The Carcinogenicity of Glyphosate

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Conflict of Interest Statement

I declare no financial interests related to the subject matter of my presentation.
How Are the IARC Monograph Evaluations Conducted?

- Procedural guidelines for participant selection, conflict of interest, stakeholder involvement & meeting conduct
- Separate criteria for review of human, animal and mechanistic evidence
- Decision process for overall evaluations

http://monographs.iarc.fr/ENG/Preamble/index.php
The IARC Monographs Evaluations: A Two-Step Process

**Cancer in humans**
- Sufficient evidence
- Limited evidence
- Inadequate evidence
- Evidence suggesting lack of carcinogenicity

**Cancer in experimental animals**
- Sufficient evidence
- Limited evidence
- Inadequate evidence
- Evidence suggesting lack of carcinogenicity

**Mechanistic and other relevant data**
- “Weak,” “moderate,” or “strong” evidence?
- Does this— or can it—occur in humans?

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**Step 1:** Categorize each line of evidence using defined terms

**Step 2:** Integrate findings in overall evaluations

**Overall evaluation**
- Group 1  *Carcinogenic to humans* (119)
- Group 2A *Probably carcinogenic to humans* (81)
- Group 2B *Possibly carcinogenic to humans* (292)
- Group 3 *Not classifiable as to its carcinogenicity to humans* (505)
- Group 4 *Probably not carcinogenic to humans* (1)
**IARC Monographs Timeline**

**IARC Secretariat:**
- Coordinate all aspects of the Monograph development
- Recruit Working Group members and organize meeting
- Search and retrieve literature
- Assure adherence to procedures

**Working Group members:**
- Write the critical reviews and develop evaluations
- Study-by-study evaluation against published criteria
- Add comments [in square brackets]
- Draft assigned sections
- Peer-review

**Invited Specialists:**
- Have critical knowledge but also a conflicting interest
- **[do not draft text or participate in evaluations]**

**Representatives of national and international health agencies:**
- Have critical knowledge but also a conflicting interest
- **[do not draft text or participate in evaluations]**

**Observers:**
- Allowed to observe but not to influence outcomes
- **[do not draft text or participate in evaluations]**

**Meeting announced (1 yr ahead):**
- Preliminary List of Agents
- Call for Data and Experts
- Request for Observer Status
- WHO CoI form posted

**Monograph in-person meeting:**
- Sub-group review, revision, summary
- Plenary review and evaluation

**Participants (and DOI) announced (2 months ahead)**

**The Lancet Oncology Publication (2 weeks later)**

**Monograph Publication (1-2 years later)**
Scientific Engagement: Glyphosate Monograph

Meeting announced (March 2014):
- Preliminary List of Agents
- Call for Data and Experts
- Request for Observer Status
- WHO CoI form posted

Participating Monograph in-person meeting (3-10 March 2015)

Participants (and DOI) announced (Jan. 2015)
The Lancet Oncology publication (March 2015)
References shared with health agencies (April 2015)
Glyphosate Monograph publication (July 2015)

- IARC meetings are open and follow transparent, published methods
- All meeting participants have full access to the data being evaluated
- Fully referenced Monographs published on-line for free download

International Agency for Research on Cancer
World Health Organization
Glyphosate: Studies

- ~1000 studies identified and screened

- **Laboratory studies**
  - “Pure” glyphosate, glyphosate formulations
    - Cancer in mice, rats
    - DNA damage (genotoxicity)

- **Human studies** (real-world exposures)
  - DNA damage—community residents before and after spraying
  - Cancer in humans—farmers, other workers

- Published Monograph: >250 references
### Cancer in Humans

Studies of exposed workers provide “limited” evidence for NHL (Non-Hodgkin lymphoma)

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Location</th>
<th>NHL Cases</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) Case-control</td>
<td>Sweden, Canada, US</td>
<td>2592</td>
<td>Increased risks, not explained by other pesticides</td>
</tr>
<tr>
<td>2) Cohort study</td>
<td>US, 2 states</td>
<td>92</td>
<td>No significant increase in risk</td>
</tr>
<tr>
<td>(Ag Health Study)</td>
<td></td>
<td></td>
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<tr>
<td>3) Meta-analysis</td>
<td></td>
<td></td>
<td>Objective method to combine all studies</td>
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<td></td>
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<td></td>
<td>Increased risks (meta risk-ratio=1.3; 95% CI,1.03–1.65; I²=0%)</td>
</tr>
</tbody>
</table>
Cancers in Mice Fed Glyphosate

Positive results in 2 of 2 feeding studies

• **Rare cancers:** *extremely important in assessing human risk*.... *but* challenging to detect signal from background noise
  - High statistical significance
  - Tumours in the absence of toxicity
  - Evaluation fully in line with accepted principles
  - Causal relationship established

