IARC's Evaluation of Glyphosate

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Collaborative on Health and the Environment Teleconference

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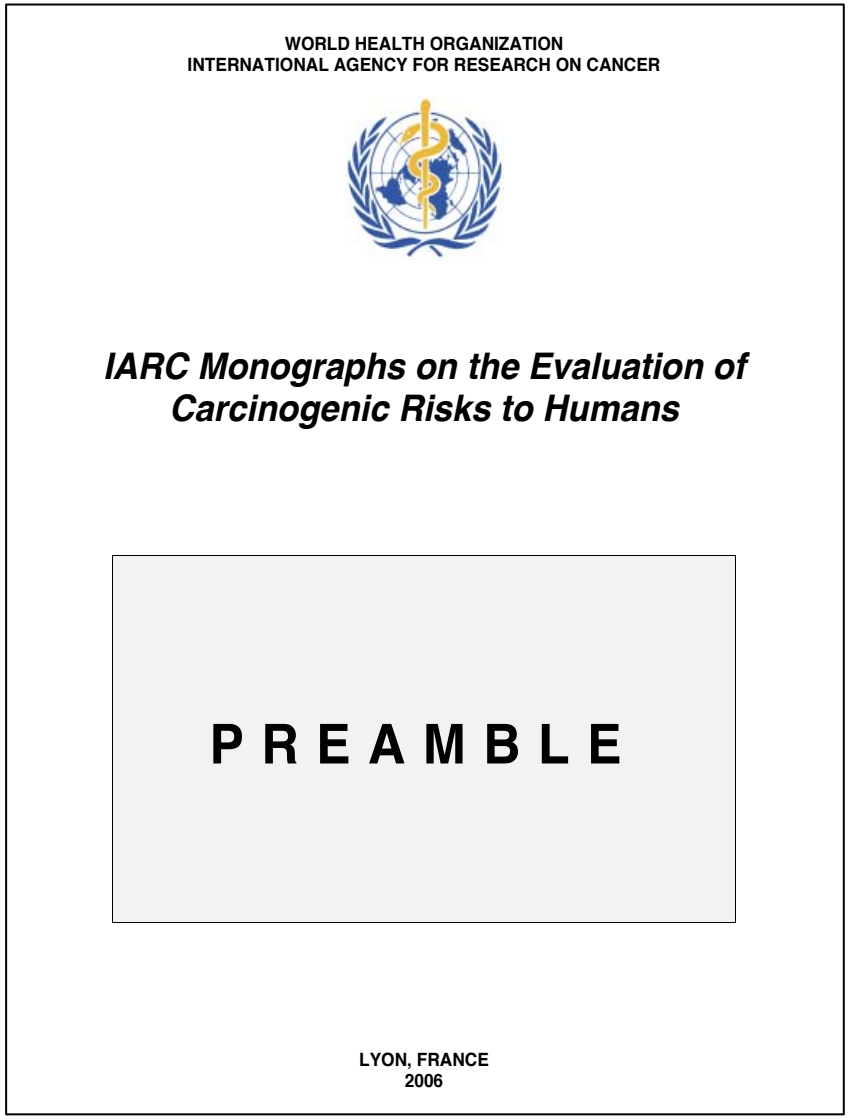
The IARC Monographs Program

