The Carcinogenicity of Glyphosate

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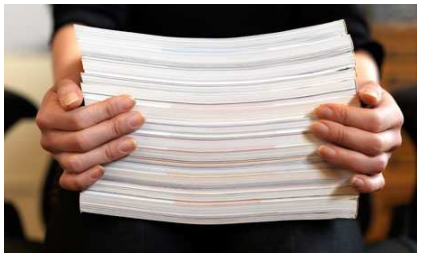
Conflict of Interest Statement

I declare no financial interests related to the subject matter of my presentation.

How Are the IARC Monograph Evaluations Conducted?



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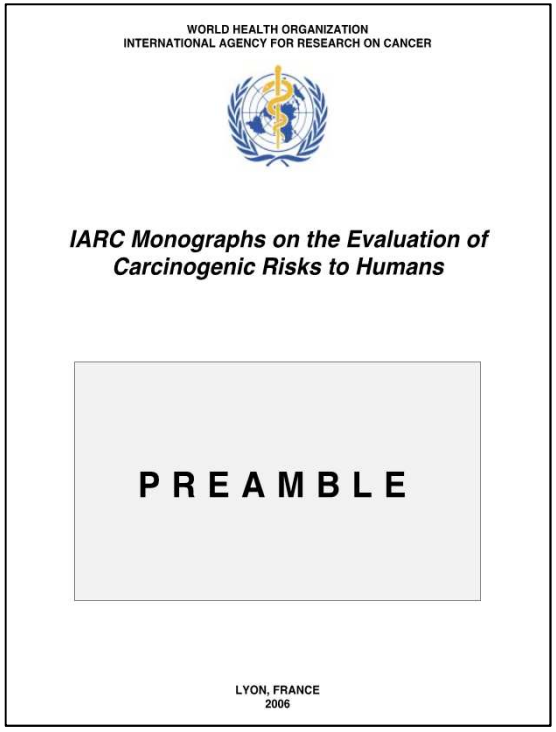

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- Procedural guidelines for participant selection, conflict of interest, stakeholder involvement & meeting conduct
- Separate criteria for review of human, animal and mechanistic evidence
- Decision process for overall evaluations

http://monographs.iarc.fr/ENG/Preamble/index.php

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 (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)*

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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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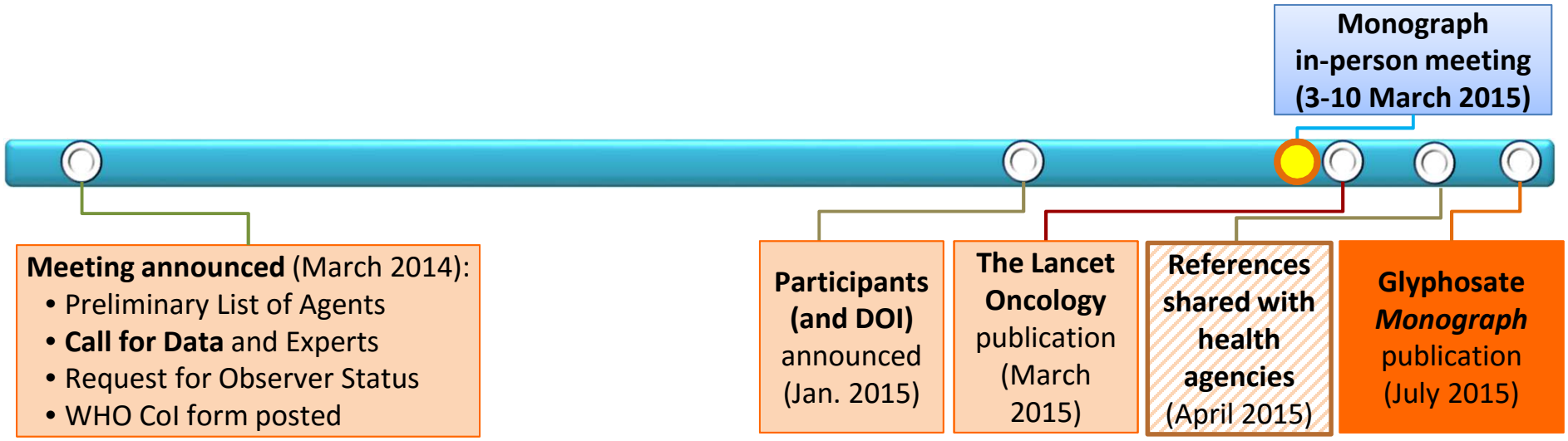
Scientific Engagement: Glyphosate *Monograph*



