The effect of immune conditions on pesticide use and the risk of non-Hodgkin lymphoma

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Towards a cancer-free workplace
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What is non-Hodgkin lymphoma (NHL)?

- Any of a large group of cancers of lymphocytes\(^1\)
- Generally, cancerous lymphocytes are found in lymph nodes but they can also spread to other parts of the lymphatic system\(^2\)
- Cause of NHL is unknown

\(^1\)National Cancer Institute 2010: http://www.cancer.gov/cancertopics/types/non-hodgkin;
Epidemiology of NHL in Canada

• Incidence rates (male and female) increased approximately 50% between 1978 and late 1990s, then stabilized.

New Cases and Age-Standardized Incidence Rates (ASIR) for Non-Hodgkin’s Lymphoma, Canada, 1974-2003

Note: Rates are standardized to the 1991 Canadian population.
Source: Surveillance and Risk Assessment Division, CCDPC, Health Canada
Epidemiology of NHL in Canada

- 5th most incident cancer overall
- 6th leading cause of all cancer deaths overall

Estimated new cases for cancers in Canada (male and female, 2011)

Estimated deaths for cancers in Canada (male and female, 2011)
Estimated new cases and age-standardized incidence rates for NHL by sex and province, Canada, 2011
Known risk factors for NHL

• Age
• Sex
• Occupational exposures
  – Pesticides, dusts, fuels, etc.
• Compromised immune system

Do immune conditions modify the association between pesticide exposure and risk of NHL?

- Two American population-based case-control studies demonstrated that the odds of NHL from pesticide exposure was higher in asthmatics compared to non-asthmatics\textsuperscript{1,2}

- One Australian population-based case-control study found no interaction between history of atopy and pesticide exposure on NHL risk\textsuperscript{3}

Objective

- To evaluate the potential interactive effect of immune conditions on the association between pesticide use and risk of NHL
Cross-Canada Study of Pesticides and Health (CCSPH)

- Population-based case-control study conducted on males in six Canadian provinces between 1991 and 1994
Study population

• Incident NHL cases (N=513) diagnosed between 1991-1994 were recruited from provincial cancer registries and hospitals

• Cases were frequency-matched by age and province with 1506 population-based controls that were identified through provincial health insurance records (Quebec, Manitoba, Saskatchewan, and Alberta), computerized telephone listings (Ontario), and voters’ lists (British Columbia)
Data collection

- **Postal questionnaire** used to obtain information about variables that were known or suspected to be related to the four cancer types, including demographics, medical and job history, and occupational exposure to select substances.

- **Telephone interview** with participants who reported 10 or more hours per year of pesticide exposure during their lifetime (from any combination of compounds) and a 15% random sample of the remainder.
## Classification of pesticide use and immune conditions

<table>
<thead>
<tr>
<th>Pesticide use</th>
<th>Immune conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. All pesticides</td>
<td>1. Asthma</td>
</tr>
<tr>
<td>2. Organochlorine insecticides</td>
<td>2. Allergies</td>
</tr>
<tr>
<td>3. Organophosphate insecticides</td>
<td>3. Asthma, allergies, and hay fever</td>
</tr>
<tr>
<td>4. Phenoxy herbicides</td>
<td></td>
</tr>
<tr>
<td>5. Number of carcinogenic pesticides</td>
<td></td>
</tr>
<tr>
<td>6. Individual pesticides:</td>
<td></td>
</tr>
<tr>
<td>a) DDT</td>
<td></td>
</tr>
<tr>
<td>b) Malathion</td>
<td></td>
</tr>
<tr>
<td>c) MCPA</td>
<td></td>
</tr>
<tr>
<td>d) Mecoprop</td>
<td></td>
</tr>
<tr>
<td>e) 2,4-D</td>
<td></td>
</tr>
</tbody>
</table>
Statistical analysis

- Multiple logistic regression was used to calculate crude and adjusted ORs and 95% CIs for the associations between the six pesticide use groups and risk of NHL using SAS.
- ORs were adjusted for age, province of residence, respondent type (self or proxy), and diesel oil exposure.
- Possible interactions were first assessed by including an interaction term in the model and evaluating the Wald chi-square test statistic and associated p-value.
- Analyses were stratified by the three groups of immunologic conditions in order to separately determine their effects on pesticide use and NHL risk.
Results: Population characteristics

- Asthma cases = 32
- Allergies cases = 125
- Asthma, allergies, and hay fever cases = 79

- Compared to controls, cases:
  - Were older
  - Had a higher use of proxy respondents
  - Were more exposed to diesel oil
    for all 3 categories of immunologic conditions

- Most cases and controls from Ontario, followed by Quebec, BC, Alberta, Manitoba, and Saskatchewan
### Asthma

