IARC Monograph Evaluation of Glyphosate

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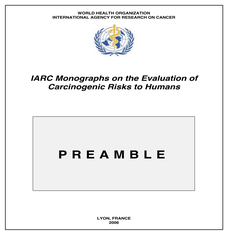
Background and Evidence for Carcinogenicity

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

Two-Step, Uniform Hierarchic Evaluations

Step 1: Categorize each line of evidence using defined terms

Cancer in humans	Cancer in Experimental animals	Mechanistic and Other Relevant Data
• *Sufficient evidence* • *Limited evidence* • *Inadequate evidence*	• *Sufficient evidence* • *Limited evidence* • *Inadequate evidence*	•"Weak," "moderate," or "strong" evidence? •Does this– or can it– occur in humans?

Step 2: Integrate findings in overall evaluations

Overall evaluation

▪ Group 1	*Carcinogenic to humans*
▪ Group 2A	*Probably carcinogenic to humans*
▪ Group 2B	*Possibly carcinogenic to humans*
▪ Group 3	*Not classifiable*

Key epidemiology studies:

Case-control studies from Canada, Sweden and the US:
- ➢ Positive association that persisted after adjustment for other pesticides

Agricultural Health Study (US) cohort study:
- ➢ No additional support for association, but does not contradict other studies

Limited evidence

Cancer bioassays (oral exposure):

Male mouse (CD-1), "pure" glyphosate:
- ➢ Rare tumours in two studies:
  - Renal tubule carcinoma [P=0.037]; adenoma/carcinoma (combined) [P=0.034];
  - Haemangiosarcoma [P=0.001]

Rat, "pure" glyphosate:
- ➢ Benign tumours in SD rats (male pancreatic islet cell adenoma in 2 studies; male hepatocellular adenoma and female thyroid C-cell adenoma in 1 study)
- ➢ No increases in 2 other studies (SD, Wistar)
- ➢ One study (Wistar) was inadequate (short duration)

Sufficient evidence

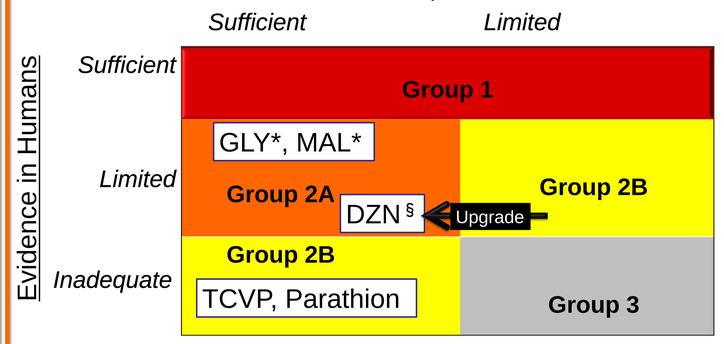
Mechanistic and other data:
10 Key characteristics of carcinogens

Key characteristic	Strength of Evidence	Operates in humans?
1. Electrophilic	Glyphosate is ***not*** electrophilic	
2. Genotoxic	Strong (glyphosate and formulations)	Can operate in humans
3. Alters DNA repair/genomic instability	No data	
4. Epigenetic alterations	No data	
5. Oxidative Stressor	Strong (glyphosate, formulations, and metabolite)	Can operate in humans
6. Induces chronic inflammation	No data	
7. Immunosuppressant	Weak	
8. Receptor-mediated effects	Weak	
9. Immortalization	No data	
10. Alters cell proliferation & death	Weak	

Strong evidence

Volume 112 Results

Evidence in Experimental Animals



Glyphosate (GLY), Malathion (MAL), Diazinon (DZN), TetrachIorvinphos (TCVP);
§ Based on limited evidence in humans and experimental animals, and strong mechanistic evidence
*** for GLY** and MAL, mechanistic evidence provided independent support of the 2A classification based on evidence in humans and in experimental animals.

Glyphosate Evaluation Summary

Cancer in humans

***Limited* evidence**
- Studies of real-world exposures
- ***Glyphosate formulations*** in different regions at different times

Cancer in experimental animals

***Sufficient* evidence**
- Studies of pure ***glyphosate***
- Rare tumours in adequate studies

Mechanistic & other relevant data

***Strong* evidence**
- Studies of real-world exposures
- Experimental studies of pure ***glyphosate***
- Experimental studies of ***glyphosate formulations***

Overall evaluation of glyphosate:

Group 2A **Probably carcinogenic to humans**

Evaluation Timeline and Publications

IARC Secretariat: Coordinate all aspects of *Monograph* development

Working Group members: Write the critical reviews and develop evaluations

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 [***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***]

IARC Secretariat:
- •Recruit Working Group members and organize meeting
- •Search and retrieve literature
- •Assure adherence to procedures

Working Group members:
- •Study-by-study evaluation against published criteria
- •Add comments [in square brackets]
- •Draft assigned sections
- •Peer-review

Monograph in-person meeting:
- •Sub-group review
- •Plenary review and evaluation

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

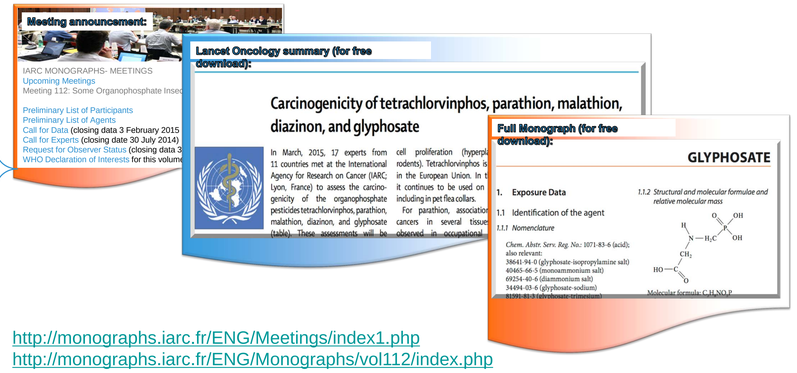
Participants and COIs announced for public scrutiny (Jan. 2015)

The Lancet Oncology publication (March 2015)

References to health agencies (April 2015)

Glyphosate *Monograph* publication (July 2015)

Online Publication:



http://monographs.iarc.fr/ENG/Meetings/index1.php
http://monographs.iarc.fr/ENG/Monographs/vol112/index.php

- Glyphosate is the most commonly used herbicide worldwide.
- In humans, evidence for carcinogenicity was *limited*; case-control studies of occupational exposures in Canada, Sweden and the USA reported increased NHL risks.
- In experimental animals, evidence for carcinogenicity was *sufficient*; glyphosate induced rare tumours in mice (renal tubule carcinoma, haemangiosarcoma)
- Strong mechanistic data (for genotoxicity, and for oxidative stress) supported the Group 2A cancer hazard classification of glyphosate.

International Agency for Research on Cancer

World Health Organization

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