IARC Evaluation of the Carcinogenicity of Pesticides: Epidemiological Evidence

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The IARC Monographs
(http://monographs.iarc.fr/indexfr.php)

- “The Encyclopedia of Carcinogens”
- Evaluate factors capable of causing cancer in humans
  - Environmental & occupational exposures
  - Chemical, physical & biologic agents
  - Drugs, foods, & personal habits
- More than 950 agents evaluated since 1971
  - 114 carcinogenic to humans (as of October 2014)
  - >330 probably or possibly carcinogenic
- National & international health agencies use the Monographs
  - To identify carcinogens
  - To support prevention or regulation
Cancer Hazard Assessment based on 3 lines of evidence

Cancer in humans

Cancer in animals

Mechanisms

Overall evaluation
Evaluating human data

- Cancer in humans
  - Preamble Part B, Section 6(a)

- Cancer in experimental animals

- Mechanistic and other relevant data

- **Sufficient evidence**
  - Causal relationship has been established
  - Chance, bias, and confounding could be ruled out with reasonable confidence

- **Limited evidence**
  - Causal interpretation is credible
  - Chance, bias, or confounding could not be ruled out

- **Inadequate evidence**
  - Studies permit no conclusion about a causal association

- **Evidence suggesting lack of carcinogenicity**
  - Several adequate studies covering the full range of exposure levels are mutually consistent in not showing a positive association at any observed level of exposure
  - Conclusion is limited to cancer sites and conditions studied
Integrating Human and Animal Evidence

**EVIDENCE IN EXPERIMENTAL ANIMALS**

<table>
<thead>
<tr>
<th>Sufficient</th>
<th>Limited</th>
<th>Inadequate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sufficient</td>
<td>Group 1 <em>(carcinogenic to humans)</em></td>
<td></td>
</tr>
<tr>
<td>Limited</td>
<td>Group 2A <em>(probably carcinogenic)</em></td>
<td>Group 2B <em>(possibly carcinogenic)</em> (exceptionally, Group 2A)</td>
</tr>
<tr>
<td>Inadequate</td>
<td>Group 2B <em>(possibly carcinogenic)</em></td>
<td>Group 3 <em>(not classifiable)</em></td>
</tr>
</tbody>
</table>
Mechanistic Modifications - when human data are less than sufficient

EVIDENCE IN EXPERIMENTAL ANIMALS

- **Sufficient**
- **Limited**
- **Inadequate**

**EVIDENCE IN HUMANS**

- **Group 1** *(carcinogenic to humans)*
- **Group 2A** *(probably carcinogenic)*
- **Group 2B** *(possibly carcinogenic)*
- **Group 3** *(not classifiable)*

Strong supporting evidence in exposed humans
Mechanistic Modifications - when human data are less than sufficient

**EVIDENCE IN EXPERIMENTAL ANIMALS**

- **Sufficient**
  - Group 1 (*carcinogenic to humans*)

- **Limited**
  - Group 2A (*probably carcinogenic*)
  - Group 2B (*possibly carcinogenic*)
    - (exceptionally, Group 2A)

- **Inadequate**
  - Group 2B (*possibly carcinogenic*)
  - Group 3 (*not classifiable*)

**Strong evidence: mechanism in animals**

**DOES NOT operate in humans**
Prior IARC Evaluations of Pesticides

75 pesticides and pesticide classes have been evaluated 1971-2014.

<table>
<thead>
<tr>
<th>Classification</th>
<th>Number</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>1</td>
<td>Arsenic and arsenical compounds, including pesticides (1980, 2012)</td>
</tr>
<tr>
<td>Group 2A</td>
<td>4</td>
<td>Non-arsenical insecticides, occupational exposure in spraying (1991) &amp; 3 others upgraded from 2B</td>
</tr>
<tr>
<td>Group 2B</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>Group 3</td>
<td>49</td>
<td>Includes 2 downgraded from 2B</td>
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</table>

Implication: Human data are inadequate for most pesticides evaluated to date.

