

SOT FDA Colloquia on Emerging Toxicological Science Challenges in Food and Ingredient Safety



**Contemporary
Issues in Risk
Assessment**

June 17, 2015



SOT FDA Colloquia on Emerging Toxicological Science Challenges in Food and Ingredient Safety

Identification and Selection of the Evidence Base for Human Health Assessments

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Conflict of Interest Statement

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



Outline

- Background to systematic review
- A protocol for cancer hazard identification: the *Preamble* to the IARC Monographs
- Identifying and selecting relevant literature: experience using HAWCproject.org
 - Case example: volume 112 (March, 2015)
 - Capturing identified studies into tabular and narrative summaries
- Future opportunities and conclusions



Key concepts: Hazard vs. Risk

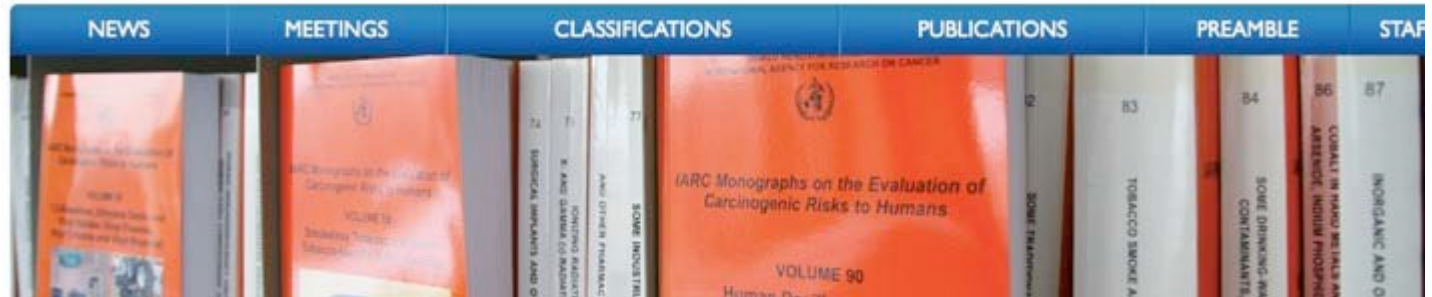
**Hazard
Identification**

International Agency for Research on Cancer



World Health
Organization

English | Français



Identify causes of human cancer: chemicals, complex mixtures, occupational exposures, physical and biological agents, lifestyle factors

**Risk
assessment**

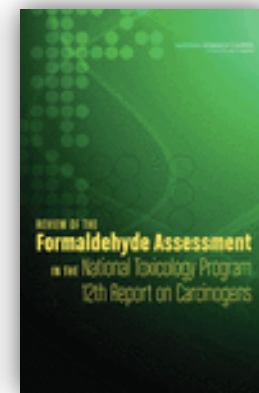
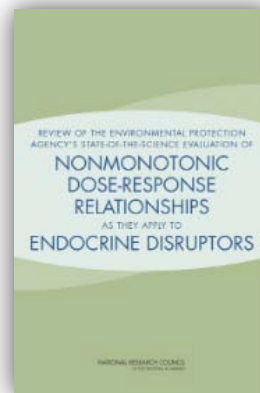
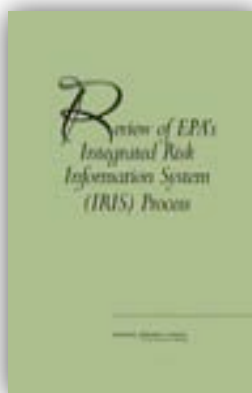
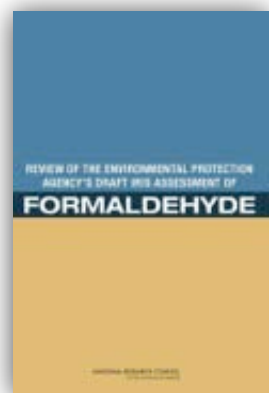


Evaluate risks: the probability that cancer will occur, taking into account the *level of exposure* to the agent



Key Recommendations: Evidence Identification, Evaluation, Synthesis

US National Research Council:



World Health Organization:

Use of evidence in WHO recommendations

Andrew D Oxman, John N Lavis, Atle Fretheim

Summary

Background WHO regulations, dating back to 1951, emphasise the role of expert opinion in the development of recommendations. However, the organisation's guidelines, approved in 2003, emphasise the use of systematic reviews for evidence of effects, processes that allow for the explicit incorporation of other types of information (including values), and evidence-informed dissemination and implementation strategies. We examined the use of evidence.



Lancet 2007; 369: 1883-89
Published Online May 9, 2007
DOI:10.1016/S0140-6736(07)60675-8

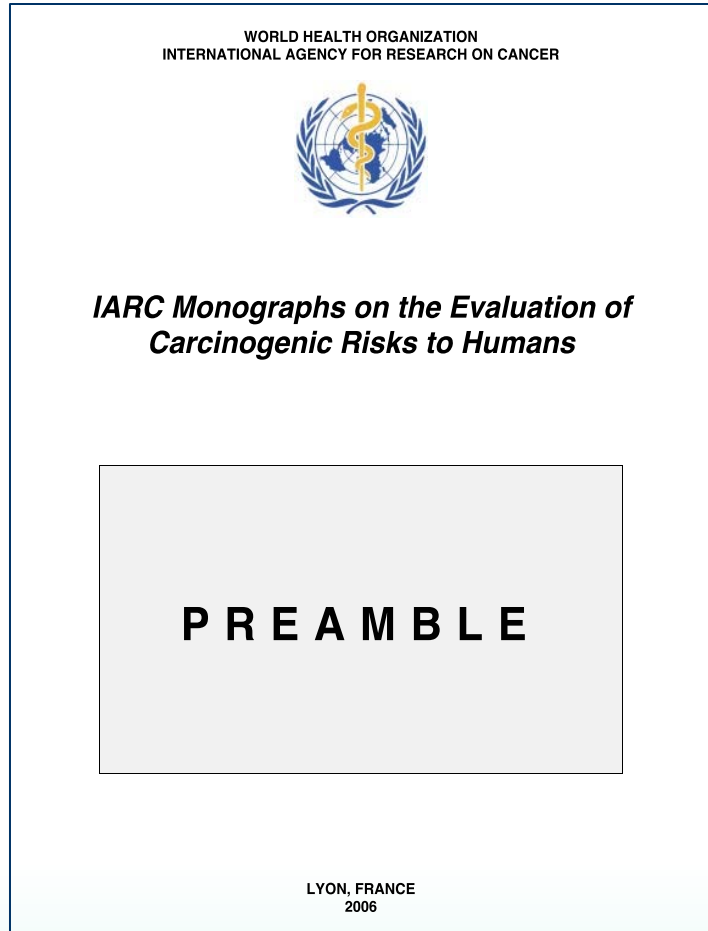
“Evidence,
evidence,
evidence”



