IARC’s Evaluation of Glyphosate

Christopher J. Portier, Ph.D.

Collaborative on Health and the Environment Teleconference

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The IARC Monographs Program

- IARC Monographs Evaluate
  - Chemicals
  - Complex substances and mixtures
  - Occupational exposures
  - Physical and biological agents
  - Personal habits
IARC Monographs Process

• Written Guidelines
  – Public Document
  – Who? What? How?
  – Roles
  – Responsibilities
  – Instructions
    • Review
    • Summary of Evidence
IARC Monograph 112 Process

- Working Group Members
  - No real or apparent conflicts of interest
    - Formal process, written declarations of interest
  - Membership
    - Working Group members – review, evaluate
    - Invited Specialist – review only
    - Representatives – government, observe only
    - Observers – interested party, observe only
    - Secretariat – support the Working Group
IARC Monograph Timeline

• 1 year before Monograph Meeting
  – Meeting announced
  – Call for experts
  – Call for data

• 8 months before Monograph Meeting
  – Working Group membership selected
  – Request for observer status opened
  – Draft sections of Monograph developed by Working Group Members
IARC Monograph Timeline

• 1 month before Monograph Meeting
  – Call for data closed
  – Draft sections distributed to Working Group members for review and comment

• At Monograph Meeting
  – Finalize review of all literature
  – Evaluate the evidence in each category
  – Complete the overall evaluation
IARC Monograph Timeline

• 1-2 weeks after Monograph Meeting
  – Publish summary in Lancet Oncology

• 4-12 months after Monograph Meeting
  – Finalize Monograph and publish
IARC: What is reviewed?

• Systematic review of human, experimental and mechanistic data
• All pertinent epidemiological studies and cancer bioassays
• Representative mechanistic data
• Studies must be publicly available
  – Sufficient detail to review
  – Reviewers cannot have been associated with the study
IARC: Evidence Review

**Human Studies**
- Extract Data
- Assess Individual Study Quality
- Rate Confidence in Body of Evidence

**Animal Studies**
- Extract Data
- Assess Individual Study Quality
- Rate Confidence in Body of Evidence

**Mechanistic Data**
- Extract Data
- Assess Individual Study Quality
- Rate Confidence in Body of Evidence
IARC: Evaluating Human Evidence
Preamble Part B, Section 6(a)

• Sufficient Evidence
  – Causal relationship is **established**
  – Chance, bias and confounding ruled out with reasonable confidence

• Limited Evidence
  – Causal interpretation is **credible**
  – Chance, bias and confounding could not be ruled out with reasonable confidence
IARC: Evaluating Human Evidence
Preamble Part B, Section 6(a)

• Inadequate Evidence
  – Studies permit no conclusion regarding causality

• Evidence suggesting lack of carcinogenicity
  – Several strong studies showing consistent lack of positive association
  – Conclusion limited to cancer sites and conditions studied
IARC: Evaluating Animal Evidence
Preamble Part B, Section 6(a)

• Sufficient Evidence
  – Causal relationship established
  – Two or more species of animals or two or more studies
  – One study where malignant neoplasms occur to an unusual degree
    • Incidence (rare tumors)
    • Site (unusual tumors)
    • Age at onset
    • Strong findings at multiple sites
IARC: Evaluating Animal Evidence
Preamble Part B, Section 6(a)

• Limited Evidence
  – Single positive experiment
  – Unresolved questions about the studies
  – Only benign neoplasms
  – Only promoting activity demonstrated

• Inadequate evidence

• Evidence suggesting lack of carcinogenicity
  – All studies negative or inadequate
  – At least two well-conducted negative studies
Group 1 consistently and strongly supported by a broad range of mechanistic and other relevant data.

Group 3 belongs to a mechanistic class with supporting evidence from mechanistic and other relevant data.

Group 4 belongs to a mechanistic class with supporting evidence from mechanistic and other relevant data.

