Emerging Issues, Regulatory Challenges

& the Science of Risk Assessment
Emerging Issues & Regulatory Challenges
(a select few)

- Green chemistry: California EPA
- Persistent, Bioaccumulative and Toxic: International Programme on Chemical Safety (IPCS)
- TSCA legislation: U.S. EPA
- State deficits: how do states share limited resources and expertise?
- Trusting colleagues’ judgments: several examples
- Collaborating to tackle issues: numerous examples
New Risk Assessment Science (a select few)

- Lead the risk assessment with Mode of Action (MOA) & exposure understanding
- Do not treat all carcinogens as equal
  - Some actually have sub-threshold doses
  - Some have multiple MOAs
- Chose uncertainty factors first based on data; then default
- Estimate risk above a sub-threshold dose (i.e., risk above the RfD)
Chemicals should be reviewed against risk-based safety standards & based on sound science.

Manufacturers should provide EPA with the necessary information to conclude that new and existing chemicals are safe for intended use.

EPA and States should have clear authority to take risk management actions when chemicals do not meet the safety standard.

Manufacturers and EPA should assess and act on priority chemicals, in a timely manner.

Green chemistry should be encouraged & provisions assuring transparency & public access to information should be strengthened.
Working together... when it’s more efficient.

- Texas & Hawaii: Arsenic in soil
- NCEA and OEHHA teaming up on determination of risk values
Case Study: Arsenic in Soil
Meanwhile in Texas...
Memorandum of Understanding

- California EPA’s Office of Environmental Health Hazard Assessment (OEHHA) and the EPA’s National Center for Environmental Assessment (NCEA)
- Mechanism of increased communication and cooperation in the development of:
  - Risk assessment methods
  - Toxicology assessments
- Help insure efficient use of state and federal resources.
Working together…

when it can’t be done alone.

- New Zealand Ministry of Health
  - Compact Fluorescent Light bulbs
- Dose Response Coalition
  - Texas, ACC, TERA, Indiana, Illinois
New Zealand: Compact Fluorescent Bulbs

Data from Stahler et al., 2008; State of Maine
Dose Response Assessment Framework:
Mechanics of conducting a risk assessment: Tools and Software to help
Working together…

to solve a complex problem.

- Mode of Action (MOA) (e.g., IPCS, ILSI, EPA)
- Genotoxicity versus mutagenicity (e.g., EPA, NCTR)
- Chemical Specific Adjustment Factor (CSAF) (IPCS, Health Canada)
- Risk above the RfD (e.g., EPA, NAS)

Point of departure

Human Exposure of Interest

Response

Extrapolation Range

Observed Range

0%

10%

BMDL

BMD

RfD

LED

ED

RSD

Dose (PBPK)

Projected Linear

(UF)

Confidence Limit on Dose

(Central Estimate)
Possible Outcomes of the MOA Evaluation (EPA, 2005; 2007)

- Insufficient evidence to establish any MOA
- Sufficient evidence for mutagenic MOA
  - Linear dose response assessment (vinyl chloride)
- Sufficient evidence for a non-mutagenic MOA
  - Sub-threshold dose response assessment (perchlorate)
- Dual MOA dose response assessment (acrylamide)
FIGURE 5-2 Committee’s suggested mode-of-action model for perchlorate toxicity in humans indicating first adverse effect in the continuum.