- 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

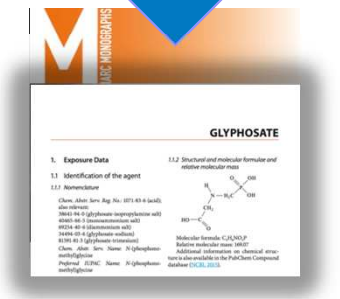
Glyphosate: Studies

- ~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

- Sweden, Canada, 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%)

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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
  - o High statistical significance
  - o Tumours in the absence of toxicity
  - o Evaluation fully in line with accepted principles
  - o Causal relationship established

➢ ***Sufficient evidence of cancer in animals***

Cancer Mechanisms: 10 Key Characteristics of Carcinogens

Key characteristic:
1. Is Electrophilic or can be metabolically activated
2. Is Genotoxic
3. Alters DNA repair or causes genomic instability
4. Induces Epigenetic Alterations
5. Induces Oxidative Stress
6. Induces chronic inflammation
7. Is Immunosuppressive
8. Modulates receptor-mediated effects
9. Causes Immortalization
10. Alters cell proliferation, cell death, or nutrient supply

- Evidence of these characteristics, especially in humans or as intermediate biomarkers in human specimens can provide **biological plausibility** for epidemiological findings and/or early warning if no epidemiology exists
- Provide the basis for a **systematic and objective approach** to identifying and evaluating mechanistic evidence