➢ **Sufficient evidence of cancer in animals**
## Cancer Mechanisms: 10 Key Characteristics of Carcinogens

<table>
<thead>
<tr>
<th>Key characteristic:</th>
<th>Evidence of these characteristics, especially in humans or as intermediate biomarkers in human specimens can provide <strong>biological plausibility</strong> for epidemiological findings and/or early warning if no epidemiology exists</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Is Electrophilic or can be metabolically activated</td>
<td>• Provide the basis for a <strong>systematic and objective approach</strong> to identifying and evaluating mechanistic evidence</td>
</tr>
<tr>
<td>2. Is Genotoxic</td>
<td></td>
</tr>
<tr>
<td>3. Alters DNA repair or causes genomic instability</td>
<td></td>
</tr>
<tr>
<td>4. Induces Epigenetic Alterations</td>
<td></td>
</tr>
<tr>
<td>5. Induces Oxidative Stress</td>
<td></td>
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<tr>
<td>6. Induces chronic inflammation</td>
<td></td>
</tr>
<tr>
<td>7. Is Immunosuppressive</td>
<td></td>
</tr>
<tr>
<td>8. Modulates receptor-mediated effects</td>
<td></td>
</tr>
<tr>
<td>9. Causes Immortalization</td>
<td></td>
</tr>
<tr>
<td>10. Alters cell proliferation, cell death, or nutrient supply</td>
<td></td>
</tr>
</tbody>
</table>

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International Agency for Research on Cancer
Key characteristics of carcinogens

1. Is Genotoxic
2. Induces Oxidative Stress

Systematic Literature Search and Review

IARC Vol 112: Mono 4- Glyphosate (2015): Literature Tagtree
**Damage to DNA (Genotoxicity)**

Residents in sprayed communities

DNA and chromosome damage in blood

*Strong evidence, glyphosate formulations:*
- Exposed community residents

*Experiments using:*
  - Human cells
  - Animal cells
  - Mammals and non-mammals
  - Negative in bacteria

*Strong evidence, glyphosate:*
- No studies in exposed humans

*Experiments using:*
  - Human cells
  - Animal cells
  - Mammals and non-mammals
  - Negative in bacteria
## Mechanisms of Cancer
### 10 Key Characteristics of Carcinogens

<table>
<thead>
<tr>
<th>Key characteristic</th>
<th>Strength of Evidence</th>
<th>Operates in humans?</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Is electrophilic or can be metabolically activated</td>
<td>Not electrophilic</td>
<td>Can operate in humans</td>
</tr>
<tr>
<td>2. Is genotoxic</td>
<td>Strong (glyphosate and formulations)</td>
<td>Can operate in humans</td>
</tr>
<tr>
<td>3. Alters DNA repair or causes genomic instability</td>
<td>No data</td>
<td>Can operate in humans</td>
</tr>
<tr>
<td>4. Induces epigenetic alterations</td>
<td>No data</td>
<td>Can operate in humans</td>
</tr>
<tr>
<td>5. Induces oxidative stress</td>
<td>Strong (glyphosate, formulations, AMPA)</td>
<td>Can operate in humans</td>
</tr>
<tr>
<td>6. Induces chronic inflammation</td>
<td>No data</td>
<td>Can operate in humans</td>
</tr>
<tr>
<td>7. Is immunosuppressive</td>
<td>Weak</td>
<td>Can operate in humans</td>
</tr>
<tr>
<td>8. Modulates receptor-mediated effects</td>
<td>Weak</td>
<td>Can operate in humans</td>
</tr>
<tr>
<td>9. Causes immortalization</td>
<td>No data</td>
<td>Can operate in humans</td>
</tr>
<tr>
<td>10. Alters cell proliferation, death, or nutrient supply</td>
<td>Weak</td>
<td>Can operate in humans</td>
</tr>
</tbody>
</table>
**Summary: Glyphosate Hazard Evaluation**

**Cancer in humans (NHL)**
- *Limited* evidence
  - Studies of real-world exposures (occupational)
  - *Glyphosate formulations* in different regions at different times

**Cancer in animals**
- *Sufficient* evidence
  - Studies of pure *glyphosate*
  - Rare cancers in valid studies

**DNA damage & oxidative stress**
- *Strong* evidence
  - Few studies of real-world exposures (communities)
  - Experimental studies of pure *glyphosate*
  - Experimental studies of *glyphosate formulations*

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**Overall evaluation of glyphosate:**

*Group 2A Probably carcinogenic to humans*
**Question 1**: What causes cancer, glyphosate or formulations?

Real-world exposures to formulations, **BUT**... similar increases in the same type of cancer (NHL) in:

- Different geographic regions
- Different times

Studies of “pure” glyphosate:

- Sufficient evidence for cancer in animals
- Strong evidence of DNA damage (genotoxicity)

➢ "Glyphosate" is probably carcinogenic to humans
**Question 2:** How was the US AHS study weighed in the evaluation?

