The International Agency for Research on Cancer (IARC) Monographs on the Evaluation of Carcinogenic Risks to Humans:

An Example of the Evaluation in Monograph Volume 112 (March 2015)

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Disclaimers:

- *This presentation **does not reflect the official views** of WHO, IARC, Texas A&M University, or any other organization or a third party, and is solely a personal view of Dr. Rusyn*
- *The information in this presentation, as it pertains to evaluations by IARC Monographs Programme, **is not final** and may be subject to change pending final editing of the Monograph*
- *The information in this presentation **is privileged** and is not to be distributed in any form to the persons not participating in this meeting*

Acknowledgements:

- *This presentation was prepared from materials received at the IARC Monographs meeting and from the Lancet Oncology publication on Monograph vol.112*

The IARC Monographs: "*The encyclopaedia of carcinogens*"

The *IARC Monographs* evaluate:

- Chemicals
- Complex substances and mixtures
- Occupational exposures
- Physical and biological agents
- Personal habits

A total of 980 agents have been evaluated (112 volumes*)

- **116** are classified as ***carcinogenic to humans*** (Group 1)
- **73** are classified as ***probably carcinogenic to humans*** (Group 2A)
- **287** are classified as ***possibly carcinogenic to humans*** (Group 2B)
- **503** are classified as ***not classifiable as to its carcinogenicity to humans*** (Group 3)
- **1** is classified as ***probably not carcinogenic to humans*** (Group 4)

National and international health agencies use the *Monographs*

- To identify potential carcinogenic hazards
- To set priorities for conducting risk assessments of chemicals
- To prevent exposures to known or suspected carcinogens

*, as of May 2015

What makes the IARC Monographs process unique?

- Consensus evaluations are carried out by the world's leading experts on each topic and/or subject area

- Real or apparent conflicts of interests are rigorously identified:
  - Before official invitation, employment, research, and financial interests of all meeting participants must be declared through WHO process
  - The Working Group members volunteer their time (reimbursed for travel/per diem)
  - At the opening of the meeting the declarations of interest are updated
  - Pertinent interests are disclosed:
    - To meeting participants
    - To the public (http://monographs.iarc.fr/)
    - In the published volume of the *Monographs*
    - In the published *The Lancet Oncology* summary [using *The Lancet* DoI criteria]

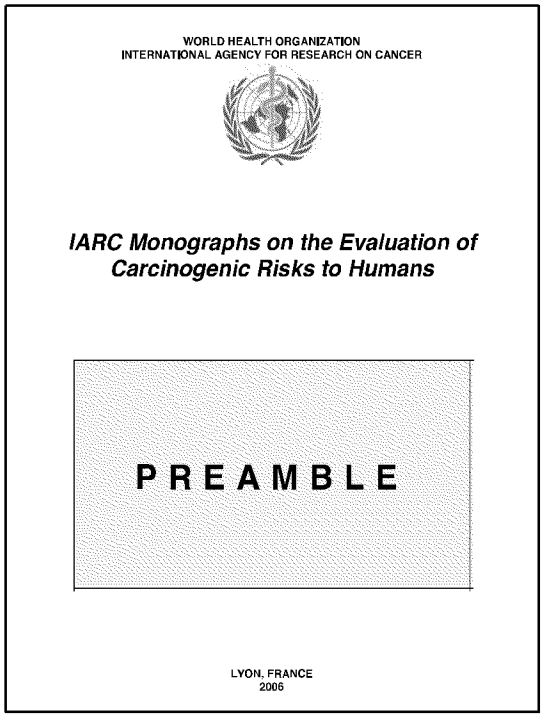
- The Monographs are systematic reviews of human, experimental, and mechanistic data that are considered ***together*** in overall evaluations

- The Working Group should be free from all attempts at interference before, during, and after the meeting

The IARC Monographs Process: What are the rules?

The *Preamble* to the IARC Monographs:

- Guidelines for evaluation are published in the *Preamble* to the Monographs
- The *Preamble* is a publicly available guidance document
- The *Preamble* undergoes periodic revisions (last in 2006) by an independent Advisory Group
- Separate criteria are detailed for review of *epidemiological*, experimental animal, and mechanistic & other relevant evidence
- Decision process for overall evaluations is explained
- Procedural guidelines for participant selection, conflict of interest, stakeholder involvement & meeting conduct are specified


WORLD HEALTH ORGANIZATION
INTERNATIONAL AGENCY FOR RESEARCH ON CANCER

IARC Monographs on the Evaluation of Carcinogenic Risks to Humans

PREAMBLE

LYON, FRANCE
2006

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

Instructions to Authors for the Preparation of Drafts for IARC Monographs:

- Are prepared by staff of the IARC Monographs programme and are provided to authors (members of the Working Group) preparing the first drafts of an IARC Monograph
- Include the details and instructions specific to each Monograph topic
- Are publicly available on the web before each Monograph meeting at: http://monographs.iarc.fr/ENG/Preamble/instructions.php

The IARC Monographs Process: What is evaluated?