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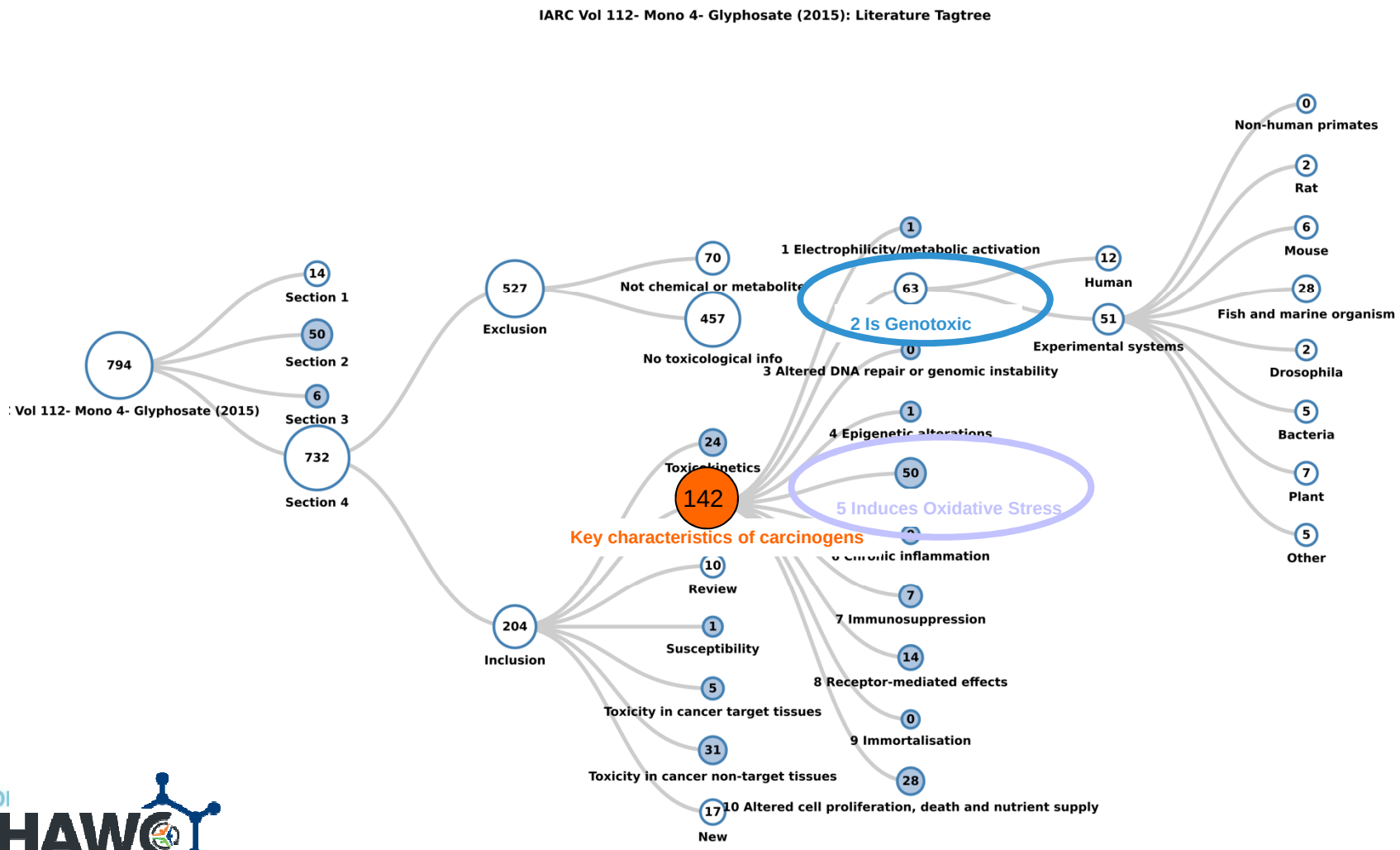
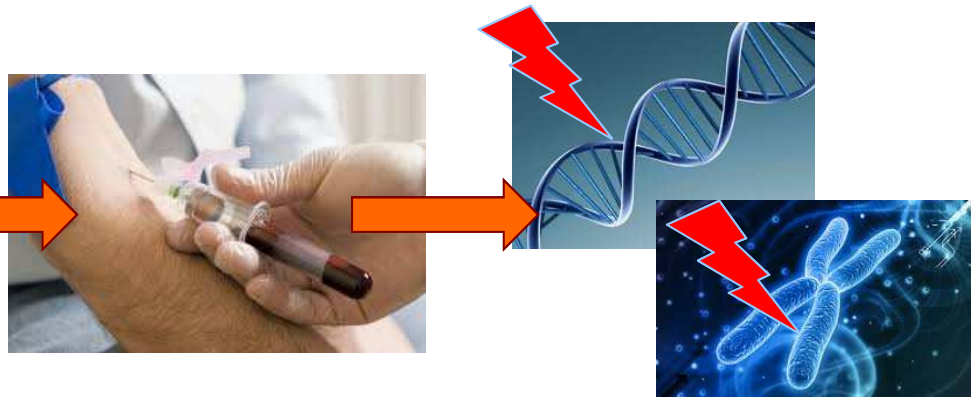
Smith MT, Guyton KZ, Gibbons CF, Fritz JM, Portier CJ, Rusyn I, DeMarini DM, Caldwell JC, Kavlock RJ, Lambert P, Hecht SS, Bucher JR, Stewart BW, Baan R, Cogliano VJ and K Straif. *Env Health Persp.*, *124(6):713-21*

Systematic Literature Search and Review



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

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

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*

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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?