IARC Overall Evaluation

Sufficient

Limited

Inadequate

ESLC

EVIDENCE IN HUMANS

EVIDENCE IN EXPERIMENTAL ANIMALS

Group 2A

Group 2B

Group 2B (exceptionally, Group 2A)

Group 3

Group 3

Group 4

Modified from Vincent Cogliano, IARC
Glyphosate - Background

- Broad-spectrum, non-selective herbicide
- First synthesized by Cilag (1950) as a possible drug
- Re-synthesized by Monsanto (1970)
- Hundreds of trade names
- Approximately 91 producers in 20 countries
• Believed to be the most heavily used herbicide in the world
  – 2012 production volume > 700 million kg
• Production has increased sharply in recent years
  – Genetically modified glyphosate-resistant crop varieties
• Exposure pathways
  – Air (during spraying)
  – Water
  – Food
Glyphosate – Human Evidence

- Literature
  - US Agricultural Health Study (AHS)
  - Multiple independent case-control studies
Glyphosate – Human Evidence

- Epidemiological studies of cancer in humans
  - More than 2 studies
    - Non-Hodgkin Lymphoma (NHL)
    - Multiple Myeloma (MM)
  - Two studies
    - Leukemia, breast cancer, prostate cancer
  - One Study
    - Adult brain, oesophageal, stomach, prostate, soft-tissue sarcoma, lung, oral cavity, colorectal, pancreas, kidney, bladder, melanoma
### Glyphosate – Key Epidemiology Studies for Non-Hodgkin Leukemia

<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th>Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agricultural Health Study (Alavanja et al., 2003)</td>
<td>Cohort – pesticide applicators and spouses</td>
<td>52 395 (+32 347 spouses), 92 cases, 4-8 years follow-up</td>
</tr>
<tr>
<td>US Midwest (De Roos et al., 2003)</td>
<td>Pooled analysis of 3 case-control studies</td>
<td>NHL: 650 cases, 1933 controls</td>
</tr>
<tr>
<td>Cross-Canada (McDuffie et al., 2001)</td>
<td>Population-based case-control</td>
<td>517 cases, 1506 controls</td>
</tr>
<tr>
<td>Swedish Case-Control Study (Eriksson et al., 2008)</td>
<td>Population-based case-control study</td>
<td>910 cases, 1016 control</td>
</tr>
<tr>
<td>Swedish Case-Control Study (Hardell et al., 1999)</td>
<td>Population-based case-control study</td>
<td>404 cases, 741 control (limited power)</td>
</tr>
</tbody>
</table>
IARC Glyphosate Evaluation

Human Evidence

- **Limited Evidence** for NHL
  - Causal interpretation is **credible**
  - Chance, bias and confounding could not be ruled out with reasonable confidence

- **Basis**
  - De Roos et al., 2003 (US), McDuffie et al., 2001 (Canada), Eriksson et al., 2008 (Sweden)
    - Positive association
    - Adjustment for other pesticides
  - Agricultural Health Study
    - No additional support for association, does not contradict
  - Positive meta-analysis
IARC Evidence in Experimental Animals

• 1 mouse feeding (glyphosate) study showed significant trend in the incidence of **renal tubule adenoma or carcinoma** (combined) in male mice; renal tubule carcinoma is a rare tumor

• 1 mouse feeding (glyphosate) study showed significant trend in the incidence of **haemangiosarcoma** in male mice

• 2 rat feeding (glyphosate) studies showed significant increase in the incidence of **pancreatic islet cell adenoma** (a benign tumor) in male rats

• 1 mouse study (GLY formulation) showed positive effect on **skin cancer** in an initiation-promotion study

• Several other oral feeding (glyphosate) and drinking water (glyphosate and glyphosate formulation) studies in rats showed no significant effects
• **Sufficient Evidence** in experimental animals
  – More than two independent studies showing a significant, biologically relevant cancer finding
## IARC Mechanistic Evidence