The *Preamble* to the IARC Monographs states:

3. Selection of agents for review

- Agents are selected for review on the basis of two main criteria:
  (a) there is evidence of human exposure, and
  (b) there is some evidence or suspicion of carcinogenicity.
- Mixed exposures may occur in occupational and environmental settings and as a result of individual and cultural habits (such as tobacco smoking and dietary practices).
- Ad-hoc Advisory Groups convened by IARC in 1984, 1989, 1991, 1993, 1998, 2003 and 2014 made recommendations as to which agents should be evaluated in the Monographs series.
- IARC may schedule other agents for review as it becomes aware of new scientific information or as national health agencies identify an urgent public health need related to cancer.
- As significant new data become available on an agent for which a Monograph exists, a re-evaluation may be made at a subsequent meeting, and a new Monograph published.

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IARC Monographs on the Evaluation of Carcinogenic Risks to Humans

INTERNAL REPORT 14/002

Report of the Advisory Group to Recommend Priorities for *IARC Monographs* during 2015–2019

18–19 April 2014

LYON, FRANCE
2014

http://monographs.iarc.fr/ENG/Publications/internrep/14-002.pdf

"High priority":

...
Pesticides - current or former widespread global use; substantial data from new epidemiological studies and recent high throughput screening.

http://dx.doi.org/10.1016/S1470-2045(14)70168-8

The IARC Monograph: What does it contain?

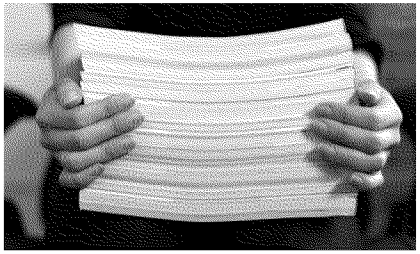
Preamble

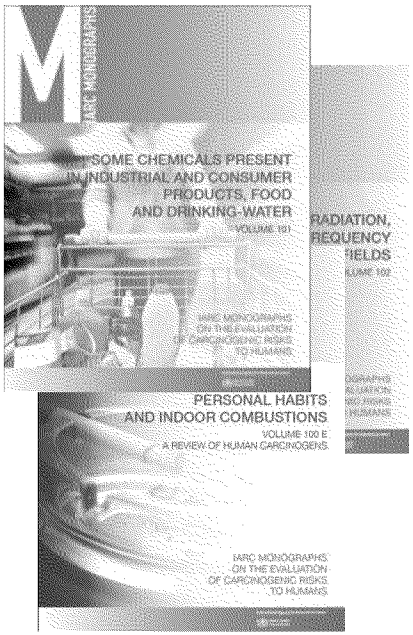
General Remarks

Several *Monographs* in one volume:

1. Exposure data — **Critical review**
2. Cancer in humans
3. Cancer in animals
4. Mechanistic and other relevant data
5. Summary
6. Evaluation and rationale — **Evaluation**

References





The IARC Monograph: What does it contain?

All pertinent epidemiological studies and cancer bioassays

- Study designs and results are detailed in tables
- Descriptions of individual studies are in text [comments in brackets]

Representative mechanistic data judged to be important by the Working Group

- Includes information on (i) toxicokinetics, (ii) representative data on the 10 key characteristics of carcinogens, (iii) data relevant to comparisons across agents and end-points, (iv) cancer susceptibility, and (v) other adverse effects
- Mechanistic and other relevant data for the agent under consideration is drawn from representative studies in humans, animals, and *in vitro*
- Written in the form of a review article [comments in brackets]

All studies must be *publicly available* (published or accepted)

- *Includes studies published in languages other than English*
- Does not consider research in progress, articles in preparation, consultant reports, or anything that is not publicly available

Each study summary should be written or reviewed by someone not associated with the study

The IARC Monographs Timeline (V. 112 example):

IARC Monographs Programme secretariat:
- Reviewing potential information sources
- Recruiting Working Group members
- Conducting literature searches
- Retrieving full text publications in PDF
- Assuring adherence to procedures

IARC Monograph Working Group members:
- Evaluating outcomes of the literature searches
- Conducting additional literature searches
- Conducting literature tagging (inclusion/exclusion)
- Reviewing selected relevant studies and evidence
- Writing assigned sections & peer-reviewing drafts