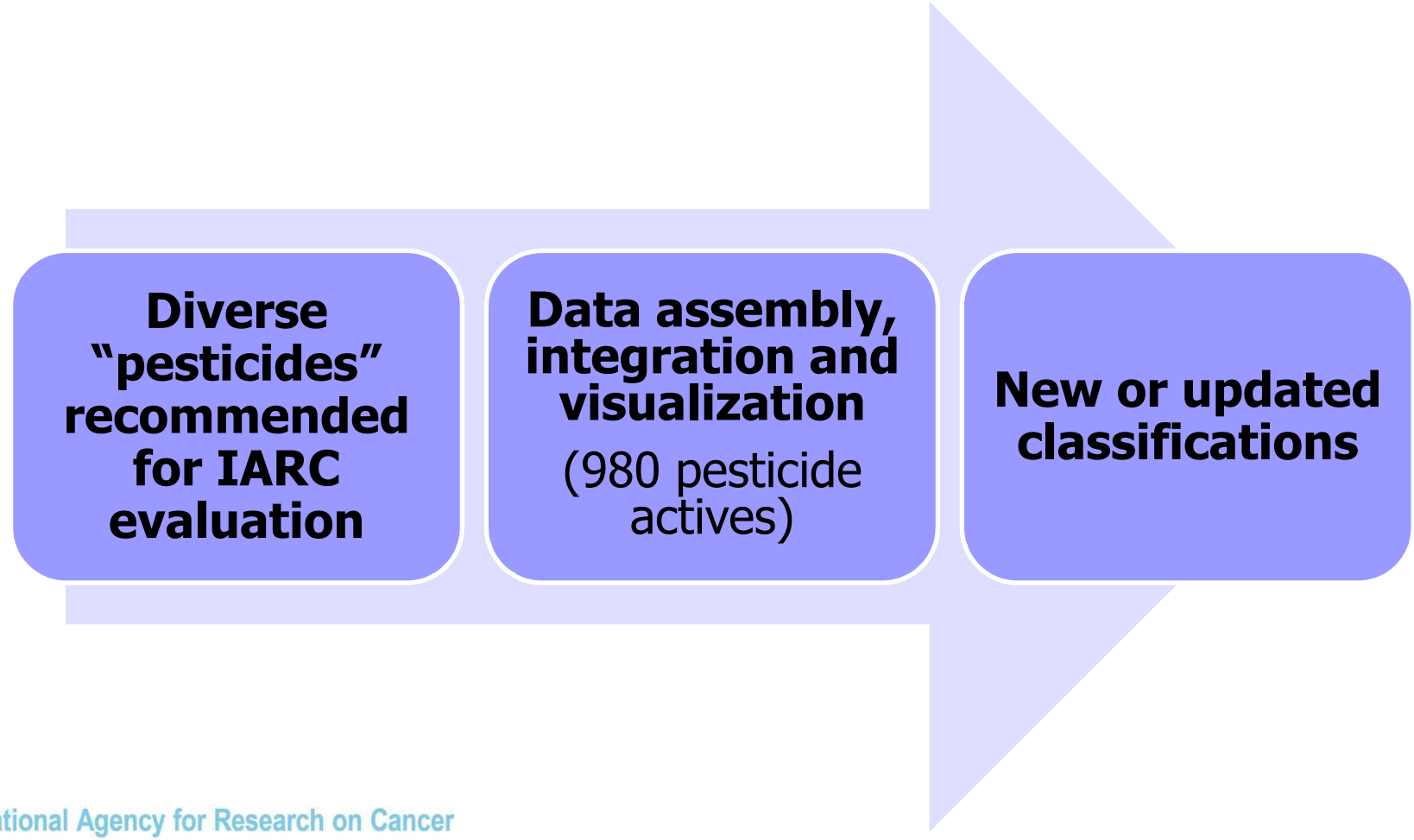
Some industry toxicology studies considered by IARC were not evaluated (not in the public domain in sufficient detail for independent review)