- 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

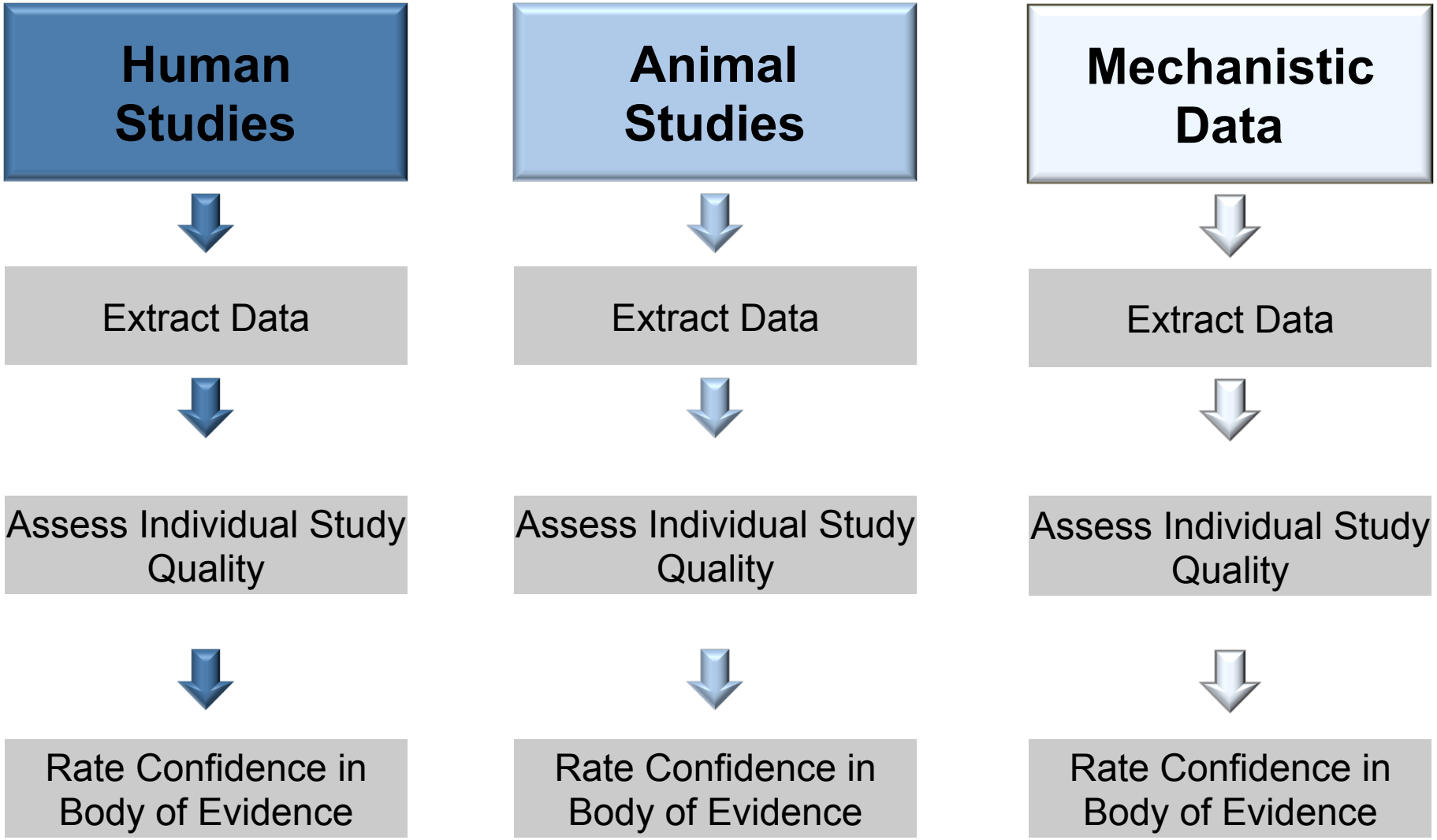
IARC Monograph Timeline

- 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



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

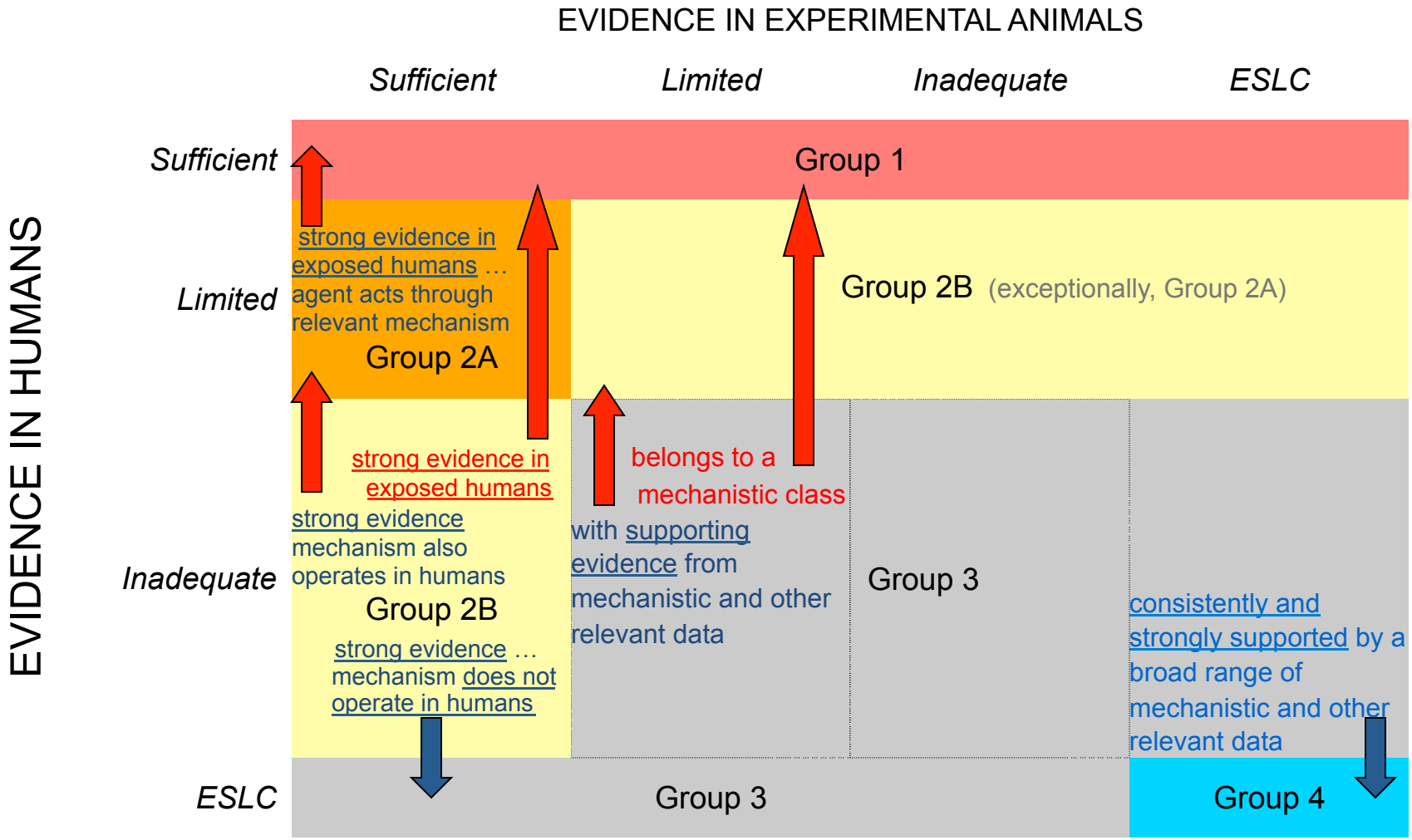
IARC: Evaluating Animal Evidence
Preamble Part B, Section 6(a)

- 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

IARC Overall Evaluation



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)
- Patent expired [1991, 2000 (US)]
- Hundreds of trade names
- Approximately 91 producers in 20 countries