NAS, 2005, EPA, 2005
Dual Mode of Action (MOA)
Probit model fitted to pooled-all thyroid tumor data shows different slopes between low & high doses.
Strategy to Identify Chemicals that are Mutagens & Carcinogens…
But not Necessarily Mutagenic Carcinogens

NCTR
    Martha Moore, Robert Heflich

TERA
    Lynne Haber, Mike Dourson

ENVIRON
    Annette Shipp, Robinan Gentry

Bruce Allen Consulting
    Bruce Allen

University of Arkansas for Medical Sciences
    Ralph Kodell

NCTR---Disclaimer: Not Official FDA Policy
Chemical Specific Adjustment Factor (CSAF)

100-fold uncertainty factor

Inter-species differences 10-fold

Toxicokinetics
AK
10 E0.6
(4.0)

Toxicodynamics
AD
10 E0.4
(2.5)

Intra-species differences 10-fold

Toxicokinetics
HK
10 E0.5
(3.2)

Toxicodynamics
HD
10 E0.5
(3.2)

Risk Above the RfD: Comparing Blood-Mercury Levels

Parts Per Billion, MeHg in Blood

Red lines indicate projected risk

Risk Above the Aldicarb RfD

(EPA/NCEA-TERA: Dourson et al., 1997)
Working together... because we’re all in this together

- 1,3-Butadiene in air
- Texas, North Carolina & Ontario
- Pesticide degradates in water
- Utilities, private well owners, drillers, farmers, NGOs, Agricultural Chemical Companies, State Health Departments, State Agricultural Agencies
Harmonization of Drinking Water Standards of Agricultural Degradates

- Diverse stakeholders need guidance
  - Utilities, private well owners, drillers, farmers, NGOs, Agricultural Companies, State Health Departments, State Agricultural Agencies

- Different interpretations can result in different standards
  - Existing, or proposed, standards for alachlor ESA vary: 20 to 1400 ug/L
  - Confusing many stakeholders
  - Resulting in unnecessarily complex regulatory environment

- Independent peer-review has increased stakeholder confidence
  - Benefits interstate commerce
  - Helps avoid unnecessary restrictions
  - Provides consistency in interpretation of results by various stakeholders
Getting Help

- Alliance for Risk Assessment (ARA): Risk Information Exchange [www.allianceforrisk.org]
- TERA: State Hazard Evaluation and Lending Program (State HELP) [www.tera.org]
- Environmental Council Of States [www.ecos.org]
- Federal & State Toxicology & Risk Assessment Committee (FSTRAC) [www.epa.gov/waterscience/fstrac]
Alliance for Risk Assessment (ARA)

Guiding Principles
- Improved communication among groups
- Transparency in development of products
- Harmonization and consistency in risk assessments
- Shared costs and human resources

Steering Committee
- Anita Meyer, United States Army Corps of Engineers
- Barbara Harper, Confederated Tribes of the Umatilla Indian Reservation
- Bette Meek, University of Ottawa/Health Canada
- Edward Ohanian, United States Environmental Protection Agency
- Michael Dourson, Toxicology Excellence for Risk Assessment
- Michael Honeycutt, Texas Commission on Environmental Quality
- Phil Wexler, National Library of Medicine
- Ruthann Rudel, Silent Spring
- William Hayes, State of Indiana
Alliance for Risk Assessment (ARA)

(www.allianceforrisk.org)

Stakeholder Process

States, Fed. Agencies, Public Interests, Industry

Initiation of Risk Issue

Document Draft

Peer Reviews

Release to Public

ARA Process

Steering Committee

Non-profit Collaborators

Risk Document Development

Training and Certification

Risk Communication

Risk Research And Tools

Peer Review & Consult

Risk Information Exchange (RiskIE)
RISKIE
Risk Information Exchange
www.alliancetorisk.org/RiskIE.htm

The only place to keep up with In-Progress Risk & Toxicity Assessments.

Includes over 5500 projects being conducted by more than 30 organizations representing 13 countries.

Free for anyone to contribute and use.
Welcome to the IRIS home page, brought to you by the U.S. Environmental Protection Agency (EPA) and its Office of Research and Development, National Center for Environmental Assessment. IRIS is a database of human health effects that may result from exposure to various substances found in the environment. IRIS was initially developed for EPA staff in response to a growing demand for consistent information on chemical substances for use in risk assessments, decision-making and regulatory activities. The information in IRIS is intended for those without extensive training in toxicology, but with some knowledge of health sciences. For more information about IRIS, read this Introduction.