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

Meeting announced (March 2014)
- Preliminary List of Agents
- Call for Data and Experts
- Request for Observer Status
- WHO CoI form posted

Call for Experts closed (July 2014)

Request for Observer Status closed (Nov. 2014)

List of Participants announced (Jan. 2015)

Call for Data closed (Feb. 2015)

The Lancet Oncology publication (March 2015)

The IARC Monographs participants:

IARC Monographs Programme secretariat: Coordinate all aspects of the meeting

Working Group members: Write the critical reviews and develop evaluations

Invited Specialists: Have critical knowledge but also a conflicting interest [***do not participate in evaluations***]

Representatives of national and international health agencies [***do not participate in evaluations***]

Observers: Allowed to observe the meeting and not to influence its outcomes

The IARC Monographs Evaluations:
A Two-Step Process

Step 1: Sub-group review and evaluation

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

- Data for each key characteristic are "weak," "moderate," or "strong"?
- Determine whether the identified mechanisms could operate in humans

Step 2: Working Group review and evaluation during Plenary session

Overall evaluation

[*Sub-group evaluations are discussed, [illegible] and adopted*]

- ☐ Group 1 *Carcinogenic to humans*
- ☐ Group 2A *Probably carcinogenic to [illegible]*
- ☐ Group 2B *Possibly carcinogenic to [illegible]*
- ☐ Group 3 *Not classifiable as to its [illegible] to humans*
- ☐ Group 4 *Probably not carcinogenic [illegible]*

Evaluating human data (Subgroup 2)

Cancer in humans — Preamble Part B, Section 6(a)	Cancer in experimental animals	Mechanistic and other relevant data

Sufficient evidence	Causal relationship has been established Chance, bias, and confounding could be ruled out with reasonable confidence
Limited evidence	Causal interpretation is credible Chance, bias, or confounding could not be ruled out
Inadequate evidence	Studies permit no conclusion about a causal association
Evidence suggesting lack of carcinogenicity	Several adequate studies covering the full range of exposure levels are mutually consistent in not showing a positive association at any observed level of exposure Conclusion is limited to cancer sites and conditions studied

Evaluating experimental animal data (Subgroup 3)

Cancer in humans	Cancer in experimental animals — Preamble Part B, Section 6(b)	Mechanistic and other relevant data

Sufficient evidence	Causal relationship has been established through either: - Multiple positive results (2 species, studies, sexes of GLP) - Single unusual result (incidence, site/type, age, multi site)
Limited evidence	Data suggest a carcinogenic effect but: (e.g.) single study, benign tumours only, promoting activity only
Inadequate evidence	Studies permit no conclusion about a carcinogenic effect
Evidence suggesting lack of carcinogenicity	Adequate studies in at least two species show that the agent is not carcinogenic Conclusion is limited to the species, tumour sites, age at exposure, and conditions and levels of exposure studied

Evaluating mechanistic and other data (Subgroup 4)

Cancer in humans

Cancer in experimental animals

Mechanistic and other relevant data

— Preamble Part B, Section 6(c)

- Are the mechanistic data "weak," "moderate," or "strong"?

Have the mechanistic events been established? Are there consistent results in different experimental systems? Is the overall database coherent?

Has each mechanism been challenged experimentally? Do studies demonstrate that suppression of key mechanistic processes leads to suppression of tumour development?

- Is the mechanism likely to be operative in humans?

