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.

IARC Evaluation of Glyphosate

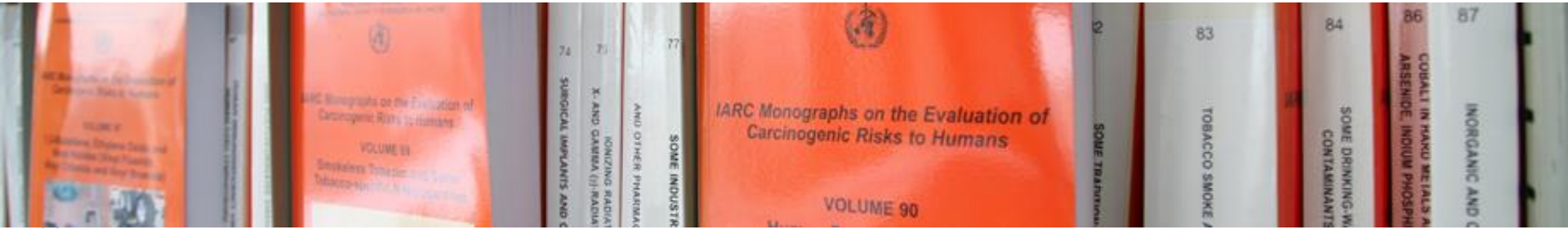
➢ ***Probably carcinogenic to humans (Group 2A)***

IARC evaluations are used as a reference worldwide

- All data in the public domain for independent scientific review
- Reviewed by the world's leading experts without vested interests

What happens after IARC identifies a carcinogen?

- Risk assessments help regulators and the public understand the extent of potential cancer risk
- Measures to reduce exposures to workers and to the public



How Are the IARC Monograph Evaluations Conducted?

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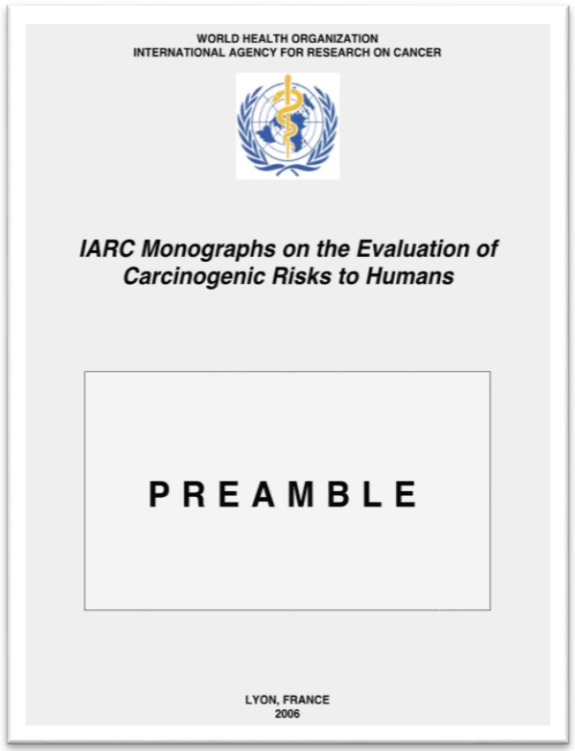

- Procedural guidelines for participant selection, conflict of interest, stakeholder involvement & meeting conduct
- Separate criteria for review of human, animal and mechanistic evidence
- Decision process for overall evaluations

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Preamble to the IARC Monographs (2006):
http://monographs.iarc.fr/ENG/Preamble/index.php

Who Does the Evaluation?