For definitions of terms in the IRIS Web site, refer to the IRIS Glossary.
Process for Assessment Development and Review

- Annual FR Notice of IRIS agenda; data call
- Literature search and review
- EPA develops draft assessment
- Internal peer review, IRIS Agency Review
- Interagency review
- External peer review with public comment period
- Final EPA approval and posting on IRIS database

This process is documented in IRIS Standard Operating Procedures, which are updated annually.
Toxnet: ITER
International Toxicity Estimates for Risk

www.tera.org/ITER

- Free chronic human health risk values for over 670 chemicals from groups around the world
- A synopsis that explains the underlying basis and rationale for each risk value and differences in risk values
- The only forum through which independent parties can share their peer reviewed risk values in a comparative manner.
What is on *ITER*?
(toxnet.nlm.nih.gov)
Summary

New Regulatory Issues
- Green chemistry, PBTs, TSCA legislation
- Share work, trust judgments and collaborate

New Risk Science
- Lead with MOA; carcinogens are not equal
- Data-based uncertainty factors; quantifying noncancer risk

Let’s work together
- When it is more efficient; when it cannot be done alone
- To solve complex problems; because we’re all in this area of public health protection together…
Extra Slides
Categorical Regression

- Advantages:
  - provides a consistent basis for calculating risk above the RfD
  - all useful data can be categorized
  - accounts for severity of toxic effect

- Limitations:
  - animal to human extrapolation is still needed
  - data are transformed into categories which loses information
## Aldicarb Clinical Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Dose (mg/kg-day)</th>
<th>Group Size</th>
<th>Clinical Signs</th>
<th>Blood Cholinesterase Inhibition</th>
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<tbody>
<tr>
<td>Haines, 1971</td>
<td>0.025</td>
<td>4</td>
<td>1 Apprehension</td>
<td>4 Whole blood</td>
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<tr>
<td></td>
<td>0.05</td>
<td>4</td>
<td>1 Runny nose</td>
<td>4 Whole blood</td>
</tr>
<tr>
<td></td>
<td>0.10</td>
<td>4</td>
<td>4 Weakness and sweating, Nausea in 2 individuals</td>
<td>4 Whole blood</td>
</tr>
<tr>
<td>Wyld et al., 1992</td>
<td>0</td>
<td>22</td>
<td>0</td>
<td>0 Plasma &amp; 0 RBC</td>
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<tr>
<td></td>
<td>0.010</td>
<td>8</td>
<td>2 Headaches</td>
<td>0 Plasma &amp; 0 RBC</td>
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<tr>
<td></td>
<td>0.025</td>
<td>12</td>
<td>1 Sweating</td>
<td>12 Plasma &amp; 11 RBC</td>
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<tr>
<td></td>
<td>0.050</td>
<td>12</td>
<td>1 Sweating</td>
<td>1 Plasma &amp; 1 RBC</td>
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<tr>
<td></td>
<td>0.06</td>
<td>1</td>
<td>1 Sweating</td>
<td>1 Plasma &amp; 1 RBC</td>
</tr>
<tr>
<td></td>
<td>0.075</td>
<td>3</td>
<td>1 Lightheadedness</td>
<td>3 Plasma &amp; 3 RBC</td>
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</table>
## Effect Categories of Aldicarb Exposure in Humans

<table>
<thead>
<tr>
<th>Study</th>
<th>Dose (mg/kg/day)</th>
<th>Group Size</th>
<th>Frequency of Responders within Categories of:</th>
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</thead>
<tbody>
<tr>
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<td></td>
<td></td>
<td>NO Effects</td>
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<tr>
<td>Wyld</td>
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<td>22 (22)</td>
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<tr>
<td>Wyld</td>
<td>0.010</td>
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<td>8 (0)</td>
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QUESTIONS????