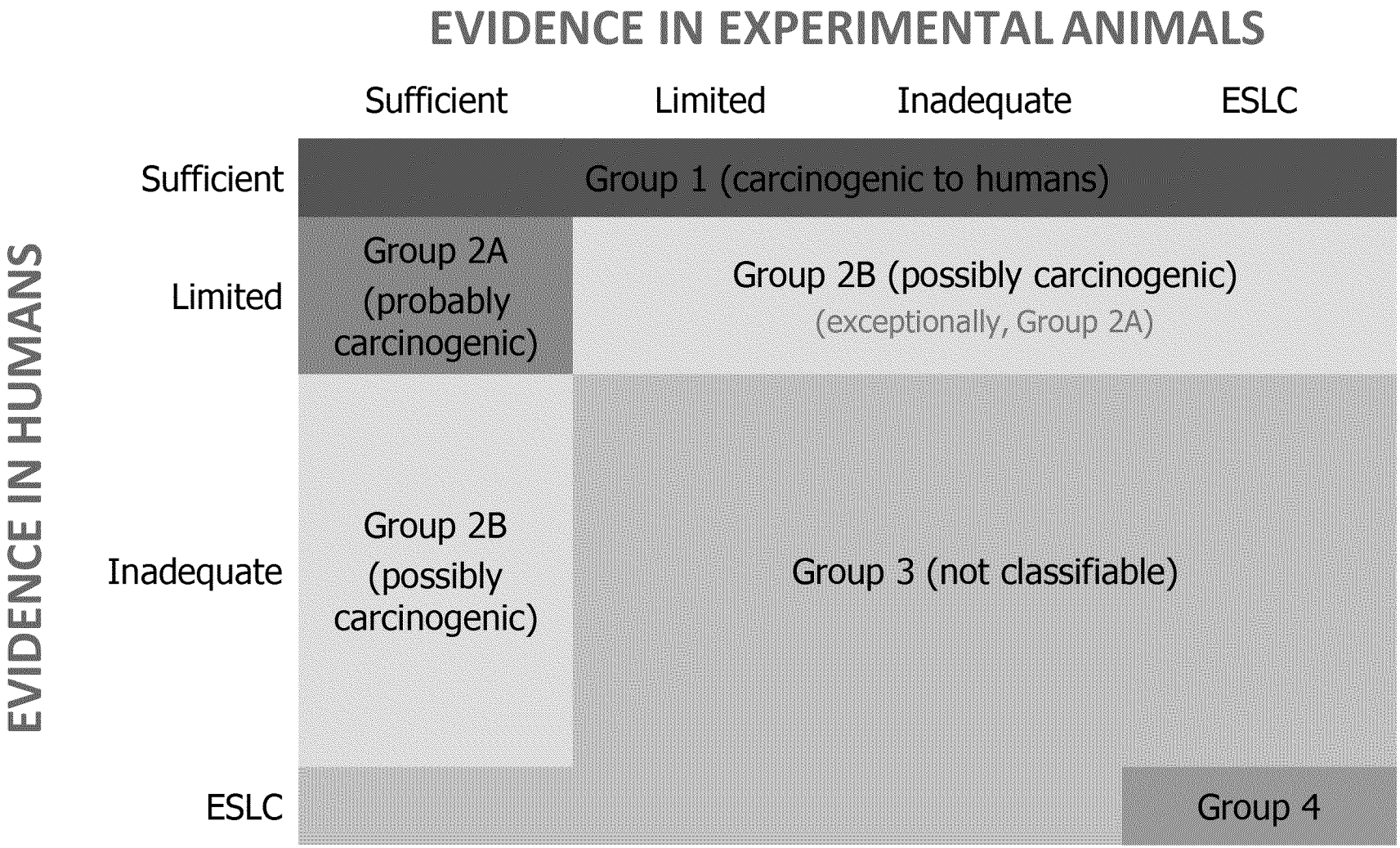
Are there alternative explanations? Could different mechanisms operate in different dose ranges, in humans and experimental animals, or in a susceptible group?

Note: an uneven level of support for different mechanisms may reflect only the resources focused on each one

Mechanistic and Other Considerations: 10 Key Characteristics of Carcinogens

Key characteristic	Example of relevant evidence
1. Electrophilic or ability to undergo metabolic activation	Parent compound or metabolite with an electrophilic structure (e.g. epoxide, quinone, etc.), formation of DNA and protein adducts
2. Genotoxic	DNA damage (DNA strand breaks, DNA-protein crosslinks, unscheduled DNA synthesis), intercalation, gene mutations, cytogenetic changes (e.g. chromosome aberrations, micronucleus formation)
3. Alters DNA repair or causes genomic instability	Alterations of DNA replication or repair (e.g. topoisomerase II, base-excision or double-strand break repair)
4. Epigenetic Alterations	DNA methylation, histone modification, microRNAs
5. Oxidative Stressor	Oxygen radicals, oxidative stress, oxidative damage to macromolecules (e.g. DNA, lipids)
6. Induces chronic inflammation	Elevated white blood cells, myeloperoxidase activity, altered cytokine and/or chemokine production
7. Immunosuppressant	Decreased immuno-surveillance, immune system dysfunction
8. Modulates receptor-mediated effects	Receptor in/activation (e.g. ER, PPAR, AhR) or modulation of exogenous ligands (including hormones)
9. Immortalization	Inhibition of senescence, cell transformation
10. Alters cell proliferation, cell death, or nutrient supply	Increased proliferation, decreased apoptosis, changes in growth factors, energetics and signaling pathways related to cellular replication or cell-cycle control, angiogenesis

In the Plenary Session, the human and experimental animal evaluations are combined



Mechanistic data can be pivotal when the human and/or experimental animal data are not conclusive