Attend meetings but do not write reviews or contribute to evaluations

IARC Secretariat
Coordinates all aspects of the evaluation

Working Group
Independent scientists without conflict of interest
Review science and develop evaluations

Invited Specialists
Scientists with relevant knowledge but a competing interest

Representatives of governments and health agencies

Observers
Scientists with a competing interest: observe but do not influence outcomes

Preamble to the IARC Monographs (2006):
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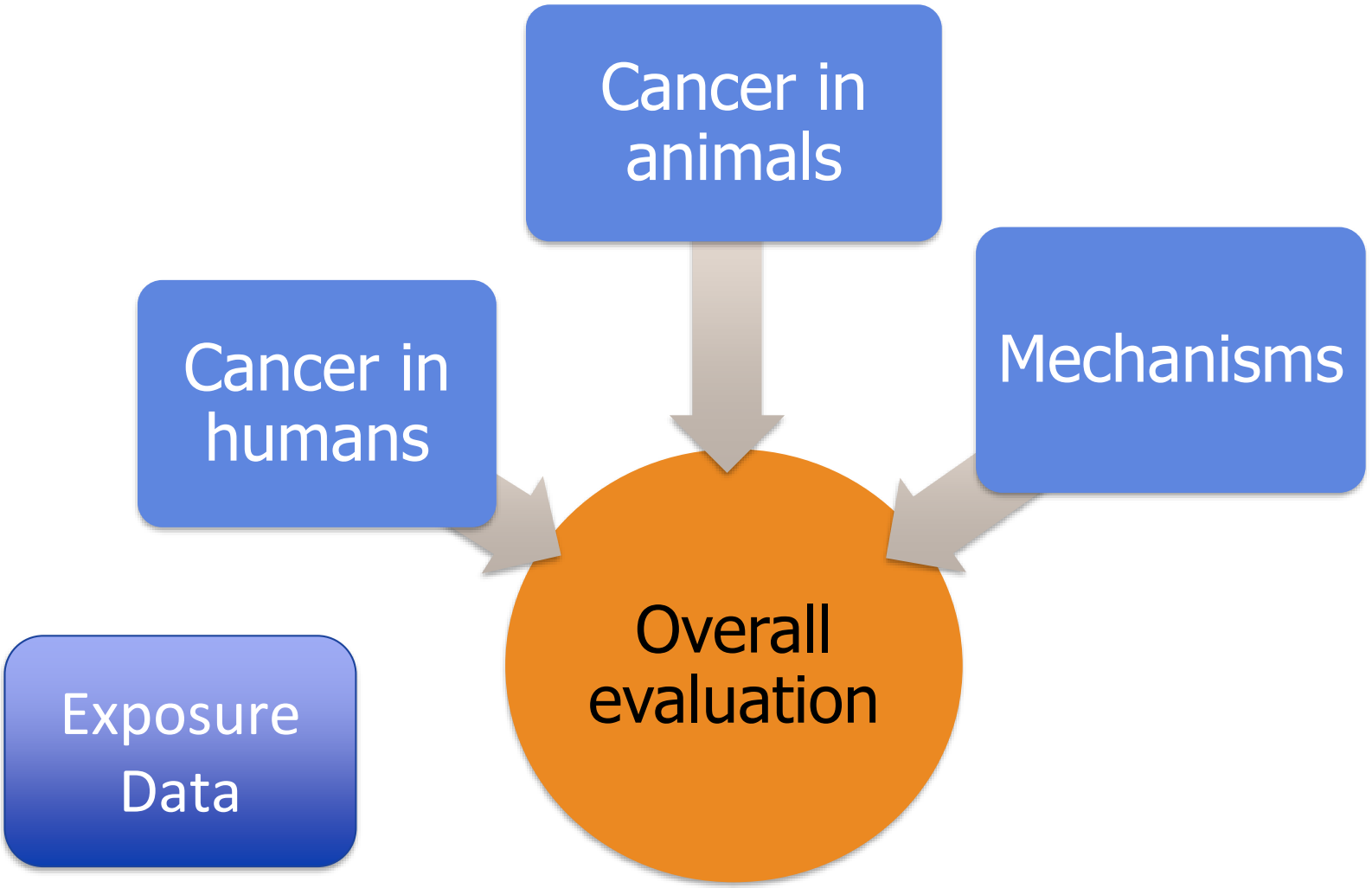
What Evidence is Considered?