- AHS is one of the largest studies of pesticides and cancer, BUT...
  - **Not the largest study of NHL** (fewer NHL cases)
  - **Short follow-up time**
    - Limited ability to detect rare cancers
- Increased risk in case-control studies
- Increased risk in combined data from all studies
  - **The AHS does not negate other studies**
  - **Altogether, the evidence is “limited”**
**Question 3**: What do unpublished toxicology studies show?

Some industry toxicology studies considered by IARC were not evaluated (not in the public domain in sufficient detail for independent review)

- Cancer studies in rodents:
  - **induction of mouse tumours at high doses**; as summarized by JMPR:
    - kidney adenomas, uncommon tumour, in males (4 of 7 studies)
    - lymphomas in males (3 of 7 studies) and females (1 of 7 studies)

- Additional negative “guideline” studies (e.g., in bacteria) *(consistent with IARC conclusion)*

- **No additional studies** in exposed humans, human cells
Prioritising Pesticides for IARC Evaluation: Overview

- Diverse “pesticides” recommended for IARC evaluation
- Data assembly, integration and visualization (980 pesticide actives)
- New or updated classifications
Prioritization approach:

- Comprehensive list of pesticides
- Automated text mining of public databases
- ~1000 pesticides mapped by chemical similarity
- Objective prioritisation for evaluation in 2015-2016

http://ehp.niehs.nih.gov/EHP186/

A. Organophosphates
B. Organochlorines
## New or Updated Classifications: Organophosphorous Pesticides

<table>
<thead>
<tr>
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<th></th>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Parathion</td>
<td>1</td>
<td>Restricted</td>
<td>6</td>
<td>578</td>
<td>3 (1987)</td>
<td>2B</td>
</tr>
<tr>
<td>Malathion</td>
<td>2</td>
<td>High</td>
<td>12</td>
<td>370</td>
<td>3 (1987)</td>
<td>2A</td>
</tr>
<tr>
<td>Diazinon</td>
<td>5</td>
<td>High</td>
<td>16</td>
<td>215</td>
<td>-</td>
<td>2A</td>
</tr>
<tr>
<td>Glyphosate</td>
<td>7</td>
<td>High</td>
<td>9</td>
<td>204</td>
<td>-</td>
<td>2A</td>
</tr>
<tr>
<td>Tetrachlorvinphos</td>
<td>13</td>
<td>Active</td>
<td>1</td>
<td>40</td>
<td>3 (1987)</td>
<td>2B</td>
</tr>
</tbody>
</table>
# New or Updated Classifications: Organochlorine Pesticides

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>DDT</td>
<td>1</td>
<td>Restricted POP</td>
<td>190</td>
<td>953</td>
<td>2B (1991)</td>
<td>2A</td>
</tr>
<tr>
<td>Lindane</td>
<td>2</td>
<td>Active POP</td>
<td>51</td>
<td>545</td>
<td>2B (1987)</td>
<td>1</td>
</tr>
<tr>
<td>PCP</td>
<td>5</td>
<td>Restricted POP</td>
<td>25</td>
<td>573</td>
<td>2B (1987)</td>
<td>1</td>
</tr>
<tr>
<td>Dieldrin</td>
<td>3/7</td>
<td>Restricted POP</td>
<td>57/25</td>
<td>484</td>
<td>3 (1987)</td>
<td>2A</td>
</tr>
</tbody>
</table>

*Note: Aldrin*
## IARC Classifications of Pesticides 1971-2016

<table>
<thead>
<tr>
<th>Classification</th>
<th>Number</th>
<th>Details/Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>3</td>
<td>Arsenic and arsenical compounds, including pesticides; Lindane; Pentachlorophenol</td>
</tr>
<tr>
<td>Group 2A</td>
<td>9</td>
<td>Captafol; DDT; Diazinon; Dieldrin, Aldrin metabolised to Dieldrin; Dimethylcarbamoyl chloride; Ethylene dibromide; Glyphosate; Malathion; Tetrachlororoazobenzene (contaminant)</td>
</tr>
<tr>
<td>Group 2B</td>
<td>27</td>
<td>Examples evaluated in 2015-2016: Parathion, Tetrachlorvinphos, 2,4,6-Trichlorophenol</td>
</tr>
<tr>
<td>Group 3</td>
<td>48</td>
<td></td>
</tr>
</tbody>
</table>
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- U.S. National Cancer Institute (since 1982)
- U.S. National Institute of Environmental Health Sciences (since 1992)
- European Commission, DG Employment, Social Affairs and Inclusion (since 1986)
Thank you! http://www.iarc.fr