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Pesticide class</th>
<th>Priority*</th>
<th>Prior evaluation</th>
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</thead>
<tbody>
<tr>
<td>Malathion</td>
<td>OP insecticide</td>
<td>High</td>
<td>1987, Group 3</td>
</tr>
<tr>
<td>Diazinon</td>
<td>OP insecticide</td>
<td>High</td>
<td>None</td>
</tr>
<tr>
<td>Lindane</td>
<td>OC insecticide</td>
<td></td>
<td>1987, 2B (HCCH)</td>
</tr>
<tr>
<td>Permethrin</td>
<td>Pyrethroid insecticide</td>
<td>High</td>
<td>1991, Group 3</td>
</tr>
<tr>
<td>Pendimethalin</td>
<td>Dinotroaniline herbicide</td>
<td>High</td>
<td>None</td>
</tr>
<tr>
<td>Carbaryl</td>
<td>Carbamate insecticide</td>
<td>High</td>
<td>1987, Group 3</td>
</tr>
<tr>
<td>DDT</td>
<td>OC insecticide</td>
<td>Medium</td>
<td>1991, Group 2B</td>
</tr>
<tr>
<td>2,4,6-trichlorphenol, pentachlorphenol, hexachlorobenzene</td>
<td>OC insecticide</td>
<td>Medium</td>
<td>1999, Group 2B (PCPs)</td>
</tr>
<tr>
<td>Fonofos, terbufos, chlorpyrifos</td>
<td>OP insecticide</td>
<td>Medium</td>
<td>None</td>
</tr>
<tr>
<td>Glyphosate</td>
<td>OP herbicide</td>
<td>Medium</td>
<td>None</td>
</tr>
<tr>
<td>Atrazine</td>
<td>Triazine herbicide</td>
<td>Medium</td>
<td>1999, Group 3</td>
</tr>
<tr>
<td>EPTC</td>
<td>Thiocarbamate herbicide</td>
<td>Medium</td>
<td>None</td>
</tr>
<tr>
<td>Biphenyl</td>
<td>Fungicide</td>
<td>Medium</td>
<td>None</td>
</tr>
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</table>

High priority based on widespread global use, data from new epidemiologic studies, cancer bioassays or high throughput screening
A Novel Approach Using Chemoinformatics

<table>
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<th>Web API</th>
<th>Query parameters</th>
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<tr>
<td>Cancer and Pesticides Epidemiological paper count</td>
<td>NCBI Eutils</td>
<td>cas numbers AND top three synonyms AND pesticide* AND cancer AND risk*[All Fields] AND humans[All Fields] AND (&quot;CI&quot; OR &quot;confidence interval&quot; OR ratio*) AND hasabstract[text]</td>
</tr>
<tr>
<td>Cancer and Pesticides animal studies paper count</td>
<td>NCBI Eutils</td>
<td>cas numbers AND top three synonyms AND pesticide* AND cancer AND animals[mesh] AND hasabstract[text]</td>
</tr>
</tbody>
</table>
## Top 10 Pesticides Identified by the Chemoinformatics Approach

<table>
<thead>
<tr>
<th>Name</th>
<th>PubChem CID</th>
<th>Class</th>
<th>PubMed Cancer EPI</th>
<th>PubMed All</th>
<th>PubChem Bioassay</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>DDT</td>
<td>3036</td>
<td>OC</td>
<td>39</td>
<td>355</td>
<td>35</td>
<td>POP/ED/SCRC</td>
</tr>
<tr>
<td>2,4,5-T</td>
<td>1480</td>
<td>Auxins</td>
<td>20</td>
<td>129</td>
<td>4</td>
<td>SCRC</td>
</tr>
<tr>
<td>Chlordane</td>
<td>5993</td>
<td>OC</td>
<td>16</td>
<td>89</td>
<td>31</td>
<td>SCRC</td>
</tr>
<tr>
<td>Hexachlorobenzene</td>
<td>8370</td>
<td>OC</td>
<td>16</td>
<td>137</td>
<td>5</td>
<td>ED/SCRC</td>
</tr>
<tr>
<td>Lindane</td>
<td>727</td>
<td>OC</td>
<td>15</td>
<td>216</td>
<td>29</td>
<td>POP/ED/SCRC</td>
</tr>
<tr>
<td>Toxaphene</td>
<td>5284469</td>
<td>OC</td>
<td>14</td>
<td>47</td>
<td>87</td>
<td>POP/SCRC</td>
</tr>
<tr>
<td>Dieldrin</td>
<td>969491</td>
<td>OC</td>
<td>11</td>
<td>137</td>
<td>40</td>
<td>POP/SCRC</td>
</tr>
<tr>
<td>Malathion</td>
<td>4004</td>
<td>OP</td>
<td>10</td>
<td>46</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>Atrazine</td>
<td>2256</td>
<td>Triazine</td>
<td>9</td>
<td>83</td>
<td>9</td>
<td>HPV</td>
</tr>
<tr>
<td>Aldrin</td>
<td>61103</td>
<td>OC</td>
<td>8</td>
<td>60</td>
<td>16</td>
<td>POP/SCRC</td>
</tr>
</tbody>
</table>