- 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



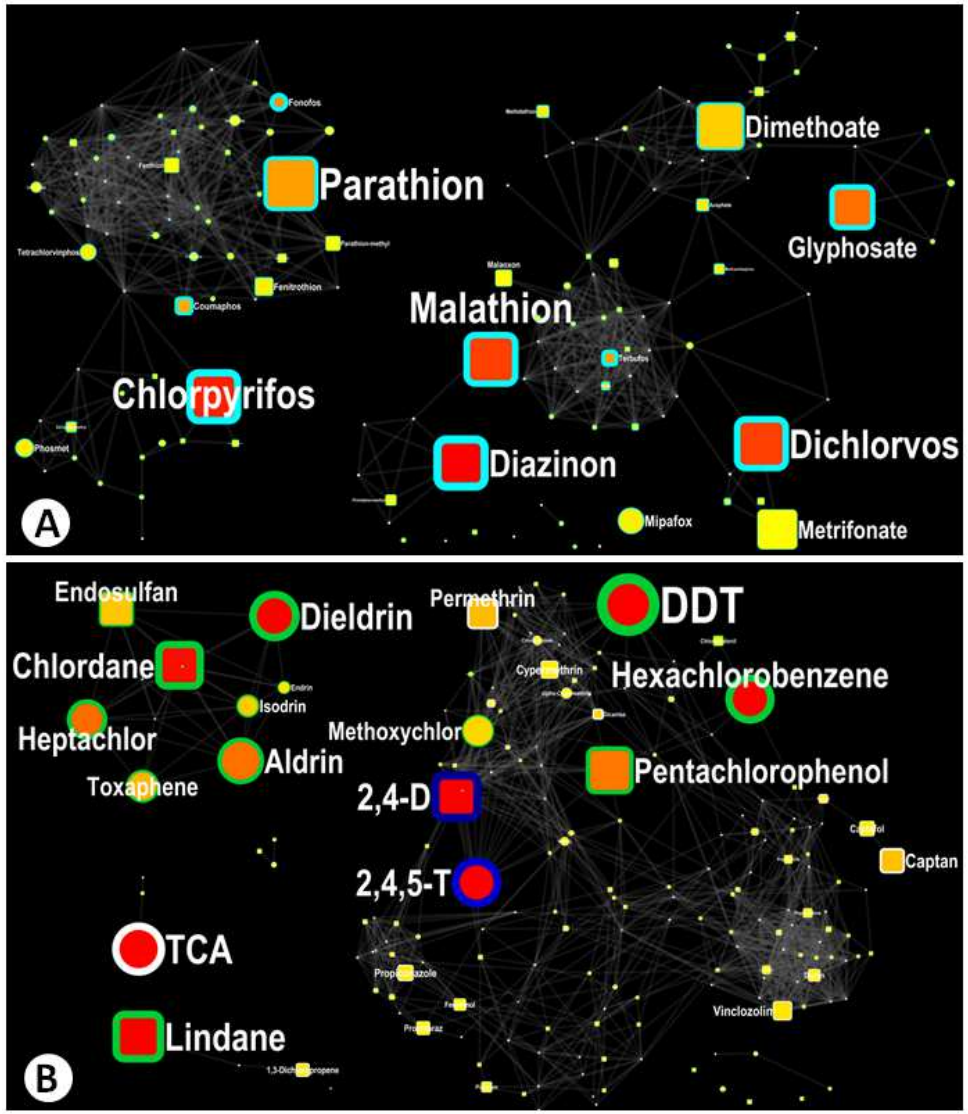
Data Assembly, Integration and Visualization: *Results*

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*

Name	Rank (within class)	Usage notes	PubMed human cancer	PubMed Mechanisms	Prior IARC (year)	Current IARC (2015)
Parathion	1	Restricted	6	578	3 (1987)	**2B**
Malathion	2	High	12	370	3 (1987)	**2A**
Diazinon	5	High	16	215	-	**2A**
Glyphosate	7	High	9	204	-	**2A**
Tetrachlor-vinphos	13	Active	1	40	3 (1987)	**2B**

New or Updated Classifications: *Organochlorine Pesticides*

Name	Rank (within class)	Usage notes	PubMed human cancer	PubMed Mechanisms	Prior IARC (year)	Current IARC (2015-2016)
DDT	1	Restricted POP	190	953	2B (1991)	**2A**
Lindane	2	Active POP	51	545	2B (1987)	**1**
PCP	5	Restricted POP	25	573	2B (1987)	**1**
Dieldrin (Aldrin → Dieldrin)	3/7	Restricted POP	57/25	484	3 (1987)	**2A**

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	

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Thank you!http://www.iarc.fr

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