Glyphosate - Background

- 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

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

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

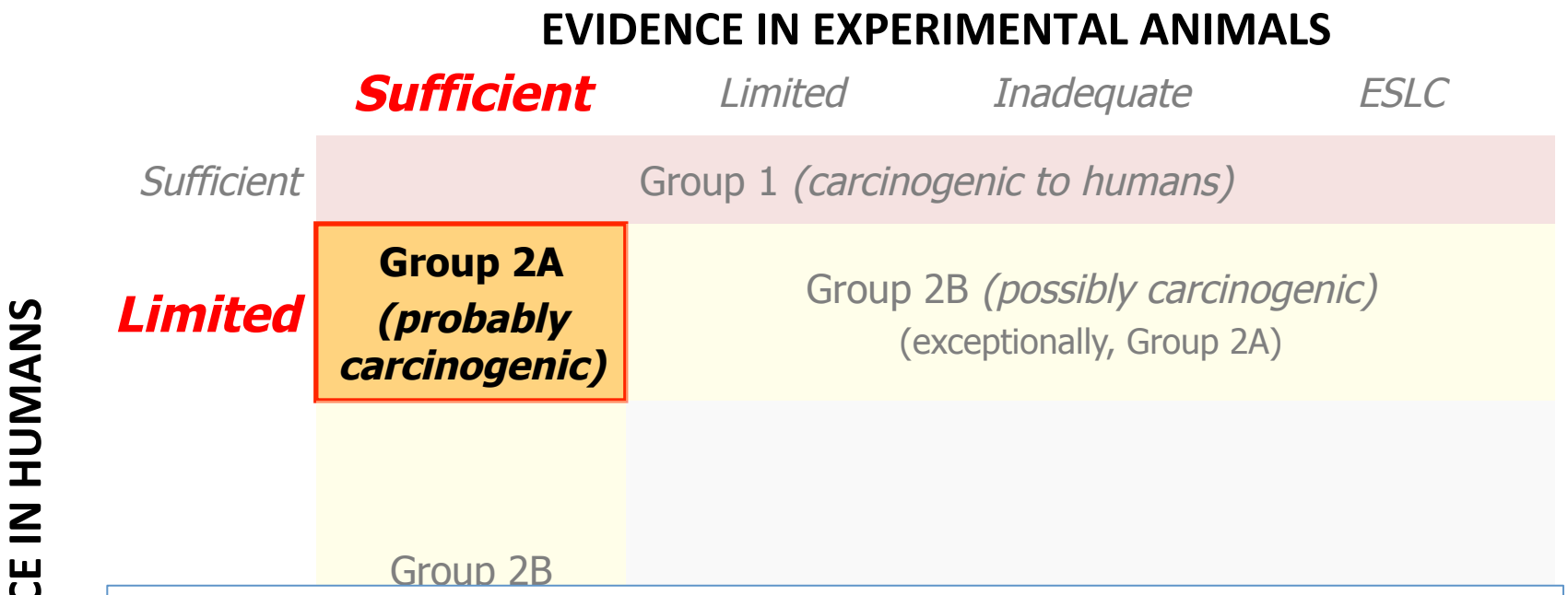
IARC Glyphosate Evaluation
Human Evidence

- **Sufficient Evidence** in experimental animals
  - More than two independent studies showing a significant, biologically relevant cancer finding

IARC Mechanistic Evidence

Key characteristic	Strength of Evidence
1. Electrophilic or ability to undergo metabolic activation	Glyphosate is ***not*** electrophilic
2. Genotoxic	Strong (G, GF)
3. Alters DNA repair or causes genomic instability	No data
4. Epigenetic Alterations	No data
5. Oxidative Stressor	Strong (G, GF and AMPA)
6. Induces chronic inflammation	No data
7. Immunosuppressant	Weak
8. Modulates receptor-mediated effects	Weak
9. Immortalization	No data
10. Alters cell proliferation, cell death, or nutrient supply	Weak

IARC Glyphosate Monograph
Overall Evidence



"*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

Guidance on the Application of the CLP Criteria, ECHA (2015)

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**

Guidance on the Application of the CLP Criteria, ECHA (2015)

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?

EFSA Glyphosate Review
Animal Carcinogenicity

Year	Strain	Length[1]	Top Dose[2]	Renal Tumors	Hemangio-sarcomas	Malignant Lymphoma
1983[5]	Crl:CD-1	24	4,841	+[3]		
1993[5]	?:CD-1	24	1,000		+	
1997	CrJ:CD-1	18	4,843	+	+	+
2001	SW	24	1,460	+		+/-[4]
2009	Crl:CD-1	18	810			+

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 from7 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