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

Contemporary Issues in Risk Assessment

June 17, 2015
Identification and Selection of the Evidence Base for Human Health Assessments

Kate Z. Guyton, PhD DABT
Senior Toxicologist
Monographs Programme
International Agency for Research on Cancer
World Health Organisation
Lyon, FRANCE
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

Risk assessment

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

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

World Health Organization:
- "Evidence, evidence, evidence"

Use of evidence in WHO recommendations

SOT FDA Colloquia on Emerging Toxicological Science Challenges in Food and Ingredient Safety
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
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](http://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

Overall evaluation

Cancer in humans

Cancer in animals

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

<table>
<thead>
<tr>
<th>Description</th>
<th>PubMed search for epidemiologic studies of cancer in humans exposed to parathion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Search Type</td>
<td>Search</td>
</tr>
<tr>
<td>Search Database</td>
<td>PubMed</td>
</tr>
<tr>
<td>Created</td>
<td>Oct. 23, 2014, 10:14 a.m.</td>
</tr>
<tr>
<td>Last Updated</td>
<td>Oct. 23, 2014, 10:14 a.m.</td>
</tr>
</tbody>
</table>

**Literature Tagging Statistics**

- Total References: 7
- Total Tagged: 7
- Total Untagged: 0

**Results from queries**

<table>
<thead>
<tr>
<th>Date last executed</th>
<th>Total references found</th>
<th>References added</th>
<th>References removed</th>
</tr>
</thead>
<tbody>
<tr>
<td>March 2, 2015, 3:16 a.m.</td>
<td>7</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Feb. 11, 2015, 3:58 a.m.</td>
<td>7</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Oct. 23, 2014, 10:14 a.m.</td>
<td>7</td>
<td>7</td>
<td>0</td>
</tr>
</tbody>
</table>
How, When, Where Were Searches Performed: *Cancer in Animals*

<table>
<thead>
<tr>
<th>Description</th>
<th>Section 8 Cancer in animals, parathion or paraoxon</th>
</tr>
</thead>
<tbody>
<tr>
<td>Search Type</td>
<td>Search</td>
</tr>
<tr>
<td>Search Database</td>
<td>PubMed</td>
</tr>
<tr>
<td>Search Text</td>
<td>(<em>parathion</em>[All Fields] OR <em>paraoxon</em>[All Fields] NOT 'methyl parathion'[All Fields]) AND <em>neoplasms</em>[MeSH Terms] AND <em>animals</em>[MeSH Terms:noexp]</td>
</tr>
<tr>
<td>Created</td>
<td>Oct. 23, 2014, 11:30 a.m.</td>
</tr>
<tr>
<td>Last Updated</td>
<td>Nov. 14, 2014, 3:19 a.m.</td>
</tr>
</tbody>
</table>

**Literature Tagging Statistics**

<table>
<thead>
<tr>
<th>Total References</th>
<th>31</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Tagged</td>
<td>31</td>
</tr>
<tr>
<td>Total Untagged</td>
<td>0</td>
</tr>
</tbody>
</table>

**Results from queries**

<table>
<thead>
<tr>
<th>Date last executed</th>
<th>Total references found</th>
<th>References added</th>
<th>References removed</th>
</tr>
</thead>
<tbody>
<tr>
<td>March 2, 2015, 3:15 a.m.</td>
<td>31</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Feb. 11, 2015, 3:57 a.m.</td>
<td>31</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Oct. 23, 2014, 11:30 a.m.</td>
<td>31</td>
<td>31</td>
<td>0</td>
</tr>
</tbody>
</table>
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).
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

- Cancer in humans
- Cancer in animals
- Overall evaluation
- Mechanisms

Overall evaluation flows into Cancer in animals, which then leads to Cancer in humans and Mechanisms.
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?

