Occupational epidemiology in practice: understanding pesticide-cancer risk in the AHS cohort and learned lessons

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Pesticide exposures
Pesticide exposure everywhere

- 6 billion lbs. of pesticides were applied worldwide in 2011 & 2012
- 11% growth in pesticide use per year 1950-2000
- >90% of US Population has detectable levels of pesticide or metabolites in urine or blood
- Worldwide over 1 billion people are occupationally exposed to pesticides
Pesticides

- Encompass many diverse chemical and chemical families
  - Herbicides
  - Insecticides
  - Fungicides
  - Fumigants
  - Rodenticides

Atwood & Paisley-Jones. USEPA. 2017
Human health effects

- Health effects of pesticides depend on the type of pesticide
- Active ingredients from pesticides subject to toxicity testing and registration
  - Experimental, in vitro study designs
- Not much post-market health effect studies available in the US

Kalyabina et al. Tox Reports. 2021
Human health effects

- Limited studies among humans
- Systematic reporting for accidental poisoning/acute exposures
  - National Poison Data System, OPP Incident Data System, National Pesticide Info Center, CDC/NIOSH SENSOR-Pesticides, CA Pesticide Illness Surv Program
- Human population studies
  - Different study designs for many different questions
  - Particularly for chronic diseases
Risk Assessment of Pesticides by USEPA

- USEPA, Office of Pesticide Programs
  - Pesticide regulation enshrined by the Federal Insecticide, Fungicide, Rodenticide Act (FIFRA)
  - Review pesticides registration on a rolling basis
- Classification of Carcinogens, Weight of Evidence Approach (2005)
  - Carcinogenic to humans
  - Likely to be carcinogenic to humans
  - Suggestive evidence of carcinogenic potential
  - Inadequate information to assess carcinogenic potential
  - Not likely to be carcinogenic to humans pesticide
Occupational vs. Environmental Pesticide Exposures

**Occupational**
- Manufacturing
- Mixing, loading, applying pesticides
- Working in treated fields/re-entry tasks
- Intermittent, “higher” exposures

**Environmental**
- Diet, drinking water, agricultural drift
- Home, lawn, and pet applications
- “Lower” exposures
Pesticide exposure assessment
Characterizing Exposure to Individual Pesticides

- Chemical specificity
  - Toxicity differs among chemicals in the same class
  - By active ingredient
- Quantitative estimate of exposure
- Intensity of exposure related to tasks, use of PPE, application method
- Mixtures?
Practical Consideration in Exposure Assessment

- Who is exposed (and who to study)?
  - Farmers/farm-owners
    - May know about the pesticides/crops
    - May or may not apply themselves
  - Farmworkers—may be highly exposed
    - Short-term work?
    - Knowledge of pesticides?
  - Regional differences based on specific farm practices
  - Intensity of exposures
Pesticide Exposure Assessment Methods

- Manufacturers
- Crop-Based Exposure Assignment
- Self-report assessment/questionnaire for individual chemicals
Assessments based on Biological Measurements

- Most pesticides in use today are not persistent
  - Urinary measurements reflect exposure in hours/days
  - Usefulness for cumulative or long-term exposure?
- Exceptions:
  - Organochlorine insecticides
  - Lindane: $\beta$-HCH, $\gamma$-HCH
  - DDT: $p,p'$-DDE, $p,p'$-DDT
  - Reflect whole body burden
How Can We Study Effects of Pesticides?