<table>
<thead>
<tr>
<th>Self-reported pesticide use(1)</th>
<th>Asthma</th>
<th></th>
<th></th>
<th>No asthma</th>
<th></th>
<th></th>
<th></th>
<th>p &gt; X²(3)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases (n=32)</td>
<td>Controls (n=107)</td>
<td>OR(2)</td>
<td>95% CI</td>
<td>Cases (n=481)</td>
<td>Controls (n=1399)</td>
<td>OR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Organo-phosphate insecticides</td>
<td>2 (6.3%)</td>
<td>12 (11%)</td>
<td>0.57</td>
<td>0.11 - 2.96</td>
<td>90 (19%)</td>
<td>157 (11%)</td>
<td>2.02</td>
<td>1.50 - 2.72</td>
</tr>
<tr>
<td>DDT</td>
<td>4 (13%)</td>
<td>2 (1.9%)</td>
<td>11.1</td>
<td>1.59 - 78.1</td>
<td>29 (6.0%)</td>
<td>57 (4.1%)</td>
<td>1.49</td>
<td>0.92 - 2.40</td>
</tr>
<tr>
<td>Malathion</td>
<td>2 (6.3%)</td>
<td>7 (6.5%)</td>
<td>1.07</td>
<td>0.18 - 6.38</td>
<td>70 (15%)</td>
<td>120 (8.6%)</td>
<td>2.01</td>
<td>1.44 - 2.80</td>
</tr>
<tr>
<td>MCPA</td>
<td>2 (6.3%)</td>
<td>1 (0.9%)</td>
<td>6.57</td>
<td>0.48 - 90.5</td>
<td>15 (3.1%)</td>
<td>45 (3.2%)</td>
<td>0.99</td>
<td>0.53 - 1.84</td>
</tr>
<tr>
<td>Mecoprop</td>
<td>3 (9.4%)</td>
<td>7 (6.5%)</td>
<td>1.42</td>
<td>0.29 - 6.99</td>
<td>48 (10%)</td>
<td>74 (5.3%)</td>
<td>2.27</td>
<td>1.52 - 3.38</td>
</tr>
</tbody>
</table>

1. Self-reported pesticide use as "yes" for each pesticide group or individual pesticide
2. ORs adjusted for age, province of residence, respondent type, and diesel oil exposure
3. Wald chi-square p value for pesticide use*immune condition interaction term in multiple logistic regression model

All values in ( ) are % of n rounded up to 2 significant digits
<table>
<thead>
<tr>
<th>Self-reported pesticide use(^{(1)})</th>
<th>Allergies</th>
<th>No allergies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases (n=125)</td>
<td>Controls (n=378)</td>
</tr>
<tr>
<td><strong>Organo-phosphate insecticides</strong></td>
<td>21 (17%)</td>
<td>55 (15%)</td>
</tr>
<tr>
<td><strong>DDT</strong></td>
<td>13 (10%)</td>
<td>15 (4.0%)</td>
</tr>
<tr>
<td><strong>Malathion</strong></td>
<td>17 (14%)</td>
<td>45 (12%)</td>
</tr>
<tr>
<td><strong>MCPA</strong></td>
<td>6 (4.8%)</td>
<td>8 (2.1%)</td>
</tr>
<tr>
<td><strong>Mecoprop</strong></td>
<td>11 (8.8%)</td>
<td>26 (6.9%)</td>
</tr>
</tbody>
</table>

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2. ORs adjusted for age, province of residence, respondent type, and diesel oil exposure
3. Wald chi-square p value for pesticide use*immune condition interaction term in multiple logistic regression model

All values in ( ) are % of n rounded up to 2 significant digits
<table>
<thead>
<tr>
<th>Self-reported pesticide use(1)</th>
<th>Asthma, allergies, or hay fever</th>
<th>No asthma, allergies, or hay fever</th>
<th>p &gt; χ²(3)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases (n=159)</td>
<td>Controls (n=462)</td>
<td>OR</td>
</tr>
<tr>
<td>Organo-phosphate insecticides</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>24 (15%)</td>
<td>58 (13%)</td>
<td>1.33</td>
</tr>
<tr>
<td>DDT</td>
<td>15 (9.4%)</td>
<td>16 (3.5%)</td>
<td>2.53</td>
</tr>
<tr>
<td>Malathion</td>
<td>19 (12%)</td>
<td>47 (10%)</td>
<td>1.25</td>
</tr>
<tr>
<td>MCPA</td>
<td>7 (4.4%)</td>
<td>9 (1.9%)</td>
<td>2.67</td>
</tr>
<tr>
<td>Mecoprop</td>
<td>16 (10%)</td>
<td>28 (6.1%)</td>
<td>1.71</td>
</tr>
</tbody>
</table>

1. Self-reported pesticide use as "yes" for each pesticide group or individual pesticide
2. ORs adjusted for age, province of residence, respondent type, and diesel oil exposure
3. Wald chi-square p value for pesticide use*immune condition interaction term in multiple logistic regression model

All values in ( ) are % of n rounded up to 2 significant digits

Towards a cancer-free workplace
Summary of results

• The odds of NHL were elevated from use of DDT and MCPA in subjects with asthma, allergies or asthma and allergies and hay fever compared to subjects without any of these immune conditions.

• On the other hand, the risks of NHL associated with the use of organophosphate insecticides, malathion, and mecoprop were higher among individuals without asthma, allergies, or asthma and allergies and hay fever versus those with any of these immune conditions.

• No interactions were statistically significant at $p=0.05$.

• There may be differences in the risk of NHL from self-reported pesticide use by immune status, or may simply be chance findings.
Limitations

- **Misclassification bias** related to self-report of pesticide use and immunologic conditions
- **Limited statistical power** to assess individual pesticides and immunologic conditions
  - E.g. 2/32 (6.3%) cases reported MCPA use and asthma diagnosis
- Did not account for **exposure determinants** (duration, intensity, frequency)
  - Duration of pesticide use has negligible effect on NHL risk\(^1\)
- Did not consider simultaneous use of commonly used **pesticide combinations**
- Cannot attribute observed risks to any specific type of pesticide exposures since there are **many sources of occupational and environmental exposures**
- Unable to perform analyses by **NHL histologic type**

Strengths

• **First case-control study** to explore the effect of immunologic conditions on the association between pesticide use and risk of NHL in Canadian men

• Includes men in six provinces with **widespread relevance in Canada**

• **Augments existing, conflicting evidence** by focusing on commonly used individual pesticides and groups of pesticides for asthma, allergies, and other immunologic conditions

• Odds ratios for NHL are **adjusted for several confounding factors**

• **Opportunity for further research** involving the use of pooled datasets
Future research opportunities

• Analyses with larger numbers or pooled studies
• Better characterization of pesticide exposures and the immune conditions of interest
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