- Document studies **identified, excluded and included**
- Use templates for **evidence display tables**
- **Establish protocols** for evaluation and synthesis



IARC Monographs Preamble: Cancer Hazard Identification Protocol



A. GENERAL PRINCIPLES AND PROCEDURES

1. Background
2. Objective and scope
3. Selection of agents for review
4. Data for the Monographs
5. Meeting participants
6. Working procedures

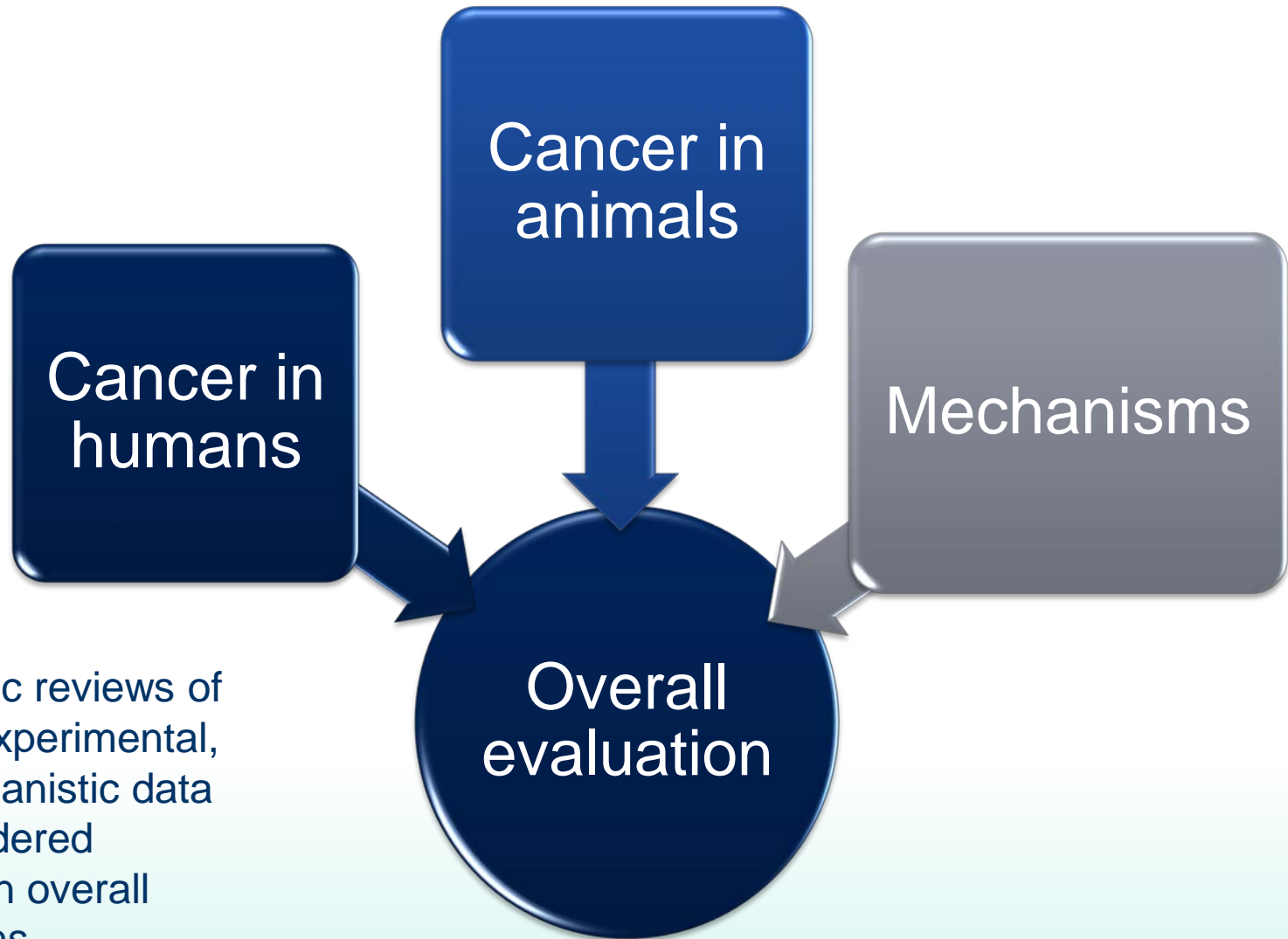
B. SCIENTIFIC REVIEW AND EVALUATION

1. Exposure data
2. Studies of cancer in humans
3. Studies of cancer in experimental animals
4. Mechanistic and other relevant data
5. Summary
6. Evaluation and rationale

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



Scientific Review and Evaluation

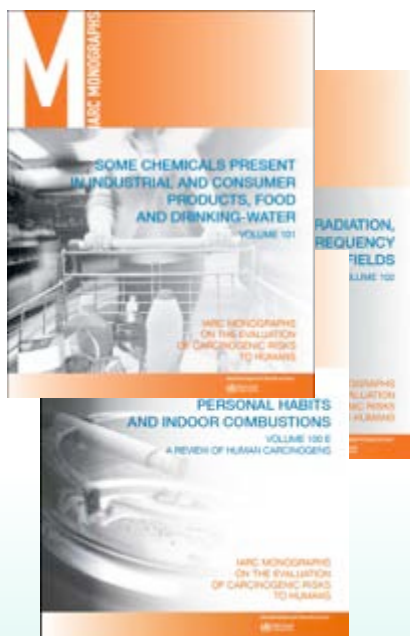


Systematic reviews of human, experimental, and mechanistic data are considered together in overall evaluations

How to Identify Relevant Published Studies?



- Literature collected by IARC; meeting participants are expected to supplement the IARC literature searches with their own searches



Considerations:

1. Monographs cite 100s to 1000s of studies
2. Evolution in experience over time:
 - Mail box(es) of papers (1970s-1980s era)
 - Electronic reference list, PDFs, indexed reference database, MyNCBI searches (early 2000s)

Challenges:

1. How, when, where were searches performed?
 - So many mechanisms, so little time: how to search systematically?
2. How to capture studies from “hand searching”?
3. Which studies were included/excluded, and why?