- Need Information on specific active ingredients
- Highly exposed population
- Large population with sufficient follow-up (cohort) or adequate number of exposed cases (case-control)
- Accurate characterization of exposure for exposure-response associations
Agricultural Health Study cohort
Agricultural Health Study
NCI NIEHS EPA NIOSH

- 57,310 licensed pesticide applicators in Iowa and North Carolina (20,518 in NC)
- 32,345 spouses of applicators (10,307 in NC)
- Iowa and North Carolina - diverse agricultural practices

AHS STUDY OVERVIEW

- Regular linkages to cancer and mortality registries*
- Linkages to identify end-stage renal disease**
- Linkages to identify Medicare claims data**

BEEA (2010-2018)  
n=1600 AHS participants  
In-person interview, including recent pesticide use  
Blood, urine and house dust

www.aghealth.nih.gov

Alvanja et al. EHP. 1996
AHS Exposure Assessment Approach

- Apply questionnaire data on individual active ingredients for etiologic analyses
- Self-report duration and frequency at enrollment
- Self-report use again since enrollment at follow-up
- Applicators provide reliable (Blair 2002) and valid (Hoppin 2002) responses related to pesticide use
## Cumulative Exposure

- **Phase I – lifetime days of use**

<table>
<thead>
<tr>
<th>Name of Pesticide</th>
<th>A. Have you ever personally mixed or applied this pesticide?</th>
<th>B. How many years did you personally mix or apply this pesticide?</th>
<th>C. In an average year when you personally used this pesticide, how many days did you do it?</th>
<th>D. When did you first personally use this pesticide?</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Herbicides (pesticides used to kill weeds)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>a. Aatrex, Atranex or other atrazine products</strong></td>
<td>[a_herbicide_cd1]</td>
<td>[a_herbicide_yr1]</td>
<td>[a_herbicide_day1]</td>
<td>[a_herbicide_fu1]</td>
</tr>
<tr>
<td>- No</td>
<td>- Yes</td>
<td>1 year or less</td>
<td>Less than 5 days</td>
<td>Before 1960</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2–5 years</td>
<td>5–9 days</td>
<td>In the 1960s</td>
</tr>
<tr>
<td></td>
<td></td>
<td>6–10 years</td>
<td>10–19 days</td>
<td>In the 1970s</td>
</tr>
<tr>
<td></td>
<td></td>
<td>11–20 years</td>
<td>20–39 days</td>
<td>In the 1980s</td>
</tr>
<tr>
<td></td>
<td></td>
<td>21–30 years</td>
<td>40–59 days</td>
<td>In the 1990s</td>
</tr>
<tr>
<td></td>
<td></td>
<td>More than 30 years</td>
<td>60–150 days</td>
<td>Mark here if you used this pesticide last year</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>More than 150 days</td>
<td></td>
</tr>
</tbody>
</table>
AHS Exposure Metrics used in Health Outcome Analyses

- Ever Use
- Frequency of Use
- Cumulative Exposure (Lifetime days of use)
  - Years * Days/year applied
- Intensity-Adjusted Cumulative Exposure
  - Cumulative Exposure * Intensity Score
Intensity-Adjusted Cumulative Exposure

- Intensity-weighting algorithm
  - Factors that affect exposure
    - Application Method (Apply)
    - Mixing chemicals (Mix)
    - Repair of equipment (Repair)
  - Use of Personal Protective Equipment (PPE)

Intensity Score = (Apply + Mix + Repair) * PPE


- Field studies
  - (Hines 2008 et al., Ann Occ Hyg, Thomas et al., JESEE, 2010A, Thomas et al., JESEE, 2010B)

Intensity score * Lifetime Days = Intensity-weighted Lifetime Days (IWLD)
Exposure metric comparison

