Uncertainty in Mixtures and Cumulative Risk Assessment

John C. Lipscomb
and
Glenn E. Rice
U.S. Environmental Protection Agency
Office of Research and Development
National Center for Environmental Assessment
Cincinnati, Ohio, USA

EFSA Scientific Colloquium No 21
Harmonisation of human and ecological risk assessment of combined exposure to multiple chemicals
Edinburgh, UK, 11-12 September 2014

The views expressed in this presentation are those of the authors and do not necessarily reflect the views or policies of the U.S. Environmental Protection Agency.
Natural Resources
Goods Production
Economic Interests
Public Health
Ecosystems

Chemicals & Chemical Mixtures
• Additives
• Byproducts
• Contaminants

Exposures
Species
Populations
RISK ASSESSMENT:
Exposure Assessment
• Hazard Identification
• Dose Response
  • Data
  • Science Policy Decisions
  • Models
  • Multiple Chemicals, Mixtures
Risk Characterization

http://www.epa.gov/raf/frameworkhhra.htm
Ecological Risk Assessment

Human Health Risk Assessment
Uncertainty versus Variability

Uncertainty is a property of the observer, may be reduced by additional research, but cannot be verified.

Variability is a property of nature, cannot be reduced by additional research, but can be verified and estimated with greater accuracy.

Some sources of uncertainty:
- Conceptual model – problem formulation
- Information & data – resources may constrain availability
- Stochasticity – level of certainty regarding natural variability
- Error – in experimental design or data analysis procedures
### Human Health Risk Assessment

#### Toxicity Testing

<table>
<thead>
<tr>
<th>Reference Value = POD / UF</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Likelihood of Effect</strong></td>
</tr>
<tr>
<td><strong>Sensitivity of Effect</strong></td>
</tr>
<tr>
<td><strong>Point of Departure</strong></td>
</tr>
<tr>
<td><strong>BMD&lt;sub&gt;L&lt;/sub&gt;</strong></td>
</tr>
<tr>
<td><strong>NOAEL</strong></td>
</tr>
<tr>
<td><strong>LOAEL</strong></td>
</tr>
<tr>
<td><strong>Mortality</strong></td>
</tr>
</tbody>
</table>

#### Risks to human population

**Human Exposure Limit**

<table>
<thead>
<tr>
<th>UF&lt;sub&gt;A&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>UF&lt;sub&gt;H&lt;/sub&gt;</td>
</tr>
<tr>
<td>UF&lt;sub&gt;S&lt;/sub&gt;</td>
</tr>
<tr>
<td>UF&lt;sub&gt;L&lt;/sub&gt;</td>
</tr>
<tr>
<td>UF&lt;sub&gt;D&lt;/sub&gt;</td>
</tr>
</tbody>
</table>
Ecological Risk Assessment
Toxicity Testing

Population and community risks

Margin of Exposure:
Ratio of Exposure Value to Effect Value

Acceptable Environmental Concentration

Uncertainty Factor
UF

Likelihood of Effect

Sensitivity of Effect

Growth
Reproduction
Mortality

Point of Departure

DOSE
Uncertainties in Mixtures Risk Assessment

Are we focused on ...

The correct chemical or mixture?
   Whole mixture?
   Similar mixture?
   Component data?

A sensitive or representative species?

A/the sensitive (critical) effect?
   In a sensitive life stage?
   For a duration representative of a lifetime exposure?
   At an appropriate response level?
Uncertainties in Mixtures Risk Assessment

What do we know about ...

Concentrations of multiple chemicals in the environmental media?
Contact with the environmental medium?
Temporal fluctuations in environmental concentrations?
The impact of fluctuations on exposure and toxicity?
Durations of exposure?
Necessity of duration adjustments?
Absorption, bioavailability, bioconcentration?
Dose additivity?
Flow Chart for Evaluating Chemical Mixtures

Whole Mixture Data Available
- Whole Mixture of Concern
  - Mixture RfD/RfC; Slope Factor
    - Whole Mixture Exposure Assessment
      - Hazard Quotient; Risk Estimate
      - Epidemiological Evaluations, Toxicity Profiles
  - Sufficiently Similar Mixture
    - Health Evaluations
      - Whole Mixture Exposure Assessment
        - Hazard Quotient; Risk Estimate
        - Epidemiological Evaluations, Toxicity Profiles

Component Data Available
- Toxicologically Similar Components
  - Dose Addition
    - Available Interactions Data
      - Relative Potency Factors
      - Integrated Additivity Methods
        - Component Exposure Assessment
          - Hazard Index
          - Index Chemical-Based Risk Estimate; Hazard Quotient
  - Mix of Toxicologically Similar & Independent Components
- Toxicologically Independent Components
  - Response Addition

Adapted from U.S. EPA, 2000
Dose Additive Models

Hazard Index Approaches
• Exposure / Acceptable Exposure Limit
• Exposure data for components
• Response data for components

Relative Potency Factor Approaches
• Based on Point of Departure
• Index Chemical
• Similarity of effect(s)
• Exposure data for mixture
• Response data for components
• Quantify potency at fixed response level
Relative Potency Factor Formula

Index Chemical Identified: overall representativeness, data completeness

RPF formula for expressing the mixture dose in terms of the index chemical:

\[ D_m = \sum_{i=1}^{n} [RPF_i \times D_i] \]

where,
- \( D_m \) = mixture dose expressed as dose of index chemical (index chemical equivalent dose = ICED)
- \( D_i \) = dose of the \( i^{th} \) mixture component \((i = 1,\ldots,n)\), and
- \( RPF_i \) = toxicity proportionality constant relative to index chemical for the \( i^{th} \) mixture component \((i = 1,\ldots,n)\)
Formula for Mixture Risk using RPF Values

\[ R_m = f_1(D_m) \]

where,

- \( R_m \) = risk posed by chemical mixture
- \( f_1(*) \) = dose-response function of index chemical
- \( D_m \) = mixture equivalent dose as index chemical

Choice of Index Chemical:

- How good is the dose-response function, \( f_1 \)?
- How similar are the other chemicals to the index chemical?
Hazard Index

Hazard Index = \( \Sigma \) HQ; HQ = E / AL
E = Exposure (Concentration, duration, absorption)
AL = Acceptable Exposure Limit (POD / UF)
There is No Index Chemical

**Screening Hazard Index**

- Single critical effect

**Hazard Index**

- Single critical effect
- Segregated by organ

**Target Organ Toxicity Dose**

- Critical & Secondary effects
- Segregated by organ
Mixtures Uncertainty Factor

In some regulatory settings, it may be deemed desirable to derive exposure standards that ... take account of cumulative exposures. In such cases, tolerable daily exposures to individual chemicals could be corrected downward by incorporating an additional “mixture uncertainty factor.” The additional uncertainty factor would have to take account of the number of chemicals to which simultaneous effective coexposure is deemed likely (NAS, 2008; p. 133).

- There are unique uncertainties associated with mixtures.
- Additivity Approaches rely on single chemical RFVs. These are generally developed to be conservative estimates of risk.
- Exposure assessments are often conservative (e.g., drinking water consumption rates).
- Inputs to additivity models appear to be sufficiently conservative.

Conclusions

Human/ecological exposure: concentration, duration, bioavailability
Experimental species: relevant, sensitive
Experimental endpoint: representative, protective, sensitive
Experimental exposures: representative of real-world exposures
Preference: Whole mixture, similar mixture, component data
  • Availability of Mode of Action information
  • Choice of additivity models