EVIDENCE IN HUMANS	EVIDENCE IN EXPERIMENTAL ANIMALS: Sufficient	Limited	Inadequate	ESLC
Sufficient	Group 1			
Limited	1 strong evidence in exposed humans Group 2A	2A belongs to a mechanistic class where other members are classified in Groups 1 or 2A Group 2B (exceptionally, Group 2A)		
Inadequate	1 strong evidence in exposed humans 2A strong evidence … mechanism also operates in humans Group 2B 3 strong evidence … mechanism does not operate in humans	2A belongs to a mechanistic class 2B with supporting evidence from mechanistic and other relevant data Group 3	2A belongs to a mechanistic class 2B with strong evidence from mechanistic and other relevant data Group 3	Group 3 4 consistently and strongly supported by a broad range of mechanistic and other relevant data
ESLC	Group 3			Group 4

Glyphosate Monograph – Human Epidemiological Evidence

Key Epidemiology Studies for Non-Hodgkin Leukemia

Literature:

- Several studies from the US Agricultural Health Study (AHS)
- Additional reports from independent case-control studies

Overall conclusion: "*Limited Evidence (non-Hodgkin lymphoma)*"

- Causal interpretation is credible
- Chance, bias and confounding could not be ruled out with reasonable confidence

Rationale for conclusion:

- US, Canadian and Swedish Case-Control Studies
  - Positive association that persisted after adjustment for other pesticides
- Agricultural Health Study
  - No additional support for association, but results do not contradict other studies

Glyphosate Monograph – Experimental Animal Evidence

- 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

Overall conclusion: "*Sufficient Evidence*"

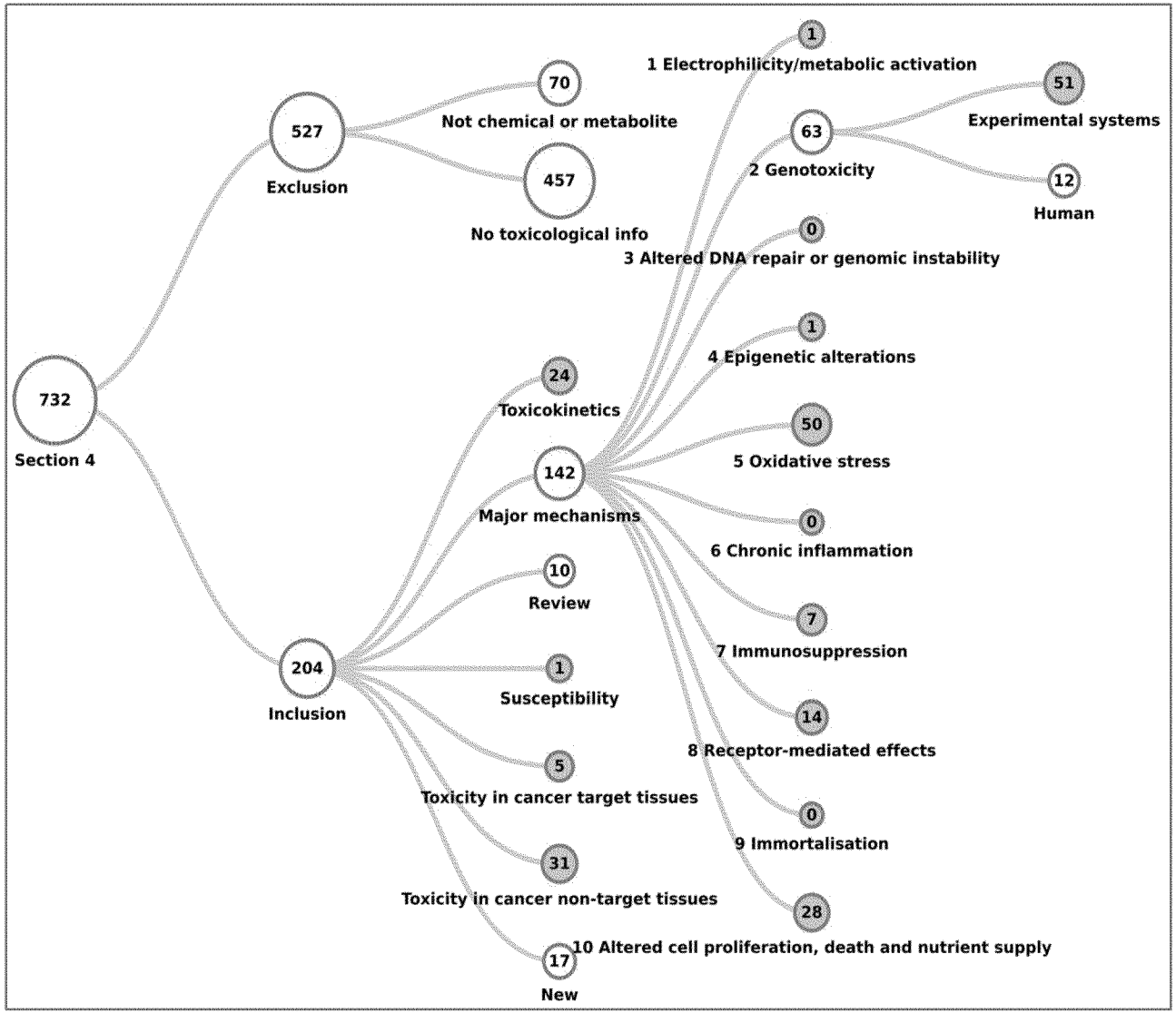
- 2 independent studies showing a significant association