<table>
<thead>
<tr>
<th>Lifetime number of exposure days</th>
<th>N</th>
<th>RR</th>
<th>95% CI</th>
<th>Intensity-weighted exposure days</th>
<th>N</th>
<th>RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No exposure</td>
<td>199</td>
<td>1.00</td>
<td>Referent</td>
<td>No exposure</td>
<td>199</td>
<td>1.00</td>
<td>Referent</td>
</tr>
<tr>
<td>&lt;20</td>
<td>32</td>
<td>1.11</td>
<td>0.75 to 1.65</td>
<td>&lt;358</td>
<td>22</td>
<td>1.09</td>
<td>0.61 to 1.53</td>
</tr>
<tr>
<td>20.0–38.8</td>
<td>16</td>
<td>0.76</td>
<td>0.44 to 1.30</td>
<td>369–1800</td>
<td>25</td>
<td>0.99</td>
<td>0.66 to 1.52</td>
</tr>
<tr>
<td>&gt;38.8</td>
<td>36</td>
<td>1.60</td>
<td>1.11 to 2.31</td>
<td>&gt;1800</td>
<td>37</td>
<td>1.41</td>
<td>0.98 to 2.04</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>P_{trend}=0.02</td>
<td></td>
<td></td>
<td></td>
<td>P_{trend}=0.08</td>
</tr>
</tbody>
</table>

Jones et al. OEM. 2014

Insecticide-impregnated ear tag on cow

Crop pesticide applicator wearing PPE
AHS Cancer Incidence

Lower overall cancer incidence

- **Reduced cigarette** smoking
- **Increased** physical activity
- Healthy worker effect

Some cancer sites are elevated compared to the general population

Farming exposures may contribute to excess cancer risk

- Pesticides, diesel engine exhaust, UV radiation, bacteria and viruses

Standardized incidence ratio

\[
SIR = \frac{\text{Observed number of cases in study population}}{\text{Expected number of cases in the study population}}
\]

**Expected number of cases** = person – years in the study population * adjusted cancer rates in reference population

Koutros et al. OEM. 2010, Lerro et al. Cancer Causes & Control. 2019
Cancer incidence in the Agricultural Health Study after 20 years of follow-up among AHS private applicators

<table>
<thead>
<tr>
<th>Site</th>
<th>N</th>
<th>SIR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Sites</td>
<td>8256</td>
<td>0.91</td>
<td>0.89, 0.93</td>
</tr>
<tr>
<td>Lip</td>
<td>63</td>
<td>2.22</td>
<td>1.71, 2.84</td>
</tr>
<tr>
<td>Esophagus</td>
<td>102</td>
<td>0.71</td>
<td>0.58, 0.86</td>
</tr>
<tr>
<td>Colon and Rectum</td>
<td>842</td>
<td>0.95</td>
<td>0.89, 1.02</td>
</tr>
<tr>
<td>Liver and Bile Duct</td>
<td>78</td>
<td>0.56</td>
<td>0.45, 0.70</td>
</tr>
<tr>
<td>Pancreas</td>
<td>183</td>
<td>0.83</td>
<td>0.72, 0.96</td>
</tr>
<tr>
<td>Larynx</td>
<td>66</td>
<td>0.48</td>
<td>0.37, 0.62</td>
</tr>
<tr>
<td>Lung and Bronchus</td>
<td>807</td>
<td>0.51</td>
<td>0.48, 0.55</td>
</tr>
<tr>
<td>Prostate</td>
<td>3169</td>
<td>1.15</td>
<td>1.11, 1.19</td>
</tr>
<tr>
<td>Testis</td>
<td>45</td>
<td>1.31</td>
<td>0.96, 1.75</td>
</tr>
<tr>
<td>Urinary Bladder</td>
<td>411</td>
<td>0.70</td>
<td>0.63, 0.77</td>
</tr>
<tr>
<td>Thyroid</td>
<td>82</td>
<td>1.15</td>
<td>0.92, 1.43</td>
</tr>
<tr>
<td>Chronic Lymphocytic Leukemia</td>
<td>166</td>
<td>1.17</td>
<td>1.00, 1.36</td>
</tr>
<tr>
<td>Diffuse Large B-Cell Lymphoma</td>
<td>145</td>
<td>1.16</td>
<td>0.98, 1.37</td>
</tr>
<tr>
<td>Follicular Lymphoma</td>
<td>81</td>
<td>1.14</td>
<td>0.91, 1.42</td>
</tr>
<tr>
<td>Multiple Myeloma</td>
<td>146</td>
<td>1.18</td>
<td>0.99, 1.38</td>
</tr>
<tr>
<td>Acute Myeloid/Monocytic Leukemia</td>
<td>86</td>
<td>1.29</td>
<td>1.03, 1.59</td>
</tr>
</tbody>
</table>