1. Specify the study question
2. Identify the relevant mechanistic events
3. Develop a literature search strategy
4. Literature searches, mechanisms of action
5. Establishment of inclusion/exclusion criteria
6. Construction of literature trees for each mechanism
7. Construct evidence tables and brief narrative summaries
8. Organize and tag evidence

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

**Description:**
- Section 4.2.1-4.2. Genotoxicity of parathion and the primary P450 metabolite, paraxon.

**Search Type:**
- Search

**Search Database:**
- PubMed

**Search Text:**
- ("parathion"[MeSH Terms] OR "parathion"[All Fields]) OR ("paraxon") OR ("paracon") OR ("paradox") OR ("methyl parathion"[MeSH Terms] OR "methyl parathion"[All Fields]) AND ("Mutagenesis[MH]" OR "Mutagenicity[Mesh]" OR "Cytogenetic Analysis[Mesh]" OR "Mutagenes"[Mesh] OR "Oncogenes"[Mesh] OR "clastogen" 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.

### Literature Tagging Statistics

<table>
<thead>
<tr>
<th>Category</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total References</td>
<td>290</td>
</tr>
<tr>
<td>Total Tagged</td>
<td>290</td>
</tr>
<tr>
<td>Total Untagged</td>
<td>0</td>
</tr>
</tbody>
</table>

### Results from queries

<table>
<thead>
<tr>
<th>Date Last Executed</th>
<th>Total References Found</th>
<th>References Added</th>
<th>References Removed</th>
</tr>
</thead>
<tbody>
<tr>
<td>March 2, 2015, 3:17 a.m.</td>
<td>290</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Feb. 11, 2015, 7:31 a.m.</td>
<td>289</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Aug. 13, 2014, 9:09 a.m.</td>
<td>286</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

And similar searches, to cover 10 “key characteristics”
How to Capture Studies from “Hand Searching”?

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

Statistics

<table>
<thead>
<tr>
<th>Category</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total References</td>
<td>1217</td>
</tr>
<tr>
<td>Total Tagged</td>
<td>1217</td>
</tr>
<tr>
<td>Total Untagged</td>
<td>0</td>
</tr>
</tbody>
</table>

Prior evaluation in Volume 30 (1983)

Articles from the archives

<table>
<thead>
<tr>
<th>Description</th>
<th>Articles cited in prior IARC Monographs (volume 30, supplement 7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Search Type</td>
<td>Import</td>
</tr>
<tr>
<td>Search Database</td>
<td>PubMed</td>
</tr>
<tr>
<td>Search Text</td>
<td>15420172, 4772941, 13862642, 14908051, 13062058, 6993936, 13206448, 101966, 740515, 461116, 537865, 119496, 4216877, 1394141, 1268370, 888817, 5031564, 14199205, 6047239, 7089924, 13701584, 13894842, 13946141, 5151664, 15390320, 1154409, 866156, 14157576, 5837408, 20604392, 9444145, 609510, 583446, 14404260, 4279630, 4714332, 81664, 5123154, 1208189, 857241, 14160507, 4357387, 5943299, 900999, 420356, 7038805, 5906458, 4941660, 1252255, 12830227, 13502056, 7364572, 4308671, 337436, 874567, 13838667, 1269562, 660561, 214351, 539831, 13582239, 6024487, 5478556, 1125467, 1190838, 708924, 901000</td>
</tr>
</tbody>
</table>

Created: Nov. 14, 2014, 7:44 a.m.
Last Updated: Nov. 14, 2014, 7:44 a.m.
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)
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
Step 1: Making an Outline

- 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

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

Manually add references to “government reports”
Step 3: Developing Tabular and Narrative Summaries

- Cancer in humans
- Cancer in animals
- Mechanisms
- Overall evaluation
Capturing Data into Tables: Cancer in Humans

IARC Table Builder

| 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 (1979-83) | Cases: 748 (83%); Cases from tumour registry, 1983, Minnesota, 1979-83 | 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 exposure. Proxy responses for deceased, though addressed in design and analysis. |