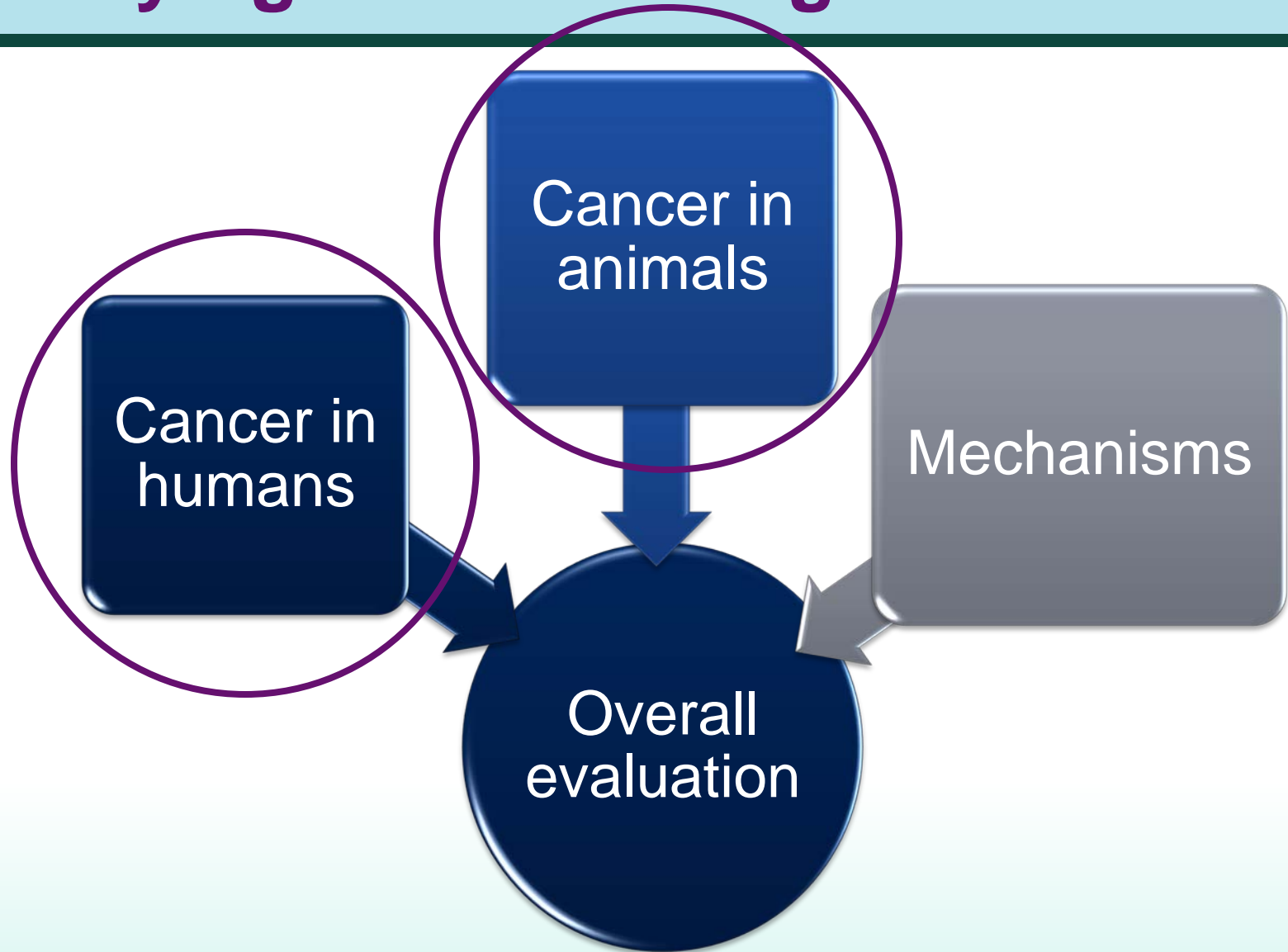


Outline

- Background to systematic review
- A protocol for cancer hazard identification: the *Preamble* to the IARC Monographs
- **Identifying and selecting relevant literature: experience using HAWCproject.org**
 - **Case example: volume 112 (March, 2015)**
 - Capturing identified studies into tabular and narrative summaries
- Future opportunities and conclusions



Identifying and Selecting the Literature



How, When, Where Were Searches Performed: *Cancer in Humans*



| | |
|-----------------|---|
| Description | PubMed search for epidemiologic studies of cancer in humans exposed to parathion |
| Search Type | Search |
| Search Database | PubMed |
| Search Text | ((("Parathion"[Mesh]OR Parathion[Text Word] OR "parathion" [All Fields]) AND (("Neoplasms"[Mesh] OR neoplasms OR cancer OR carcinogenic OR tumor)) AND ("Epidemiology"[Mesh] OR "Epidemiologic Studies"[Mesh] OR epidemiolog* OR case-referent OR "Occupational Exposure"[Mesh] OR workers OR cohort)) |
| Created | Oct. 23, 2014, 10:14 a.m. |
| Last Updated | Oct. 23, 2014, 10:14 a.m. |

Literature Tagging Statistics

| | |
|------------------|---|
| Total References | 7 |
| Total Tagged | 7 |
| Total Untagged | 0 |

Reference details

[View by tag](#)

[Visualization](#)

Results from queries

| Date last executed | Total references found | References added | References removed |
|---------------------------|------------------------|------------------|--------------------|
| March 2, 2015, 3:16 a.m. | 7 | 0 | 0 |
| Feb. 11, 2015, 3:58 a.m. | 7 | 0 | 0 |
| Oct. 23, 2014, 10:14 a.m. | 7 | 7 | 0 |



How, When, Where Were Searches Performed: *Cancer in Animals*



| | |
|-----------------|--|
| Description | Section 3 Cancer in animals, parathion or paraoxon |
| Search Type | Search |
| Search Database | PubMed |
| Search Text | ("parathion"[All Fields] OR "paraoxon"[All Fields] NOT "methyl parathion"[All Fields]) AND "neoplasms"[MeSH Terms] AND "animals"[MeSH Terms:noexp] |
| Created | Oct. 23, 2014, 11:30 a.m. |
| Last Updated | Nov. 14, 2014, 3:19 a.m. |

Literature Tagging Statistics

| | |
|------------------|----|
| Total References | 31 |
| Total Tagged | 31 |
| Total Untagged | 0 |

Reference details

[View by tag](#)

[Visualization](#)

Results from queries

| Date last executed | Total references found | References added | References removed |
|---------------------------|------------------------|------------------|--------------------|
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| Feb. 11, 2015, 3:57 a.m. | 31 | 0 | 0 |
| Oct. 23, 2014, 11:30 a.m. | 31 | 31 | 0 |



Inclusion/Exclusion of Studies: *Cancer in Humans, Cancer in Animals*



Using “Tags” to track disposition of each identified study

- Function as exclusion criteria for any excluded studies
- Document the evidence stream(s) pertinent for included studies
- Can be applied by Working Group (v112) or Secretariat for further Working Group review (v113)

Tags used in assessment

- Section 1
- Section 2
- Exclusion
 - Case report/series
 - Cross-sectional study
 - Ecological study
 - No data for this agent
 - No primary data (review/commentary)
 - Not cancer outcome
- Inclusion
 - Case-control study
 - Cohort study
- Section 3
- Exclusion
 - Cancer endpoints not evaluated
 - Not chemical or metabolite
 - No primary data
- Inclusion



