EVOLUTION OF THE CANCER RISK ASSESSMENT: HAVE WE ADVANCED?

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OVERVIEW

- 1986 vs. 2005 USEPA Cancer Risk Assessment Guidelines
- Cancer Risk Assessment: Case Example
- Global Cancer Risk Assessment: Hazard vs. Risk

“Those who cannot remember the past are condemned to repeat it.”

George Santayana (in *The Life of Reason*, 1905)
## USEPA CANCER RISK ASSESSMENT GUIDELINES

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Cancer classifications based on alpha-numerical categories:</td>
<td>Cancer classifications based narrative cancer descriptors:</td>
</tr>
<tr>
<td>A - Known carcinogens</td>
<td>- Carcinogenic to Humans</td>
</tr>
<tr>
<td>B - Probable</td>
<td>- Likely to Be Carcinogenic to Humans</td>
</tr>
<tr>
<td>C - Possible</td>
<td>- Suggestive Evidence of Carcinogenic Potential</td>
</tr>
<tr>
<td>D - Not classifiable</td>
<td>- Not Likely to Be Carcinogenic to Humans</td>
</tr>
<tr>
<td>E - No evidence</td>
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**IPCS/WHO AND USEPA MODE OF ACTION FRAMEWORK**

- Postulated mode of action
  - Identify sequence of key events on the path to cancer
- Experimental support
  - Concordance of dose-response for key events with that for tumors
  - Temporal relationships for key events & tumors
- Biological plausibility & coherence
- Strength, consistency & specificity
- Other alternative modes of action
- Identify uncertainties and key data gaps
- Conclusion - narrative characterization
“Mechanism of action”
(more detailed understanding at biochemical & molecular level)

versus

“Mode of action”
(identification of **key & obligatory** steps)
MECHANISTIC DATA IN RISK ASSESSMENT

• Identify
  • Key biological (early precursor) events leading to adverse toxicities (Mode of Action)

• Inform
  • Human relevance of animal findings
  • Dose response extrapolation
  • Life stage susceptibilities

• Understand
  • Common pathways of toxicity

• Promote
  • Consistent harmonized approach to risk assessment for all health endpoints
CASE EXAMPLE: DIMETHYLARSINIC ACID

- Science Issue Paper: “Mode of Carcinogenic Action for Cacodylic Acid (Dimethylarsinic Acid, DMA\textsuperscript{V}) and Recommendations for Dose Response Extrapolation” (July 26, 2005)
  - [http://www.epa.gov/oppsrrd1/reregistration/cacodylic_acid](http://www.epa.gov/oppsrrd1/reregistration/cacodylic_acid)
- EPA’s Science Advisory Board (SAB) reviewed the special issue paper in September, 2005
  - SAB report December 27, 2005
AVAILABLE CANCER DATA

• Metabolic profile to identify toxic moiety
• Genotoxicity data are mostly negative demonstrating no DNA reactivity
• No Human Epidemiology Data
• Standard 2-year rodent bioassays in rat and mouse
  • Bladder carcinogen in rats
    • via oral dietary -100 ppm (9.4 mg/kg bw per day)
    • via drinking water- 50 & 200 ppm
    • females more sensitive than males
  • Not carcinogenic in mice
    • Up to 500 ppm in B6C3F (Gurr et al., 1989)
    • 121 ppm in C57 XC3H/Anf or AKR (NCI 1969)
WEIGHT OF SCIENTIFIC EVIDENCE

Weight of Evidence

- Extensive experimental cellular and laboratory animal data to demonstrate consistency and reproducibility
- Considerations of the quality of the data and integrations of all positive and negative findings
- Biological plausibility of the postulated mode of action
METABOLISM OF ARSENIC

Alternate steps of oxidative methylation & reduction

Methylation → Reduction

Pesticide Chemical
DIMETHYLARLSINIC ACID
GENOTOXIC?