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The IARC Monographs Evaluations:
A Two-Step Process

Step 1: Categorize each line of evidence using defined terms

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?*

Step 2: Integrate findings in overall evaluations

Overall evaluation

- Group 1 *Carcinogenic to humans (120)*
- Group 2A *Probably carcinogenic to humans (81)*
- Group 2B *Possibly carcinogenic to humans (294)*
- 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

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, revision, summary
- Plenary review and evaluation

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

Participants (and DOI) announced (2 months ahead)

The Lancet Oncology Publication (2 weeks later)

Monograph Publication (1-2 years later)

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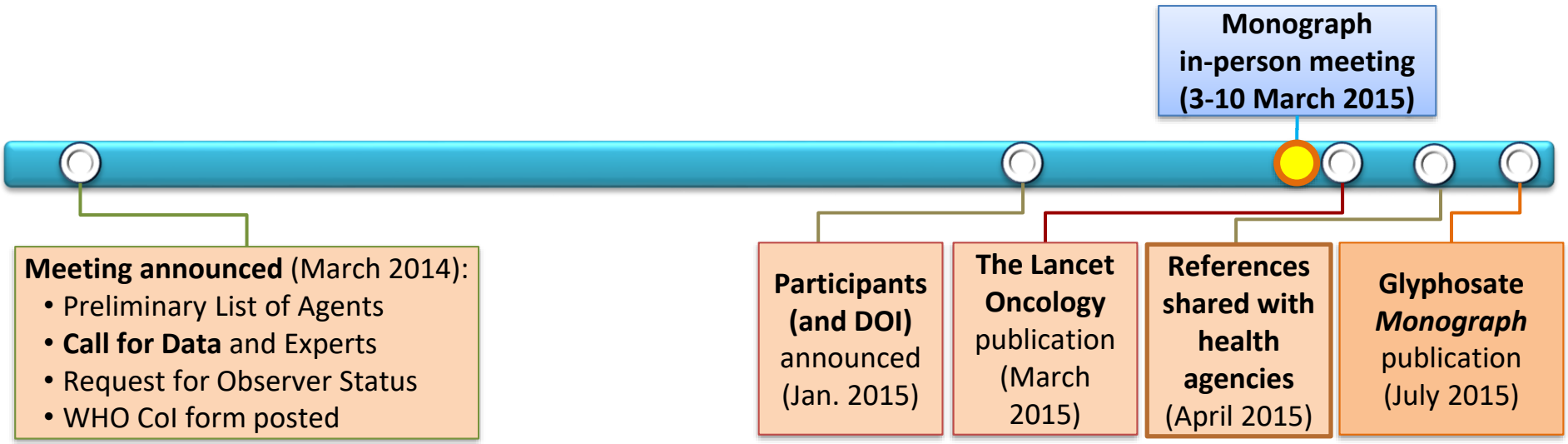
Scientific engagement: Glyphosate *Monograph*



- 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

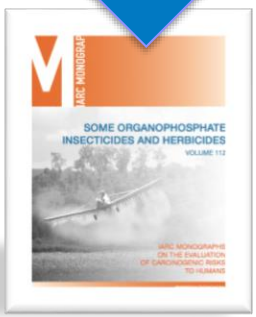
Glyphosate: Studies

- ~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***



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Cancer in Humans

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

1) Case-control studies

- Canada, Sweden, US
- **2592 NHL cases**
- **Increased risks**, not explained by other pesticides

2) Cohort study (Ag Health Study)

- US, 2 states
- **92 NHL cases**
- No significant increase in risk

3) Meta-analysis

- Objective method to combine **all studies**
- **Increased risks** (meta risk-ratio=1.3; 95% CI,1.03−1.65; I^2=0%)

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***

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

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***

Overall evaluation of glyphosate:

Group 2A *Probably carcinogenic to humans*

Organization

From Recommendation to Evaluation

How to prioritize pesticides for cancer hazard evaluation?