Visualization- Included/Excluded *Cancer in Humans, Cancer in Animals*



Statistics

Total References 1217 (1158 from searches, 59 from imports)

Total Tagged 1217

Total Untagged 0

Reference details

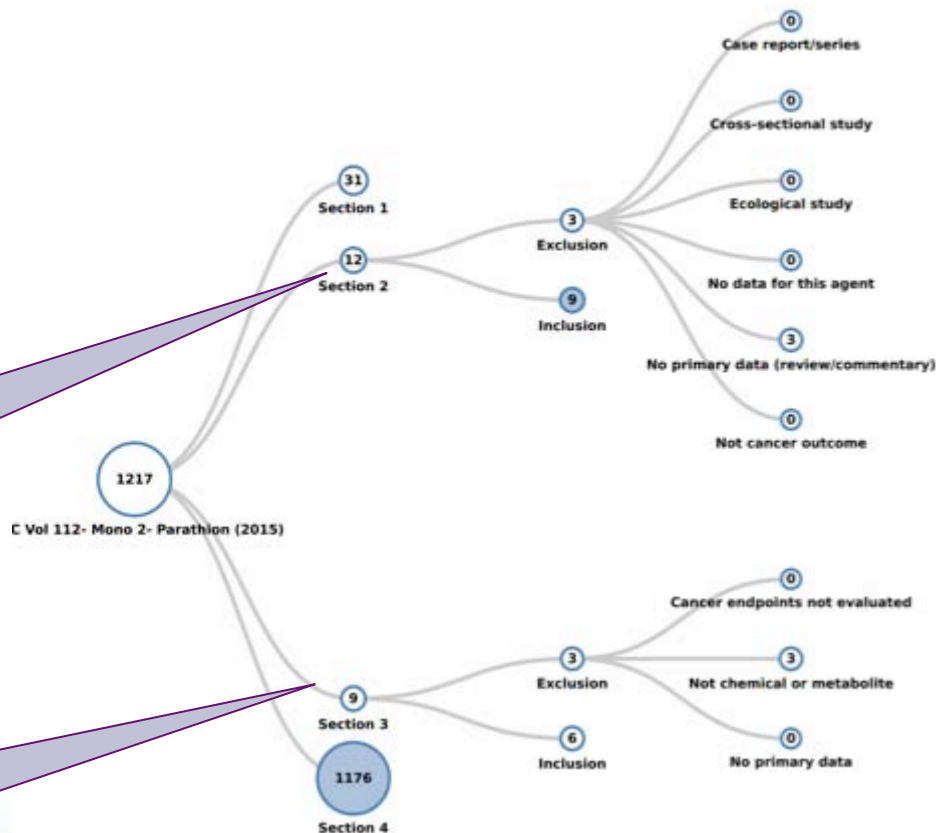
View by tag

Visualization

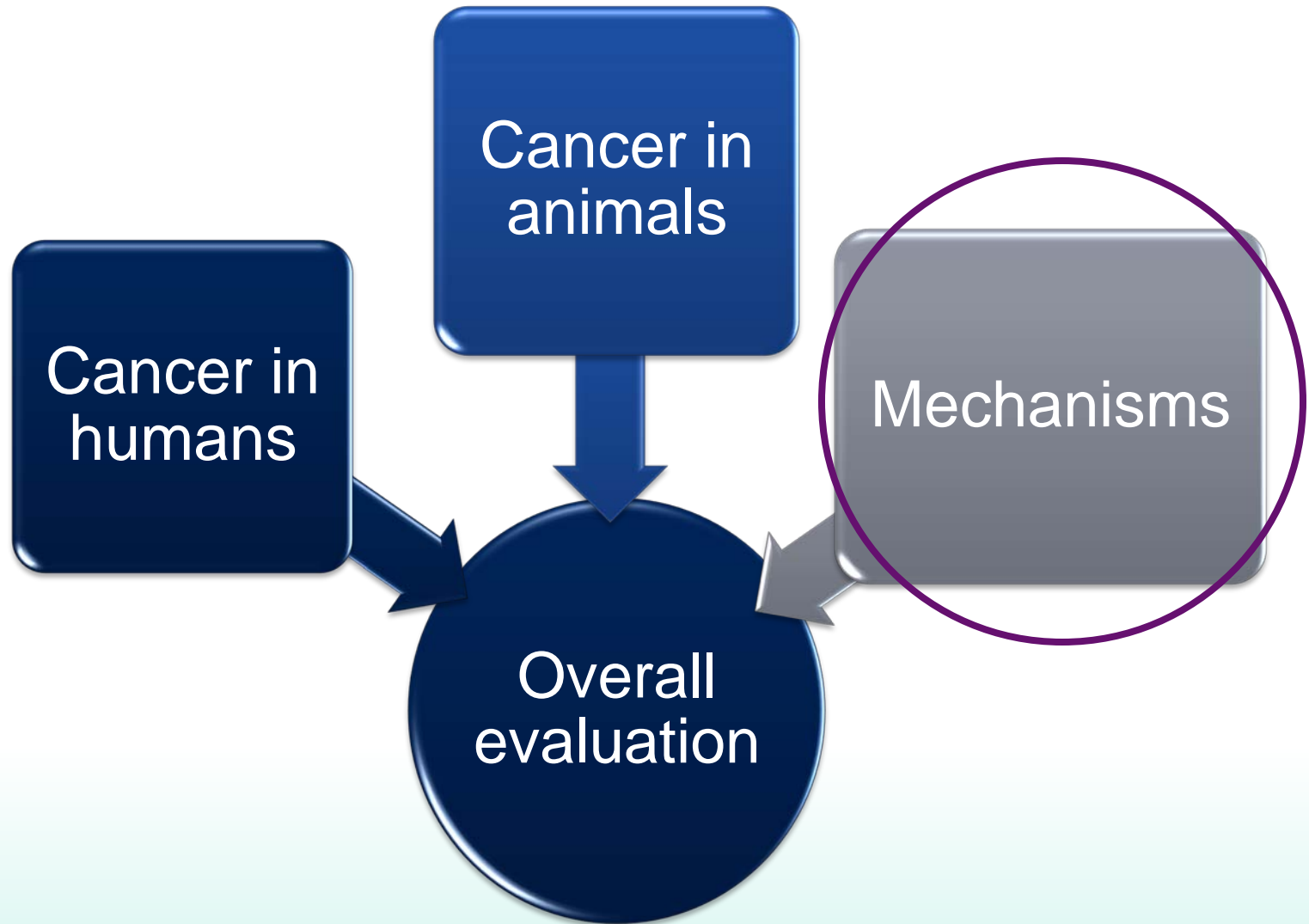
Search

Cancer in Humans

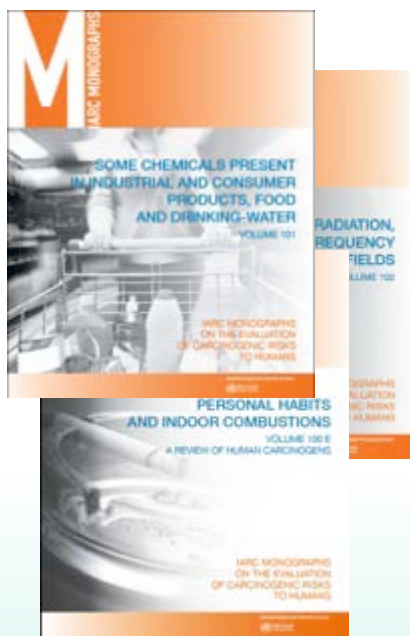
Cancer in Animals



Identifying and Selecting the Literature



Mechanistic Studies: Special Challenges

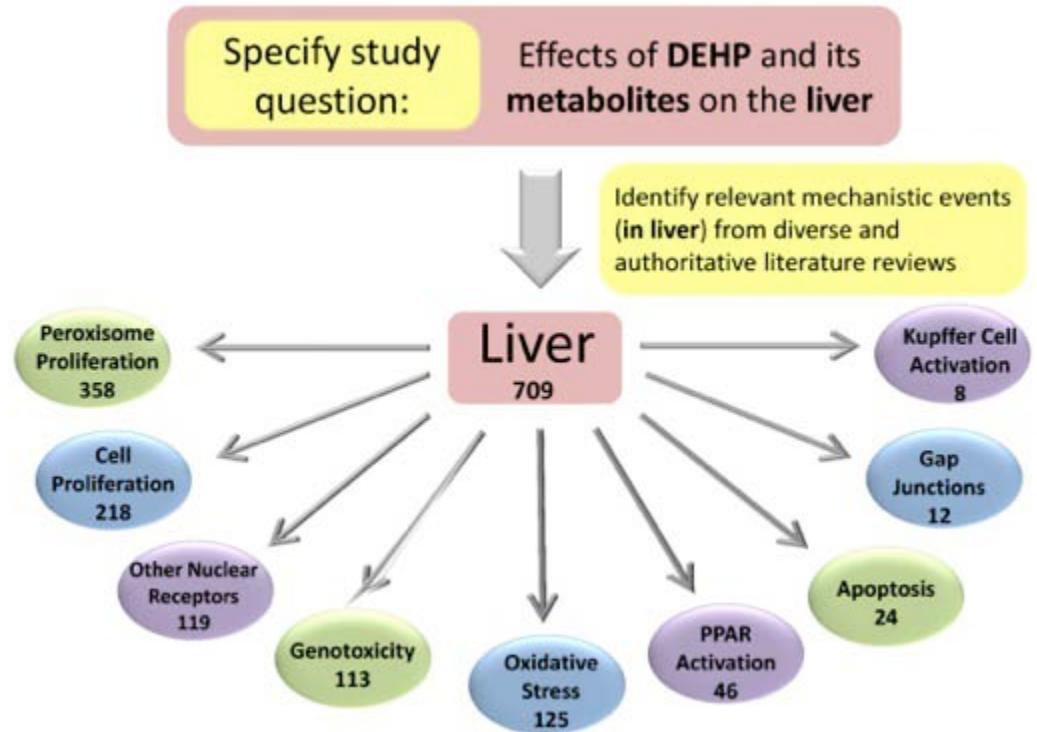
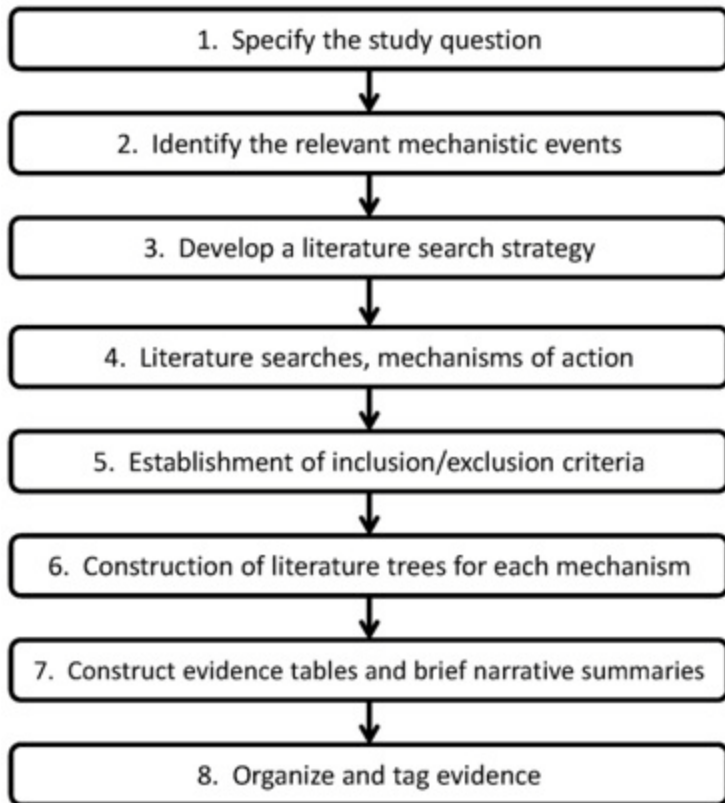


Insights from Volume 100 and Recent Advisory Groups:

- Monographs consider representative studies to give a concise description of the relevant data and issues
- Increasing volume and complexity of mechanistic literature
- **Systematic identification of mechanistic data is needed (i.e., pertinent to 10 key characteristics of carcinogens)**
- Analysis of high-throughput/-content data (including from curated government databases) is encouraged



How to Systematically Identify Mechanistic Studies?



Source: ME Kushman, A Kraft, KZ Guyton, WA Chiu, SL Makris, and Ivan Rusyn. A systematic approach for identifying, evaluating, and presenting mechanistic evidence in human health assessments. *Regul Toxicol Pharmacol.* 2013 Nov;67(2):266-77.