Lerro et al. Cancer Causes & Control. 2019
Cancer incidence in the Agricultural Health Study after 20 years of follow-up among AHS spouses

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>N</th>
<th>SIR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Sites</td>
<td>3720</td>
<td>0.89</td>
<td>0.86, 0.92</td>
</tr>
<tr>
<td>Esophagus</td>
<td>9</td>
<td>0.51</td>
<td>0.23, 0.97</td>
</tr>
<tr>
<td>Colon and Rectum</td>
<td>346</td>
<td>0.87</td>
<td>0.78, 0.96</td>
</tr>
<tr>
<td>Pancreas</td>
<td>71</td>
<td>0.69</td>
<td>0.54, 0.87</td>
</tr>
<tr>
<td>Peritoneum</td>
<td>21</td>
<td>1.80</td>
<td>1.11, 2.75</td>
</tr>
<tr>
<td>Lung and Bronchus</td>
<td>252</td>
<td>0.41</td>
<td>0.36, 0.46</td>
</tr>
<tr>
<td>Melanoma of the Skin</td>
<td>177</td>
<td>1.21</td>
<td>1.04, 1.40</td>
</tr>
<tr>
<td>Breast</td>
<td>1389</td>
<td>1.05</td>
<td>0.99, 1.11</td>
</tr>
<tr>
<td>Cervix Uteri</td>
<td>29</td>
<td>0.50</td>
<td>0.34, 0.72</td>
</tr>
<tr>
<td>Corpus and Uterus</td>
<td>323</td>
<td>1.13</td>
<td>1.01, 1.27</td>
</tr>
<tr>
<td>Ovary and Fallopian Tube</td>
<td>122</td>
<td>0.87</td>
<td>0.72, 1.04</td>
</tr>
<tr>
<td>Thyroid</td>
<td>118</td>
<td>1.20</td>
<td>0.99, 1.44</td>
</tr>
<tr>
<td>Chronic Lymphocytic Leukemia</td>
<td>43</td>
<td>0.88</td>
<td>0.63, 1.18</td>
</tr>
<tr>
<td>Diffuse Large B-Cell Lymphoma</td>
<td>70</td>
<td>1.23</td>
<td>0.96, 1.55</td>
</tr>
<tr>
<td>Marginal Zone Lymphoma</td>
<td>25</td>
<td>1.46</td>
<td>0.95, 2.16</td>
</tr>
<tr>
<td>Follicular Lymphoma</td>
<td>54</td>
<td>1.33</td>
<td>1.00, 1.74</td>
</tr>
<tr>
<td>Acute Myeloid/Monoctic Leukemia</td>
<td>33</td>
<td>1.21</td>
<td>0.83, 1.69</td>
</tr>
</tbody>
</table>

Lerro et al. Cancer Causes & Control. 2019
Pesticide-cancer risk analysis: Atrazine
Atrazine

- Second most applied herbicide in the US
- Commonly applied on corn, sorghum, and sugar cane
- Water soluble and persistent
  - Prevalent contaminant in soil and water
- Known endocrine disruptor
- Currently banned in the European Union (EU)
Atrazine cancer epidemiology

• Few epidemiologic studies
• Suggestive associations with:
  • Prostate (MacLennan et al. *J Occup Environ Med.* 2002)
  • Kidney (Andreotti et al. *EHP.* 2020)
  • Other sites (e.g., stomach, ovarian, pediatric cancers)
• Heterogeneity in study design, exposure assessment, and power
• Last comprehensive cancer epidemiological study focused on occupational exposures among farmers conducted in 2011, \( n=3,146 \) (Beane Freeman et al. *EHP.* 2011)
Re-examine the association between occupational atrazine use and cancer risk within the AHS cohort