Glyphosate Monograph – Mechanistic and Other Considerations:

Analysis of the Evidence for 10 Key Characteristics of Carcinogens

Systematic literature search tree for the Glyphosate Monograph:

Last searches were conducted March 2, 2015



Key characteristic
1. Electrophilic or ability to undergo metabolic activation
2. Genotoxic
3. Alters DNA repair or causes genomic instability
4. Epigenetic Alterations
5. Oxidative Stressor
6. Induces chronic inflammation
7. Immunosuppressant
8. Modulates receptor-mediated effects
9. Immortalization
10. Alters cell proliferation, cell death, or nutrient supply

Glyphosate Monograph – Mechanistic and Other Considerations:

10 Key Characteristics of Carcinogens

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

Working Group conclusion:

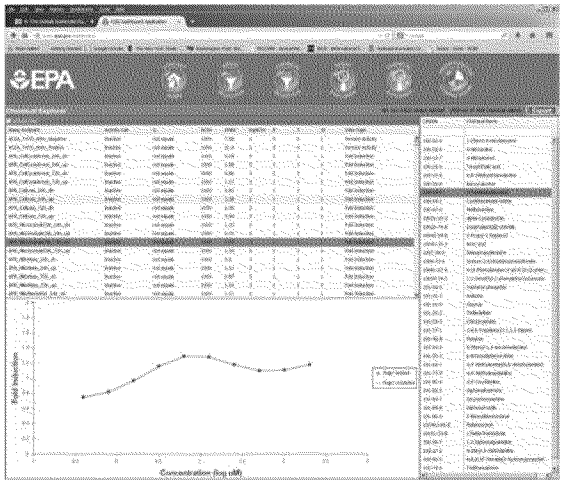
"Overall, the mechanistic data provide strong support for carcinogenicity findings of both glyphosate and glyphosate formulations. This includes strong evidence for genotoxicity and oxidative stress. There is evidence that these effects can operate in humans."

ToxCast iCSS dashboard

(http://actor.epa.gov/dashboard/)

- 821 assays
- 1860 chemicals

- Data are fully exportable



- 3 "experts" mapped each assay to 10 "key characteristics"

- 3 additional "experts" reviewed mapping and made suggestions

- Consensus cross-reference of assays to "key characteristics" and sub-categories was developed

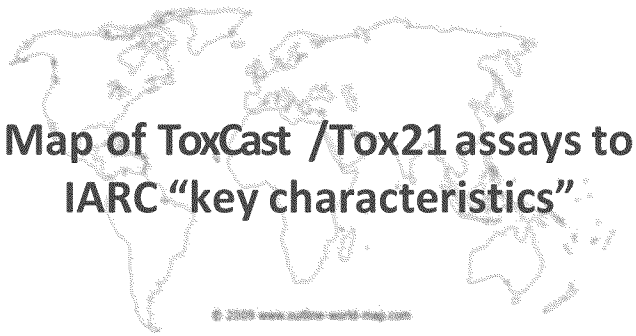
274 ToxCast /Tox21 assays mapped to "key characteristics" of known human carcinogens:

Key characteristic	1. Electrophilic or ability to undergo metabolic activation	2. Genotoxic	4. Epigenetic alterations	5. Oxidative stressor	6. Induce chronic inflammation	8. Modulate receptor-mediated effects	10. Alter cell proliferation, cell death and nutrient supply
Sub-characteristics	**31 assays:** •CYP inhibition (29) •Aromatase inhib. (2)	**9 assays:** •p53 activation	**11 assays:** •DNA binding (4) •Transformation (7)	**18 assays:** •Metalloproteinase (5) •Oxidative stress (7) •Oxidative stress marker (6)	**45 assays:** •Cell adhesion (14) •Cytokines (29) •NFkB (2)	**92 assays:** • AhR (2) • AR (11) • ER (18) • FXR (7) • Others (18) • PPAR (12) • PXR_VDR (7) • RAR (6)	**68 assays:** • Cell cycle (16) • Cytotoxicity (41) • Mitochondrial toxicity (7) • Proliferation (4)

