use
- Several methods for classifying pesticides

Limitations

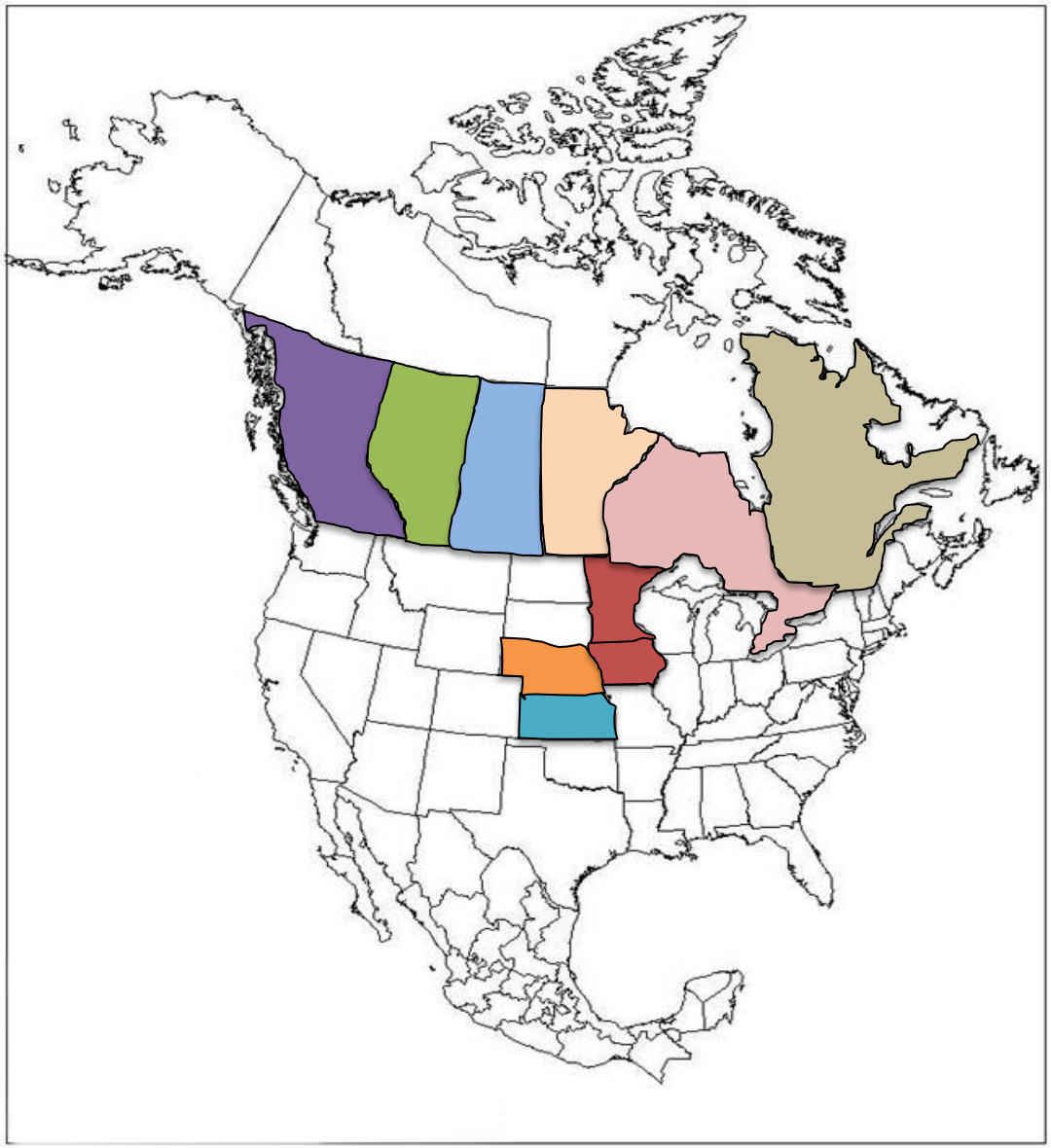
- Modest response rates for cases and controls (~ 50%)
- Self-reported exposure information: measurement error
- Lack of information about intensity, duration (and frequency) of pesticide use
- Small numbers for certain analyses

New Initiative: the North American Pooled Project (NAPP)



Cancer type	NCI studies	CCSPH	Total
Non-Hodgkin lymphoma	1,174	513	1,687
Follicular	340	74	414
Diffuse	436	132	568
Small lymphocytic	121	26	147
Other	277	281	558
Multiple myeloma	245	342	587
Soft tissue sarcoma	133	357	490
Hodgkin lymphoma	191	316	507
Controls	2,655	1,357	4,012

North American Pooled Project



Towards a cancer-free workplace

Kansas case-control study

- Cases diagnosed between 1976-1982
- Non-Hodgkin lymphoma: N=170
- Hodgkin lymphoma: N=121
- Soft tissue sarcoma: N=133
- Controls: N=948
- White men ≥21 years old
- Telephone interviews and pesticide supplier surveys

Hoar SK et al. JAMA 1986;256:1141-1147.