6,631 exposed cancer cases- a two-fold increase since the 2011 study
Updated cumulative exposures
Unlagged Atrazine Use and Risk of **Lung Cancer** in AHS Applicators

Adjusted for age, state, education, smoking, alcohol, family history of cancer, alachlor, metolachlor, trifluralin and 2,4-D

Remigio et al.. In revision
Unlagged Atrazine Use and Risk of Aggressive Prostate Cancer in AHS Applicators

n=558 exposed cases

Aggressive prostate

p-trend= 0.13

Aggressive prostate cancer ~ Gleason score at or above 8 | Grade or stage at or above 3 | Prostate cancer as cause of death

Remigio et al.. In revision

Adjusted for age, state, education, smoking, alcohol, family history of cancer, alachlor, metolachlor, trifluralin and 2,4-D
25-year Lagged Atrazine Use and Risk of **Kidney Cancer** in AHS Applicators

n=224 exposed cases

Adjusted for age, state, education, smoking, alcohol, family history of cancer, alachlor, metolachlor, trifluralin and 2,4-D

Remigio et al.. In revision
25-year Lagged Atrazine Use and Risk of **Pharyngeal Cancer** in AHS Applicators

**n=31 exposed cases**

**p-trend = 0.06**

Adjusted for age, state, education, smoking, alcohol, family history of cancer, alachlor, metolachlor, trifluralin and 2,4-D

Remigio et al.. In revision
More Results

- Additional suggestive increased risk by age groups
  - Below 50 years: NHL (ever), and significant p-trends with subtypes (Mature B-cell lymphoma)
  - Below 60 years: aggressive prostate (p-trend=0.001, p-interaction=0.0005)
  - 70 and older: esophageal (ever)

- No meaningful associations were found in other sites
Evidence of biological plausibility from Corn Farmer Study

- Atrazine exposure can influence oxidative stress (a key characteristic of a carcinogen)
- A molecular epidemiologic study found a short-term relationship between atrazine exposure and 8-hydroxy-2'-deoxyguanosine (8-OhdG) in analyses restricted to individuals with measures of atrazine mercapturate above the detection limit

Lerro et al., Environ Mol Mutagen. 2017
Pesticides and Cancer

- Pesticide use and lung cancer risk (Bonner et al., EHP 2017)
- Insecticide use and breast cancer in AHS spouses (Engel et al., EHP 2017)
- Alachlor use and cancer incidence (Lerro et al., JNCI 2018)
- Glyphosate use and cancer incidence (Andreotti et al., JNCI 2018)
- Organochlorines and cancer risk in AHS spouses (Louis et al., Environ Health 2018)
- Pesticide use and aggressive prostate cancer (Pardo et al., 2020)
- Pesticide use and breast cancer among AHS spouses (Werder et al., Environ Health 2020)
- Pesticide use and kidney cancer (Andreotti et al., Environ Epi 2020)
- Dicamba use and cancer incidence (Lerro et al., Int J Epi 2021)
- Pesticide use and thyroid cancer among AHS males (Lerro et al. Environ Intl 2021)
- Pesticide use and MGUS (Hofmann et al., EHP 2021)

Pesticides and Other Outcomes

- Thyroid disease
- Allergic and non-allergic wheeze
- Olfactory impairment
- Rheumatoid arthritis
- Parkinson’s Disease
- Sleep Apnea
- Shingles

AHS data contributed to more than 139 publications in last 5 years; 382 since 1996
Learned Lessons

- Data and work behind estimating long-term exposures
- Quality results dependent on quality data (lines of evidence)
  - Feeds into weight of evidence approaches for determining risk
- New methodologies are out there: Mixtures
Acknowledgements

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www.aghealth.nih.gov