POP = Persistent Organic Pollutant  
HPV = High production volume chemical  
ED = Suspected endocrine-disrupting activity  
SCRC = Listed under Stockholm and/or Rotterdam convention
Upcoming IARC Evaluations of Pesticides

**Meeting 112:** Some Organophosphate Insecticides and Herbicides: Diazinon, Glyphosate, Malathion, Parathion, and Tetrachlorvinphos (3-10 March 2015)

- Preliminary List of Agents
- Call for Data (closing date 3 February 2015)
- Call for Experts (closing date 30 July 2014)
- Request for Observer Status (closing date 3 November 2014)
- WHO Declaration of Interests for this volume
- Instructions for Authors
- Preliminary List of Participants

**Meeting 113:** Some Organochlorine Insecticides and Some Chlorophenoxy Herbicides (2-9 June 2015)

- Preliminary List of Agents
- Call for Data (closing date 2 May 2015)
- Call for Experts (closing date 10 October 2014)
- Request for Observer Status (closing date 2 February 2015)
- WHO Declaration of Interests for this volume
- Instructions for Authors
# Epidemiologic Data Available for Evaluation: IARC Monographs 112 & 113

<table>
<thead>
<tr>
<th>Agent</th>
<th>Total Studies</th>
<th>Cohort</th>
<th>Case-Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>DDT</td>
<td>114</td>
<td>77</td>
<td>33</td>
</tr>
<tr>
<td>2,4-D</td>
<td>57</td>
<td>28</td>
<td>29</td>
</tr>
<tr>
<td>Malathion</td>
<td>27</td>
<td>7</td>
<td>20</td>
</tr>
<tr>
<td>Lindane</td>
<td>24</td>
<td>5</td>
<td>19</td>
</tr>
<tr>
<td>Diazinon</td>
<td>21</td>
<td>9</td>
<td>12</td>
</tr>
<tr>
<td>Glyphosate</td>
<td>16</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Parathion</td>
<td>9</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Tetrachlorvinphos</td>
<td>4</td>
<td>1</td>
<td>3</td>
</tr>
</tbody>
</table>
The Epidemiologic Database on Pesticides
Literature tree for DDT
IARC Monograph 113
Challenges in Evaluating Epidemiologic Data on Pesticides and Cancer

• Need for data on specific pesticides
• Exposure to multiple agents
• Small numbers
  • Low prevalence of significant exposure
  • Rare endpoints
• Need for quantitative exposure data
• Importance of establishing dose-response
• Potential for nonlinear effects (e.g., non-genotoxic mechanisms)
Challenges in Epidemiologic Research on Pesticides (and Cancer)

- Finding appropriate study populations
  - Large numbers exposed at low levels or small numbers exposed at high(er) levels

- Exposure assessment
  - Assessment of individual pesticides
  - Objective exposure measures
  - Quantitative exposure estimation
  - Estimating historical exposures
  - Biomarkers for less persistent compounds
General Features of Studies That Are More Likely to Contribute to Sufficient Evidence

- Cohort & case-control studies
- Clear presentation of methods & results
- Focused on the exposure of interest
- High-quality exposure assessment
  - Quantitative estimates
- Control of important confounders
- High-quality analysis
  - Internal comparisons
  - Thorough exposure-response assessment
  - Consideration of latency
Conclusions

• Human data are *inadequate* for most pesticides evaluated by IARC to date
• Numerous pesticides can be prioritised for evaluation or re-evaluation
• Hazard identification and risk assessment need *more and better* epidemiologic data
• Especially:
  • Studies with adequate sample size
  • Quantitative exposure data
  • Exposure-response data