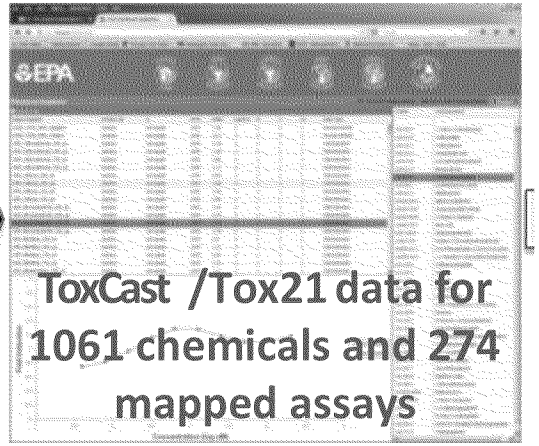
No assay coverage for these "key characteristics"

3. Alter DNA repair or cause genomic instability	7. Immunosuppressant	9. Immortalization

What did Matt and Ivan do?

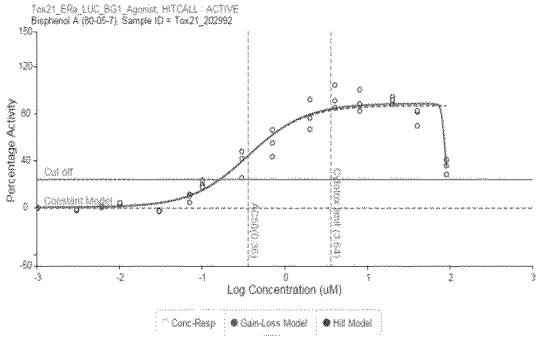


Map of ToxCast /Tox21 assays to IARC "key characteristics"



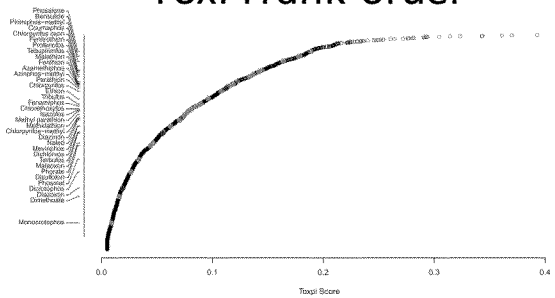
ToxCast /Tox21 data for 1061 chemicals and 274 mapped assays

Calculated "active/inactive" for each chemical

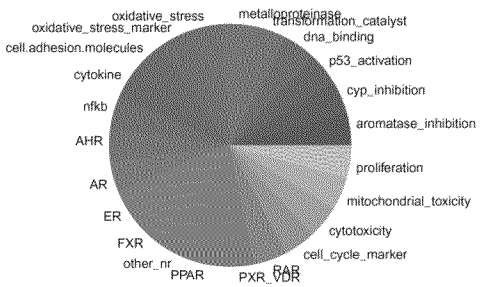


Ran ToxPi software

ToxPi rank-order



ToxPi pie charts



Reported results

Research **2010**

Endocrine Profiling and Prioritization of Environmental Chemicals Using ToxCast Data

David M. Reif,[1] Matthew T. Martin,[1] Shirlee W. Tan,[2] Keith A. Houck,[1] Richard S. Judson,[1] Ann M. Richard,[1] Thomas B. Knudsen,[1] David J. Dix,[1] and Robert J. Kavlock[1]

[1]National Center for Computational Toxicology, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, North Carolina, USA; [2]Office of Science Coordination and Policy, Office of Pollution Prevention, Pesticides and Toxic Substances, U.S. Environmental Protection Agency, Washington, DC, USA

BIOINFORMATICS **APPLICATIONS NOTE** *Vol. 29 no. 3 2013, pages 402–403 doi:10.1093/bioinformatics/bts686*

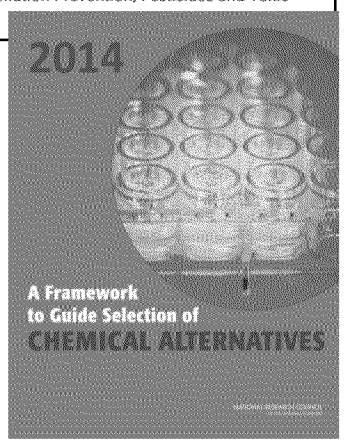
Systems biology Advance Access publication November 29, 2012