- Pre-defined, required/optional fields with drop-down lists
- Ability to toggle between numbers and plots
- Working Group comments captured
## Example animal bioassay evidence

**Volume 106: Trichloroethylene**

<table>
<thead>
<tr>
<th>Study design</th>
<th>Route</th>
<th>Results</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Study design:</td>
<td>Skin application</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Species, strain (sex):</td>
<td>Trichloroethylene, &gt;99.9% acetone</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Age at start:</td>
<td>0, 10, 50 mg/kg bw</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Duration:</td>
<td>2x/d for 103 wk</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Reference:</td>
<td>20, 50, 50</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>19, 46, 32</td>
<td></td>
</tr>
</tbody>
</table>

**Full carcinogenicity**

**Mouse, B6C3F1 (M)**

- 6-8 wk old
- 110 wk

**Radican et al. (2008)**

- Skin application: 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

**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:**

---

**Actions:**
- Create new row
- Reorder rows
- Make full-screen
- Download Excel
- Download Word: HTML table recreation
- Show all rows
- Toggle QA flags
Capturing Data into Tables: Mechanistic Data

IARC Table Builder

<table>
<thead>
<tr>
<th>Genotoxicity evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hover-over field labels for more descriptive text. Fields marked with an asterisk (*) are required.</td>
</tr>
</tbody>
</table>

- **Reference**: Select reference from library
- **Data class**: Animal in vivo
- **Agent**: Parathion

- **Species**: Mouse
- **Strain**: B6C3F1
- **Endpoint**: Chromosomal damage
- **Endpoint test**: Micronuclei
- **Sex**: Male
- **Tissue**: Bone marrow
- **Result**: +/-
- **LEC or HIC**: 14.9

**Comments**

Statistical methods not provided for significance determination

**Dose, duration can be captured**

Dropdown options change according to assay system, endpoint

Results can be sorted by any field
## Narrative Summaries: Address Pre-Specified Decision Criteria

<table>
<thead>
<tr>
<th>Cancer in humans</th>
<th>Cancer in experimental animals</th>
<th>Mechanistic and other relevant data</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>— Preamble Part B, Section 6(b)</td>
<td></td>
</tr>
</tbody>
</table>

- **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)

- **Data suggest** a carcinogenic effect but: (e.g.) single study, benign tumours only, promoting activity only

### Evidence Categories

- **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

<table>
<thead>
<tr>
<th></th>
<th>Sufficient</th>
<th>Limited</th>
<th>Inadequate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sufficient</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Limited</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inadequate</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Group 1 \((\text{carcinogenic to humans})\)

Group 2A \((\text{probably carcinogenic})\)

Group 2B \((\text{possibly carcinogenic})\)

(exceptically, Group 2A)

Group 2B \((\text{possibly carcinogenic})\)

Group 3 \((\text{not classifiable})\)
The Final, Final Step: Bringing in Mechanistic Data

<table>
<thead>
<tr>
<th>EVIDENCE IN HUMANS</th>
<th>EVIDENCE IN EXPERIMENTAL ANIMALS</th>
<th>ESLC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sufficient</td>
<td>Sufficient</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 strong evidence in exposed humans</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Group 2A</td>
<td></td>
</tr>
<tr>
<td>Limited</td>
<td>Limited</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 strong evidence in exposed humans</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2A belongs to a mechanistic class where other members are classified in Groups 1 or 2A</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Group 2B</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2A belongs to a mechanistic class</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2A with supporting evidence from mechanistic and other relevant data</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Group 3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2A belongs to a mechanistic class</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2B with strong evidence from mechanistic and other relevant data</td>
<td></td>
</tr>
<tr>
<td>Inadequate</td>
<td>Inadequate</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3 strong evidence ... mechanism does not operate in humans</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Group 3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4 consistently and strongly supported by a broad range of mechanistic and other relevant data</td>
<td></td>
</tr>
<tr>
<td>ESLC</td>
<td>ESLC</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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