<table>
<thead>
<tr>
<th>Key characteristic</th>
<th>Strength of Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Electrophilic or ability to undergo metabolic activation</td>
<td>Glyphosate is <em>not</em> electrophilic</td>
</tr>
<tr>
<td>2. Genotoxic</td>
<td>Strong (G, GF)</td>
</tr>
<tr>
<td>3. Alters DNA repair or causes genomic instability</td>
<td>No data</td>
</tr>
<tr>
<td>4. Epigenetic Alterations</td>
<td>No data</td>
</tr>
<tr>
<td>5. Oxidative Stressor</td>
<td>Strong (G, GF and AMPA)</td>
</tr>
<tr>
<td>6. Induces chronic inflammation</td>
<td>No data</td>
</tr>
<tr>
<td>7. Immunosuppressant</td>
<td>Weak</td>
</tr>
<tr>
<td>8. Modulates receptor-mediated effects</td>
<td>Weak</td>
</tr>
<tr>
<td>9. Immortalization</td>
<td>No data</td>
</tr>
<tr>
<td>10. Alters cell proliferation, cell death, or nutrient supply</td>
<td>Weak</td>
</tr>
</tbody>
</table>
“for […] glyphosate, the mechanistic evidence provided independent support of the 2A classification based on evidence of carcinogenicity in humans and experimental animals”
(The Lancet Oncology; March 20, 2015)
CLP Guidance on Carcinogenicity

• Category 1: Known or presumed human carcinogens
  – Category 1A, known to have carcinogenic potential for humans, classification is largely based on human evidence
  – Category 1B, presumed to have carcinogenic potential for humans, classification is largely based on animal evidence

CLP Guidance on Carcinogenicity (continued)

• The classification in Category 1A and 1B is based on strength of evidence together with additional considerations (see section 3.6.2.2). Such evidence may be derived from:
  – human studies that establish a causal relationship between human exposure to a substance and the development of cancer (known human carcinogen); or
  – animal experiments for which there is sufficient (1) evidence to demonstrate animal carcinogenicity (presumed human carcinogen).

• In addition, on a case-by-case basis, scientific judgement may warrant a decision of presumed human carcinogenicity derived from studies showing **limited evidence of carcinogenicity in humans together with limited evidence of carcinogenicity in experimental animals**

EFSA – What is reviewed for reassessment?

• All new data since the last review
• All endpoints
  – Including non-cancer endpoints
• Assessment is based upon
  – Reassessment document provided by industry
    • BfR and EFSA comment on document
    • Analysis of study results based upon submitted documents
  – All pertinent epidemiological studies and cancer bioassays
  – Representative mechanistic data
  – Studies may not be publicly available
  – Reviewers submit Declaration of Interests
    • Some of these are blank?
<table>
<thead>
<tr>
<th>Year</th>
<th>Strain</th>
<th>Length</th>
<th>Top Dose</th>
<th>Renal Tumors</th>
<th>Hemangiosarcomas</th>
<th>Malignant Lymphoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>1983</td>
<td>Crl:CD-1</td>
<td>24</td>
<td>4,841</td>
<td>+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1993</td>
<td>?:CD-1</td>
<td>24</td>
<td>1,000</td>
<td></td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>1997</td>
<td>CrJ:CD-1</td>
<td>18</td>
<td>4,843</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>2001</td>
<td>SW</td>
<td>24</td>
<td>1,460</td>
<td>+</td>
<td></td>
<td>+/-</td>
</tr>
<tr>
<td>2009</td>
<td>Crl:CD-1</td>
<td>18</td>
<td>810</td>
<td></td>
<td></td>
<td>+</td>
</tr>
</tbody>
</table>

1 – months; 2 – mg/kg bw/day; 3 - + indicates a p-value of <0.05 as calculated by BfR using the Armitage linear trend test in proportions; 4 – p=0.066; 5 – studies evaluated in IARC review

Historical Control Data used: collected 1987-96, 51 control groups from Crl:CD-1 mice from 7 different research laboratories using mice from 3 different Charles River Laboratories production sites with sacrifice at ages 18-24 months

Renal Adenoma: 41 studies no tumors, 3 studies 1 tumor, 2 studies 2 tumors
Renal Carcinoma: 42 studies no tumors, 4 studies 1 tumor
EFSA compared to IARC

• Agreed with the IARC on *limited evidence* in humans
  – dismissed the association as “insufficiently consistent” with no justification.

• Dismissed evidence of renal tumors in 3 mouse studies, hemangiosarcoma in 2 mouse studies and malignant lymphoma in 2 mouse studies
  – Inappropriate historical control dataset used in an incorrect manner and ignoring established guidelines cited in their report
  – Trend test not convincing, Doses too high

• Down-weighted laboratory and human evidence of genotoxicity.

• Confirmed glyphosate induces oxidative stress
  – Not relevant for cancer because no other indications