How, When, Where Were Searches Performed: *Mechanisms*



| | |
|-----------------|--|
| Description | Section 4.2.1-4.2. Genotoxicity of parathion and the primary P450 metabolite, paraoxon |
| Search Type | Search |
| Search Database | PubMed |
| Search Text | ("parathion"[MeSH Terms] OR "parathion"[All Fields]) OR ("paraoxon"[MeSH Terms] OR "paraoxon"[All Fields]) OR ("methyl parathion"[MeSH Terms] OR "methyl parathion"[All Fields]) AND ("Mutagenesis"[MeSH Terms] OR "Mutagenesis"[All Fields]) OR ("Cytogenetic Analysis"[Mesh] OR "Mutagens"[Mesh] OR "Oncogenes"[Mesh] OR "Carcinogenesis"[Mesh] OR "Carcinogenesis"[All Fields]) OR "Carcinogenesis" OR "genetic toxicology" OR "strand break" OR "unscheduled DNA synthesis" OR "SCE" OR "chromatid" OR "micronucleus") |
| Created | Aug. 13, 2014, 9:08 a.m. |
| Last Updated | Sept. 29, 2014, 5:40 a.m. |

And similar searches, to cover 10 "key characteristics"

Literature Tagging Statistics

| | |
|-------------------|---|
| Total References | 290 |
| Total Tagged | 290 |
| Total Untagged | 0 |
| Reference details | View by tag Visualization |

Results from queries

| Date last executed | Total references found | References added | References removed |
|--------------------------|------------------------|------------------|--------------------|
| March 2, 2015, 3:17 a.m. | 290 | 1 | 0 |
| Feb. 11, 2015, 7:31 a.m. | 289 | 3 | 0 |
| Aug. 13, 2014, 9:09 a.m. | 286 | 286 | 0 |



How to Capture Studies from “Hand Searching”?



References for IARC Vol 112- Mono 2- Parathion (2015)

Statistics

| | |
|------------------|---|
| Total References | 1217 (1158 from searches 59 from imports) |
| Total Tagged | 1217 |
| Total Untagged | 0 |

Prior evaluation in Volume 30 (1983)

Reference details

[View by tag](#) [Visualization](#) [Search](#)

Articles from the archives

Actions

| | |
|-----------------|---|
| Description | Articles cited in prior IARC Monographs (volume 30, supplement 7) |
| Search Type | Import |
| Search Database | PubMed |
| Search Text | 15420172, 4772941, 13862642, 14908051, 13062058, 6993936, 13206448, 101966, 740515, 461116, 537865, 119496, 4216877, 1394141, 1268370, 888817, 5031564, 14199205, 6047239, 7089924, 13701584, 13894842, 13946141, 5151664, 15393020, 1154409, 886156, 14157576, 5837408, 20604392, 944415, 609510, 583446, 14404260, 4279630, 4714332, 81664, 5123154, 1208189, 857241, 14160507, 4357387, 5943299, 900999, 420356, 7038805, 5906458, 4941660, 1252255, 12830227, 13502056, 7364572, 4306871, 337436, 874587, 13838667, 1269562, 660561, 214351, 539831, 13582239, 6024487, 5478556, 1125467, 1190838, 708924, 901000 |
| Created | Nov. 14, 2014, 7:44 a.m. |
| Last Updated | Nov. 14, 2014, 7:44 a.m. |

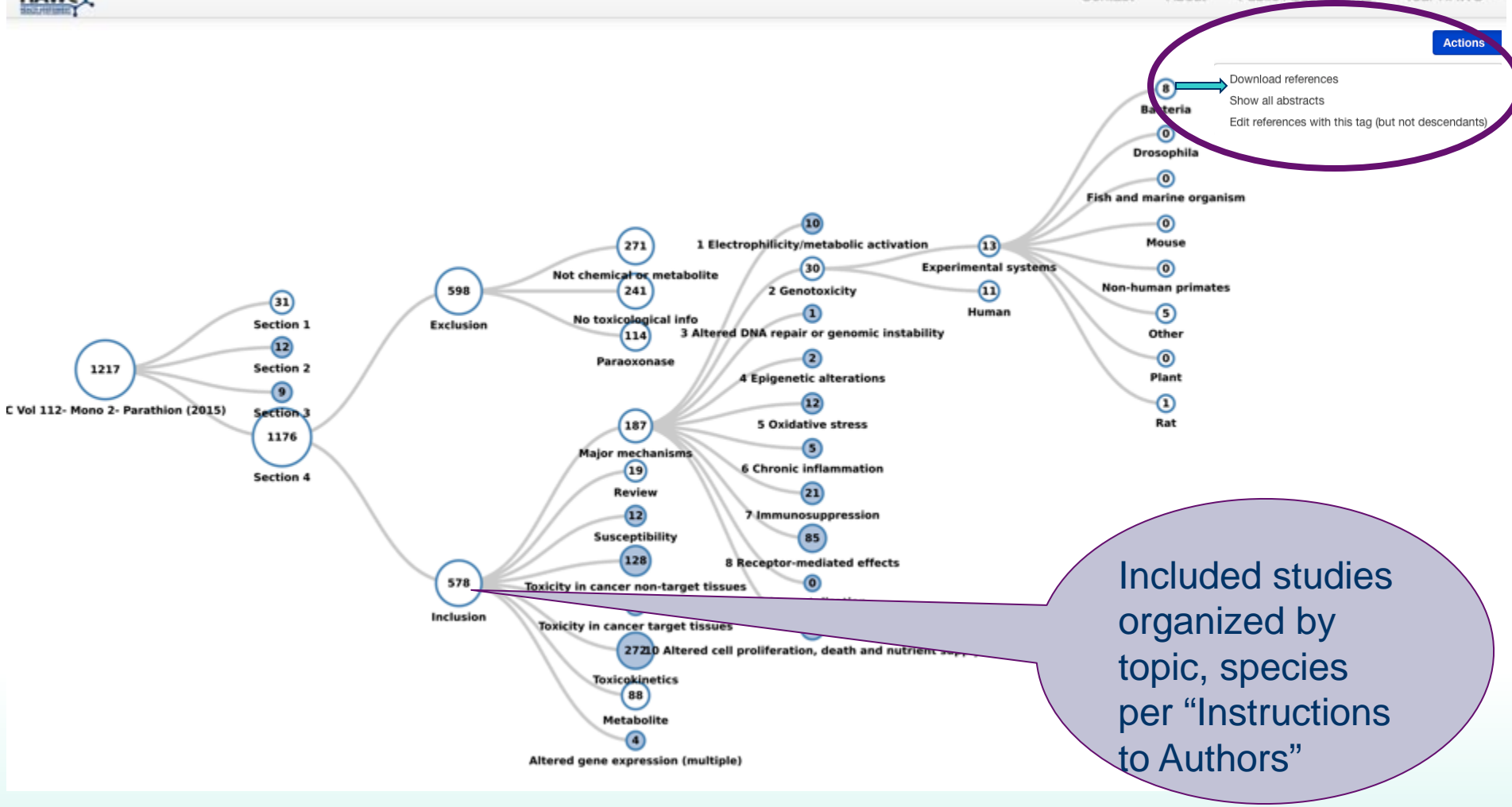


Visualization- Included/Excluded Mechanistic Studies



Actions

Download references
Show all abstracts
Edit references with this tag (but not descendants)



Included studies organized by topic, species per "Instructions to Authors"



What about Additional Sources of (Publicly Available) Data?