- Neither DMA\textsuperscript{V} or DMA\textsuperscript{III} are direct acting point/gene mutagens
- Both are clastogenic but DMA\textsuperscript{III} is the more potent
  - \textit{In vitro} data only and does not occur in the bladder
- DNA damage appears to result from an \textit{indirect mechanism} (ROS/oxidative damage)
  - DMA\textsuperscript{III} \rightarrow DMA\textsuperscript{V}
DMA$^V$ Postulated Mode of Action

Measurable Key Events in Target Tissue

DMA$^{III}$ Metabolite

Urothelial Toxicity

Regenerative Proliferation

Hyperplasia

Urinary bladder from a female F344 rat treated with 100 ppm DMA$^V$

BrdU Labeling

Urinary Bladder Tumors

Sustained
## Association of Key Precursor Events & Bladder Tumors in F344 Rats

<table>
<thead>
<tr>
<th>Dose (mg/kg bw/day)</th>
<th>Metabolism DMA&lt;sup&gt;v&lt;/sup&gt; → DMA&lt;sup&gt;III&lt;/sup&gt;</th>
<th>Urothelial Toxicity</th>
<th>Regenerative Proliferation</th>
<th>Urothelial Hyperplasia</th>
<th>Transitional Cell Carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.2 (2 ppm)</td>
<td>+ (wk 3-0.03 ± 0.01 µM)</td>
<td>+ (wk 10-6/10, grade 3 or 4)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>1 (10 ppm)</td>
<td>+ (wk 3-0.12 ± 0.02 µM)</td>
<td>+ (wk 3-2/7, grade 3) (wk-10; 8/10, grade 3 or 4)</td>
<td>slight (wk 10 - 1.5X ↑)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>4 (40 ppm)</td>
<td>+ (wk 3-0.28 ± 0.09 µM)</td>
<td>+ (wk 3-7/7, grade 3) (wk 10-5/10, grade 3 or 4)</td>
<td>+ (wk 10 - 4.3X ↑)</td>
<td>+ (wk 10-4/10)</td>
<td>-</td>
</tr>
<tr>
<td>9.4 (100 ppm)</td>
<td>+ (wk 3-0.55 ± 0.15 µM)</td>
<td>+ (6 hrs-6/7, grade 3) (24 hrs-4/7, grade 3 or 4) (wk 10-10/10, grade 4 or 5)</td>
<td>+ (wk 1-2.2X) (wk 2-3.9X)</td>
<td>+ (wk 10-9/10)</td>
<td>+ (papilloma first obs at wk 107; carcinoma first obs at wk 87)</td>
</tr>
</tbody>
</table>
CACODYLYC ACID: KEY EVENTS
TEMPORAL RELATIONSHIP

DMA^III \leftrightarrow DMA^V

6 hours  Urothelial Cytotoxicity
1 Week   Regenerative Proliferation
8-10 weeks  Hyperplasia
104 weeks  Tumors

Urinary bladder from a female F344 treated with 100 ppm DMA^V
BrdU labeling
Urinary bladder tumors
CYTOTOXIC MODE OF ACTION

• **Strength, Consistency & Specificity**
  - Consistency of association found in repeated experiments within a lab & among different labs
  - Specificity - Inhibition of DMA\(^V\) $\rightarrow$ DMA\(^{III}\) reduced cytotoxicity
  - Essentiality - Cessation of exposure to DMA\(^V\) results in recovery of tissue (i.e., hyperplasia)

• **Biological Plausibility & Coherence**
  - Regenerative proliferation associated with persistent toxicity appears to be a risk factor for bladder cancer in humans
MODE OF ACTION CONCLUSIONS

- Sequence of key events leading to bladder tumors measurable & supported by robust data
- Biologically plausible established for the postulated cytotoxic mode of action
- Uncertainties are present but do not discount scientific support
  - cellular target for cytotoxicity not understood
  - unknown cytotoxic metabolites found in urine (after drinking water exposure)
HUMAN RELEVANCE FRAMEWORK

• Risk Sciences Institute-ILSI
  • Comparability or concordance analysis of the key events & relevant biology between the laboratory species & humans
    • Tumor Responses: Meek et al., 2003, Critical Reviews in Toxicology Vol 33/Issue 6, 581-653
    • Reproductive, Developmental, Neurotoxicity Responses: Seed et al., 2005 Critical Reviews in Toxicology Vol 35/Issue 8-9, 63-781
    • Update MOA and HRF: Meek et al., 2014, J. Appl. Toxicol. Vol 34, 1-18
  • Extended human relevance analysis to include mutagenic carcinogens & non-cancer end points

Formation of the WHO/IPCS Human Relevance Framework
## SPECIES CONCORDANCE ANALYSIS