Iowa/Minnesota case-control study

- Iowa: cases diagnosed between 1981-1983
- Minnesota: cases diagnosed between 1980-1982
- Non-Hodgkin lymphoma: N=622
- Multiple myeloma (Iowa only): N=173
- Controls: N=1245
- White men ≥30 years old
- In-person and supplemental telephone interviews

Cantor KP et al. Cancer Res 1992;52:2447-2455.

Nebraska case-control study

- Cases diagnosed between 1983-1986
- Non-Hodgkin lymphoma: N=385
- Hodgkin lymphoma: N=70
- Multiple myeloma: N=72
- Controls: N=1432
- White men and women
  ≥21 years old
- Telephone interviews

Zahm SH et al. Epidemiol 1990;1:349-356.

Why pool?

- Larger sample size = more statistical power
- Evaluate associations with cancer, including NHL sub-types:
  - Individual pesticides and groups of pesticides
  - Combinations of major use pesticides
  - Combinations of pesticides based on their carcinogenic potential
  - Effect modification by immune conditions, family history and other factors
  - Agricultural exposures other than pesticides
- Re-assess suggestive or positive associations

Status of the North American Pooled Project

- Data transfer agreement in place between OCRC and U.S. NCI
- CCSPH data at U.S. NCI for pooling
  - Standardized approach and definitions
  - Completed:
    - NHL sub-types
    - Use of individual insecticides, herbicides, fungicides
    - Demographic characteristics (age, smoking)
  - Ongoing or for specific analyses:
    - Assignment of chemical classes
    - Medical conditions
    - Other agricultural exposures
- Full, pooled dataset will be transferred back to OCRC

Pesticide use information

Number of individual pesticides with reported use in both countries:

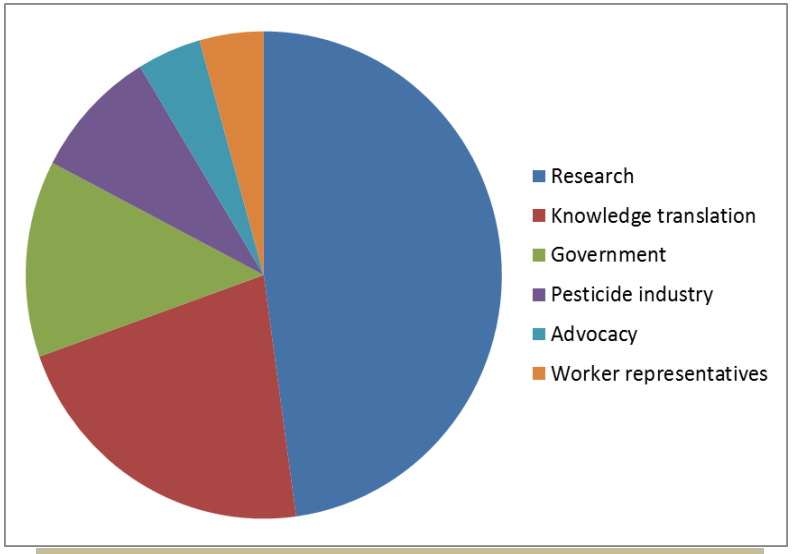
- 21 herbicides
- 20 insecticides
- 2 fungicides

Many more reported in only one country, but in same chemical class as pesticides in other country

- Days of use
- Years of use
- Use of personal protective equipment
- Application method
- Crop versus animal insecticides

CIHR Knowledge Dissemination Grant, Workshop

- Researchers and Stakeholders, Toronto, May 27, 2013
- Key Objectives:
  - Share key results from U.S. case-control studies & CCSPH
  - Introduce NAPP
  - Identify stakeholder knowledge needs to inform research priorities for the NAPP



22 participants attended workshop with expertise in cancer epidemiology, agricultural extension, pesticide exposure assessment, toxicology, risk assessment, regulation, KTE, policy, and represented government, advocacy organizations, academia, industry, and extension.

NAPP Research Priorities, Workshop summary

- Research priorities for the analysis of the NAPP included:
  - Improved quantitative measures of pesticide exposures
  - Evaluation of other agricultural exposures (diesel, grain dust), confounding, and interactions (smoking, immune conditions, gene-environment)
  - Non-occupational pesticide exposure (work vs. home)
  - Factors that modify exposure (formulations, application methods, PPE)
- Workshop report currently being finalized, will be posted on OCRC website

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- **Canadian Institutes for Health Research, OCRC, US NCI**

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