Cancer in Humans:

- Published studies: Public “call for data” may identify recent publications

Cancer in Animals:

- *“Data from governmental reports that are publicly available”* (US NTP, Japan JBRC, etc): Must provide sufficient detail for independent assessment

Mechanisms:

- Published studies (frequently voluminous)
- *“Data from governmental reports that are publicly available”*
 - Included in bioassay reports or databases (e.g., ToxRefDB)
 - High-throughput testing databases (e.g., Tox21)



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Step 1: Making an Outline

International Agency for Research on Cancer

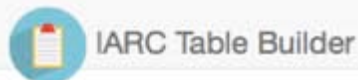


- PAR. 4.2. Mechanisms of carcinogenesis + ↑ ↓ ↻ ✖
 - PAR. 4.2.1 Genetic and related effects + ↑ ↓ ↻ ✖
 - PAR a). Humans + ↑ ↓ ↻ ✖
 - PAR b). Experimental systems + ↑ ↓ ↻ ✖
 - PAR. 4.2.2 Receptor-mediated effects + ↑ ↓ ↻ ✖
 - PAR a). Humans + ↑ ↓ ↻ ✖
 - PAR b). Experimental systems + ↑ ↓ ↻ ✖
 - PAR. 4.2.3 Oxidative stress, inflammation and imr
 - PAR a). Humans + ↑ ↓ ↻ ✖
 - PAR b). Experimental systems + ↑ ↓ ↻ ✖
 - PAR. 4.2.4 Altered cell proliferation or death + ↑ ↓ ↻ ✖
 - PAR a). Humans + ↑ ↓ ↻ ✖
 - PAR b). Experimental systems + ↑ ↓ ↻ ✖
 - PAR. 4.2.5 Other mechanisms + ↑ ↓ ↻ ✖
- PAR. 4.3. Data relevant to comparisons across agen
 - PAR. 4.3.1. Humans + ↑ ↓ ↻ ✖
 - PAR. 4.3.2. Experimental systems + ↑ ↓ ↻ ✖
- PAR. 4.4. Cancer susceptibility data + ↑ ↓ ↻ ✖
- PAR. 4.5. Other adverse effects + ↑ ↓ ↻ ✖
 - PAR. 4.5.1. Humans + ↑ ↓ ↻ ✖
 - PAR. 4.5.2. Experimental systems + ↑ ↓ ↻ ✖

- Online publication tools can facilitate contributions and peer reviews from multiple authors
- Assignments reflect topics, amount of literature to be covered, expertise
- Many other options:
 - Open Monograph (open source)
 - SharePoint
 - Structured folders on (shared) drive/cloud
 - HAWCProject.org- direct link to dose-response



Step 2: Including All Relevant Studies into the Database



Mono 2 Parathion: References

Actions ▾

- + Add a reference
- ⬆ Bulk upload
- 📄 Download Excel

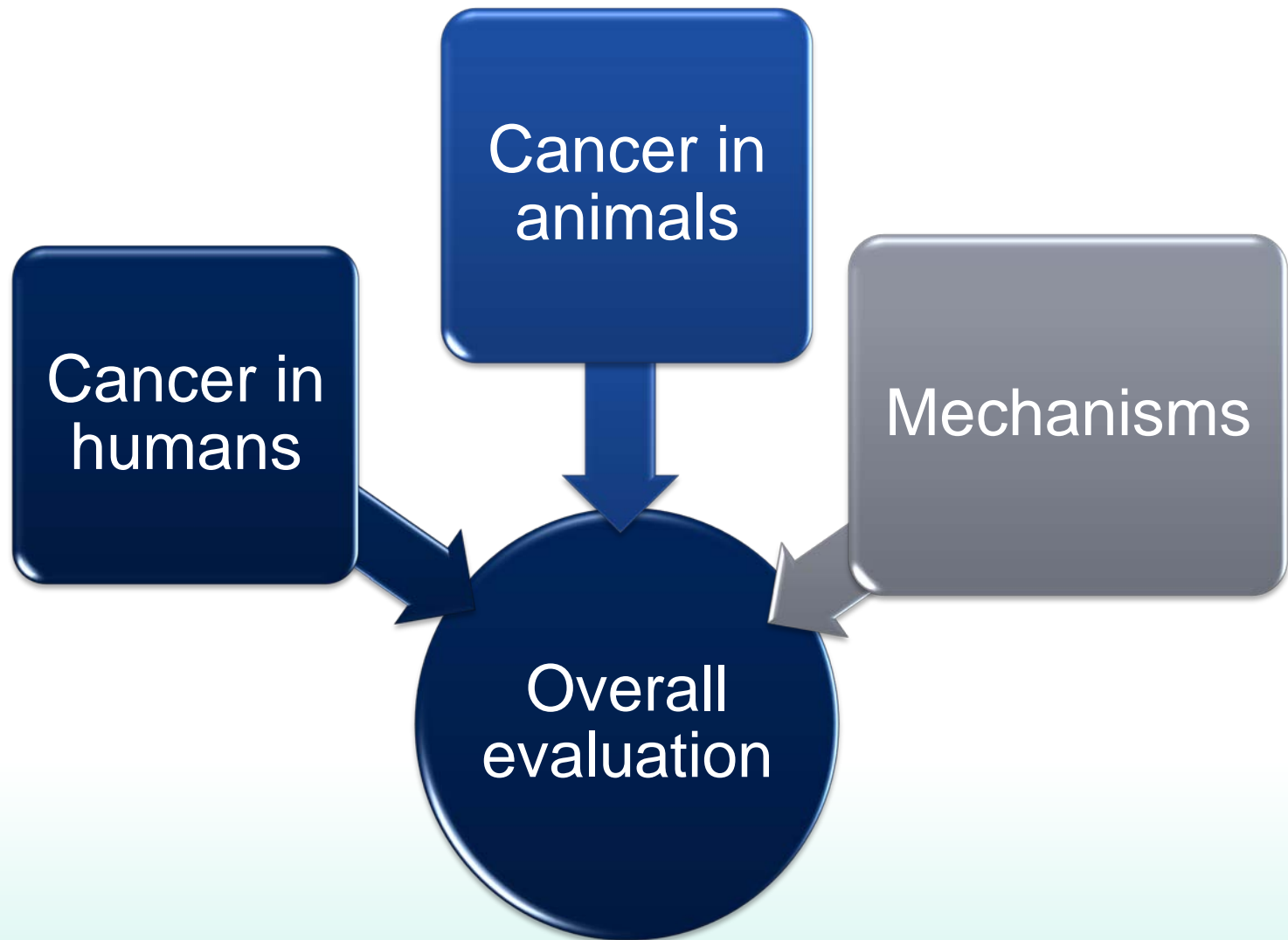
| Short Reference Name | Full Citation |
|---|--|
| ALDRIDGE (1950) | ALDRIDGE WN. Some properties of specific cholinesterase inhibitors. Reference to the mechanism of action by cholinesterase inhibition by diethyl phosphorothioate (E 605) and analogues.. <i>Biochem J</i> . 1950 Aug;44(2):281-9. PubMed PMID: 13700000. |
| ARTERBERRY et al. (1961) | ARTERBERRY JD, DURHAM WF, ELLIOTT RA. The effect of paraoxon on the excretion of 2,4-dinitrophenol.. <i>Arch Environ Health</i> . 1961;16:1-10. PubMed PMID: 13700000. |
| Abbas and Hayton (1997) | Abbas R, Hayton WL. A physiological model for paraoxon in rainbow trout. <i>Toxicol Appl Pharmacol</i> . 1997 Jul;145(1):192-200. PubMed PMID: 9200000. |
| Abbas et al. (1996) | Abbas R, Schultz IR, Doddapaneni S, Hayton WL. The effect of paraoxon in rainbow trout after intraperitoneal administration and water exposure.. <i>Toxicol Appl Pharmacol</i> . 1996 Jun;134(2):100-10. PubMed PMID: 8560474. |
| Adigun et al. (2010) | Adigun AA, Wrench N, Levin ED, Seidler FJ, Slotkin TA. Neonatal parathion exposure and interaction with a high fat diet in adulthood: Adenylyl cyclase-mediated cell signaling in heart, liver and cerebellum.. <i>Brain Res Bull</i> . 2010 Aug;87(8):1000-10. PubMed PMID: 20074626. |
| Agarwal et al. (1982) | Agarwal DK, Misra D, Agarwal S, Seth PK, Kohli JD. Influence of sex hormones on the cholinesterase activity of parathion and paraoxon in plasma, erythrocytes, and brain.. <i>J Toxicol Environ Health</i> . 1982;7(1):1-10. PubMed PMID: 7097796. |
| Agyeman and Sultatos (1998) | Agyeman AA, Sultatos LG. The actions of the H2-blocker cimetidine on the toxicology of paraoxon in rainbow trout. <i>Toxicology</i> . 1998 Jul 17;128(3):207-18. PubMed PMID: 9750043. |