<table>
<thead>
<tr>
<th>Key Event</th>
<th>Rats</th>
<th>Humans</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence of DMA\textsuperscript{III} in urine (KE #1)</td>
<td>Yes</td>
<td>Yes (based on As\textsuperscript{i})</td>
</tr>
<tr>
<td>Persistent cytotoxicity (KE #2)</td>
<td>Yes</td>
<td>Possible</td>
</tr>
<tr>
<td>Persistent regenerative prolif/hyperplasia (KE #3)</td>
<td>Yes</td>
<td>Possible</td>
</tr>
<tr>
<td>Bladder Tumors (KE #4)</td>
<td>Yes</td>
<td>Possible (no human data)</td>
</tr>
</tbody>
</table>
1. Rat data developed for DMA\textsuperscript{V} most appropriate data for quantifying cancer risk (mg/kg bw/day)\textsuperscript{-1}

2. MOA for the development of bladder tumors in rats established based on sustained and regenerative proliferation

3. The rat MOA is plausible in humans

4. The MOA supports nonlinear extrapolation of cancer risk to DMA\textsuperscript{V}
DOSE RESPONSE CONSIDERATIONS

• Dose response extrapolation should be based on considerations of MOA which supports nonlinearity
  • Must be sufficient DMA\textsuperscript{III} to produce cell killing & sufficient cell killing to lead to regenerative proliferation
  • Cytotoxicity & enhanced proliferation need to be sustained

• Point of Departure (NOAEL) based on cell proliferation should be protective of DMA’s carcinogenic & promoting effects
  • “Not Likely to Be Carcinogenic to Humans”
GLOBAL HARMONIZED PESTICIDE REGISTRATIONS

• Since the early 2000’s, global pesticide registration dossiers have harmonized on data requirements and endpoint selection – robust data set for cancer determination

• As reflective in the ability to harmonize on the hazard characterizations, including cancer classifications, global regulatory authorities appear to have more similarities than differences in their data reviews – risk assessments should be harmonized

• To what extent can these similarities and differences be explained and differentiated by the approach taken in the overall pesticide assessment?
GLOBAL PESTICIDE REGULATORY AUTHORITIES: RISK vs. HAZARD BASED APPROACH

**RISK BASED APPROACH**
- US EPA
- PMRA/Health Canada
- WHO/FAO JMPR
- EU-EFSA
- EU-some Member States
- APVMA
- China-ICAMA
- Others

**HAZARD BASED APPROACH**
- IARC – e.g. glyphosate, 2,4-D, red meat, hair dresser, pickled vegetables, coffee, etc. are considered carcinogens based on *hazard only* considerations.
HAS THE CANCER RISK ASSESSMENT PROCESS ADVANCED?

1986
• Alpha numerical categories (e.g. A, B, C, D and E)
• Statistical significance
• Linearized multistage model – Global86
• Relevant to humans

2005
• Weight of Evidence Characterization
• Biological plausibility and coherence
• Mode of Action – Regulate on non-cancer POD (POD x UF)
• Human Relevance Framework
SUMMARY

• Cancer risk assessment has advanced with the adoption of the Mode of Action and Human Relevance Frameworks

• MOA and Human Relevance Framework allows:
  • Explicit process for organizing, analyzing data and integrating evidence (WoE)
  • Transparently documents (and enhances communication of) data, analysis and WoE for MOA
  • Promotes the use of all available data that are relevant for MOA
  • Defines the “key events” that are relevant for risk assessment purposes
  • Delineates types of data that are preferred over worst case default options
  • Helps to identify critical data and/or research needs that would add value to the MOA considerations
  • Promote harmonization of risk assessment for all endpoints to ensure human health protection

“Change is the law of life. And those who look only to the past or the present are certain to miss the future.” John F. Kennedy
Thank you

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QUANTITATIVE CANCER MODELS

• Linearized multistage model (Crump et al.)
  • Linearity of the dose response of low doses
  • Follows a polynomial form subject to background corrections

• Benchmark Dose Methodology
  • Choose low end of the observable dose response curve
  • Lower confidence bound usually 95% of the effective dose (LED10) causing 10% increase in
tumor incidence compared against concurrent controls

• Threshold Reference Dose Value Using a Point of Departure
  • Establish the dose at which prevention of the earlier precursor key event will be protective of
tumor outcomes