- Comprehensive list of pesticides
- Automated text mining of public databases
- Data visualization by chemical class:
  A. Organophosphorus
  B. Organochlorine

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

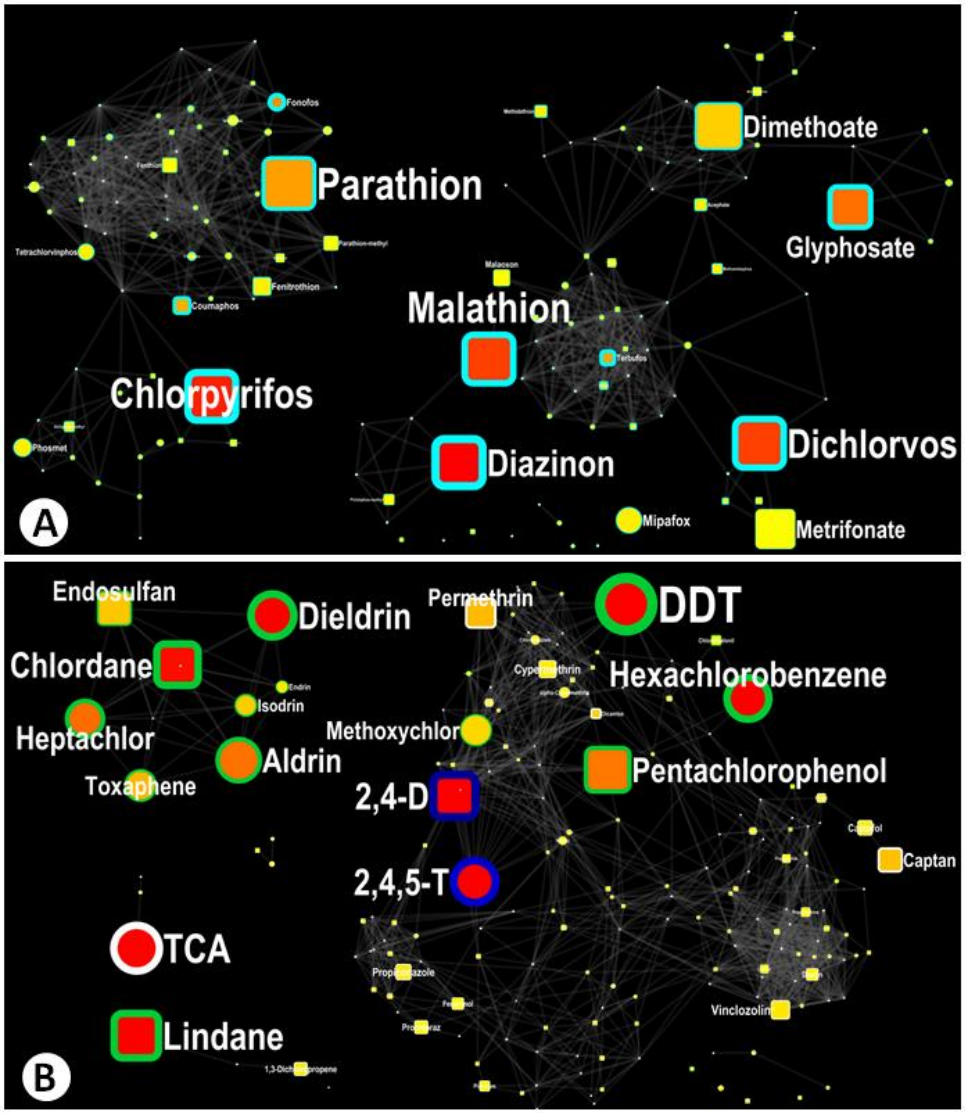

Figure 2, from Guha et al. Environ Health Perspect. 2016 124(12):1823-1829.

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IARC Classifications of Pesticides 1971-2016

Classification	Number	Details/Comments
Group 1	3	Arsenic and arsenical compounds, including pesticides; **Lindane; Pentachlorophenol**
Group 2A	9	Captafol; **DDT; Diazinon; Dieldrin, Aldrin metabolised to Dieldrin**; Dimethylcarbamoyl chloride; Ethylene dibromide; **Glyphosate; Malathion; Tetrachloroazobenzene (contaminant)**
Group 2B	27	Examples evaluated in 2015-2016: **Parathion, Tetrachlorvinphos, 2,4,6-Trichlorophenol**
Group 3	48	