Bulk upload of HAWC “included” studies (with links to PubMed)

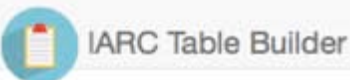
Manually add references to “government reports”



Step 3: Developing Tabular and Narrative Summaries



Capturing Data into Tables: *Cancer in Humans*



Volume 112: Mono 2 Parathion

| Reference, location, follow-up/enrollment period, study-design | Population size, description, exposure assessment method | Organ site (ICD code) | Exposure category or level | Exposed cases/deaths | Risk estimate (95% CI) | Covariates controlled | Comments |
|--|--|-----------------------|---|----------------------|------------------------|-------------------------------------|---|
| Waddell et al. (2001) USA Kansas (1979-84) Minnesota (1983-84) C | Cases: 748 (83%); Cases from tumour | NHL | Ever used parathion in agriculture Ever used parathion | 5 | 2.9 (0.9-9.7) | age, state, proxy/direct respondent | Strengths: Large sample size; Targeted populations allowed study of agricultural pesticides; Comprehensive assessment of covariates and confounders Limitations: Limited power for rare exposures; Multiplicity of exposures; Proxy responses for deceased (though addressed in design analysis) |

Pre-defined, required/optional fields with drop-down lists

Ability to toggle between numbers and plots

Working Group comments captured



Capturing Data into Tables: *Cancer in Animals*



Example animal bioassay evidence

Volume 106: Trichloroethylene

| Study design | Route | | |
|---|---|---|--|
| Species, strain (sex) | Agent tested, purity | | |
| Age at start | Vehicle | | |
| Duration | Dose(s) | | |
| Reference | # animals at start | Results | Significance |
| | # surviving animals | | |
| Full carcinogenicity Mouse , B6C3F1 (M) 6-8 wk old 110 wk Radican et al. (2008) | Skin application Trichloroethylene, >99.9% acetone 0, 10, 50 mg/kg bw 2x/d for 103 wk 20, 50, 50 19, 46, 32 | skin: squamous cell carcinoma Tumour incidence: 0/19, 7/49*, 17/42** Tumour multiplicity: NR, 0.9, NR Total tumours: NR, 11, 24 | *p<0.05; **p<0.001; Fisher exact test |

Actions ▾

- + Create new row
- ☰ Reorder rows
- ↗ Make full-screen
- 📄 Download Excel**
- 📄 Download Word: HTML table recreation**
- ↗ Show all rows
- 🚪 Toggle QA flags

Principal strengths:

- Covers most of the life span.
- Studies in both males and females.

Principal limitations:

- Inadequate numbers of animals.
- Only one dose group.

Other comments:



Capturing Data into Tables: *Mechanistic Data*



Genotoxicity evidence Special characters

Hover-over field labels for more descriptive text. Fields marked with an asterisk (*) are required.

Reference* **Data class*** **Agent***
[Pesch et al. \(2000\)](#)

Species* **Strain*** **Sex*** **Tissue***

Endpoint* **Endpoint test*** **Route*** **Duration*** **Dosing regimen***

Result* **LEC or HIC** **Dosing units*** **Doses tested***

Comments
Statistical methods not provided for significance determination

Dropdown options change according to assay system, endpoint

Dose, duration can be captured

Results can be sorted by any field



Narrative Summaries: Address Pre-Specified Decision Criteria

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



The Final Step: Integrating Evidence to Reach Overall Conclusion

EVIDENCE IN EXPERIMENTAL ANIMALS

Sufficient

Limited

Inadequate

EVIDENCE IN HUMANS

Sufficient

Group 1 (*carcinogenic to humans*)

Limited

Group 2A
(*probably carcinogenic*)

Group 2B (*possibly carcinogenic*)
(exceptionally, Group 2A)

Inadequate

Group 2B
(*possibly carcinogenic*)

Group 3 (*not classifiable*)



The Final, Final Step: Bringing in Mechanistic Data

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



Summary

- Systematic review is fundamental in cancer hazard identification
- The *Preamble* to the IARC Monographs is a published protocol for who, what, how and when (and even where!) evaluations are conducted
- On-line tools can aid:
 - Identifying and managing a voluminous and complex scientific literature
 - Alignment of tabular presentations with “strength of evidence” conclusions



Acknowledgments

SOT/FDA Organizers

Betty Eidemiller (SOT)

Suzy Fitzpatrick (FDA)

Allen Rudman (FDA)

Andy Shapiro, MS
(NIEHS/NTP)

The IARC Monographs
Volume 112 Working Group

The IARC Monographs Staff