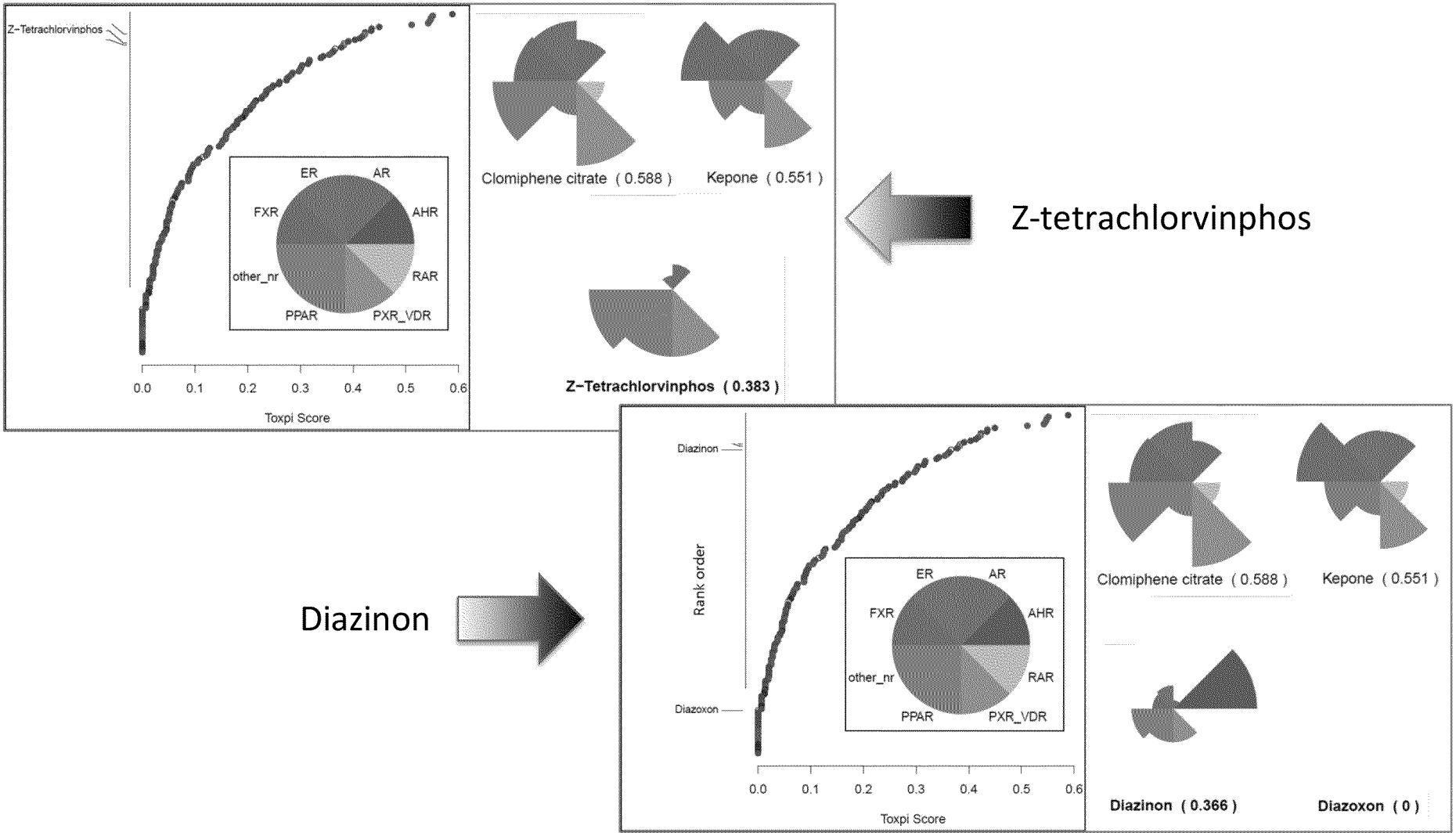
ToxPi GUI: an interactive visualization tool for transparent integration of data from diverse sources of evidence

David M. Reif[1,*], Myroslav Sypa[2], Eric F. Lock[2], Fred A. Wright[3], Ander Wilson[1], Tommy Cathey[4], Richard R. Judson[1] and Ivan Rusyn[2]

[1]National Center for Computational Toxicology, U.S. Environmental Protection Agency, Durham, [2]Departments of Environmental Sciences and Engineering and [3]Department of Biostatistics, University of North Carolina, Chapel Hill and [4]Lockheed Martin Corporation, Information Systems & Global Services, Durham, NC, USA

Associate Editor: Olga Troyanskaya **2013**



Key characteristic	8. Modulate receptor-mediated events
Sub-characteristics	**92 assays:** AhR (2); AR (11); ER (18); FXR (7); Others (18); PPAR (12); PXR_VDR (7); RAR (6)

Mono. 112 agents vs other IARC-evaluated compounds that have ToxCast /Tox21 data (n=178)