Cumulative Risk Assessment: Theory, Practice and Perspective

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What is Cumulative Risk?

Cumulative risk is the combined risks from aggregate exposures to multiple agents or stressors, which may include chemicals, biological or physical agents.

Cumulative risk assessment (CRA) is an analysis, characterization, and possible quantification of the combined risks to human health or the environment from multiple agents or stressors.

Features of Cumulative Risk Assessment

Multiple chemical, physical, biological stressors
Complex, multiple-route exposures
Stakeholder emphasis
Human health and ecology
Population vulnerabilities
Benefits of healthy communities
Benefits of healthy ecosystems
Population focus
Cumulative Risk Assessment

Population-Based
   General population
   Susceptible (?) groups

Characterize Exposures
   Sources & components
   Routes of exposure

Group Components
   Target tissues / outcomes
   Toxicokinetics
   Mode(s) of action

Characterize & Communicate Risk
   Health concerns
   Components
   Sources
U.S. EPA CRA Theory and Practice

- Methodology for Multipathway Exposures to Combustor Emissions (1998)
- 4 CRA’s & Guidance on Cumulative Risk of Pesticides (2002b;2006a,b,c;2007a)
- Concepts, Methods and Data Sources for Cumulative Health Risk Assessment of Multiple Chemicals, Exposures and Effects: A Resource Document (2007b)
- Planning & Scoping for Cumulative Risk Assessment (1997)
- Planning & Scoping Lessons Learned (2002a)
- 5 White Papers on CRA: Directions for CRA, Vulnerability, Combined Effects from Multiple Stressors, Environmental Mixtures, Biomarkers (2007c)
- Continuing Risk Assessment Forum CRA Efforts
Steps for Conducting a Cumulative Risk Assessment
(Adapted from US EPA, 2007b)

**STEPS**

1) Identify Initiating Factor

2) Characterize Population based on Initiating Factor

3) Generate Chemical (Stressor) List

4) Identify Links between Chemicals (Stressors) and Subpopulations

5) Quantify Exposure for General Population & Subpopulations, Form Initial Exposure Groups

6) Quantify Dose-Response for Initial Toxicity-based Chemical (Stressor) Groups

7) Integrate Exposure & Dose-Response. Refine Exposure and Toxicity Assessments

8) Conduct Risk Characterization

**OUTPUTS**

- Population Profile Including Vulnerability Factors
- List of Relevant Chemicals And Other Stressors
- Conceptual Model
- Epidemiologic Evaluations
- Chemical (Stressor) Groups by Media & Time
- Chemical (Stressor) Groups by Toxicity
- Integrated Chemical (Stressor) Groups
- Final Cumulative RA
Considerations For CRA

Initiating factors

Population illness

Data Sources

Sources, releases

Public health data

Integrated characterization

Chemical concentrations

Population subgroup sensitivities

Population vulnerabilities

Mixtures toxicity

Multi-route exposures

Multiple-chemical fate

Organics in air or soil, transported to water and accumulated in fish

Inhalation, ingestion, dermal exposures from air, water, soil, fish, produce

Incidence of infant mortality, hospital admission rates

Genetic susceptibility, children, elderly

Homes close to pollutant sources, poor health care, subsistence fishers

Aroclor: reproductive effects, diesel exhaust: lung cancer, drinking water disinfectant byproducts: bladder cancer

Source: EPA, 2007b
What are Vulnerability Factors?

Cumulative risk assessment is population-based with stakeholder emphasis and consideration of **Vulnerability Factors:**

- Susceptibility/Sensitivity (e.g., genetics, age, race)
- Differential exposure (e.g., cultural practices)
- Differential preparedness (e.g., lack of access to health care)
- Differential ability to recover (e.g., poor nutrition)

Cumulative Risk Characterization

- Several Stressors
- Multiple Exposure Routes
- Several Effects Over Time
- Joint Exposure-Response
- Population Based

Combined Exposures

- Dermal + Inhalation + Oral
- Developmental & Reproductive Effects
- Cancer
- Time

More Risk

“Dose” of Multiple Stressors

Subsistence Fishermen

Elderly

Immuno-compromised

Pregnant Women
Exposure $\rightarrow$ Dose $\rightarrow$ Response

1. **External dose** $\rightarrow$ **Internal dose** $\rightarrow$ **Toxic Response**
2. **External dose** $\rightarrow$ **Internal dose** $\rightarrow$ **Toxic Response**
3. **External dose** $\rightarrow$ **Internal dose** $\rightarrow$ **Target organ dose** $\rightarrow$ **Toxic Response**
4. **External dose** $\rightarrow$ **Internal dose** $\rightarrow$ **Target organ dose** $\rightarrow$ **Target organ metabolism** $\rightarrow$ **Toxic Response**
5. **External dose** $\rightarrow$ **Internal dose** $\rightarrow$ **Target organ dose** $\rightarrow$ **Target organ metabolism** $\rightarrow$ **Target organ responses** $\rightarrow$ **Toxic Response**
Co-Exposures and Responses

Consideration of internal dose refines chemical groupings:

Persistence, or not, of chemicals inside the body.
Persisteice of effects beyond termination of chemical exposure:

• Induction of metabolism
• Altered tissue sensitivity

The timing of exposures relative to one another (the order in which the exposures occur)
The time between temporally separated exposures
2000 (ORD)

Mode - A series of key events and processes starting with interaction of an agent with a cell, and proceeding through operational and anatomical changes causing disease formation (US EPA Suppl. Mixtures Guidance).

Mechanism - A more detailed understanding and description of events, often at the molecular level, than is meant by mode of action.
Similarity / Groupings: Options

By Mechanism of Action (e.g., decreased hydroxylation of T)

By Mode of Action (Favored Approach) Decreased Androgen-Receptor Interaction

By Target Tissue or Health Outcome

(Figure 3-4, NAS, 2008)
Component Based Methods for Chemical Mixtures Risk Assessment: Apply to Integrated Exposure/Toxicity Groups

- Multiple Toxicological Effects for Each Component
  - Multivariate Statistical Models: Categorical Regression Modeling with Hazard Index & Response Addition
- Toxicological Interactions Data
  - Weight of Evidence Evaluations, Interaction Based Hazard Index
- Toxicologically Similar Components (Multi-Route Exposures)
  - Dose Addition: Hazard Index, Relative Potency Factors
- Mix of Toxicologically Similar and Independent Components Or Groups
  - Integrated Additivity Methods: Using Both Dose Addition & Response Addition
- Toxicologically Independent Components
  - Response Addition

Risk Characterization and Uncertainty Analysis
Hazard Index (HI) Method (Based on Dose Addition)

\[
HI = \sum_{i=1}^{n} \frac{Estimated \ Intake_i}{RfD_i}
\]

Sums the exposure of each mixture component divided by an allowable level of that chemical. Interpreted as an indication of potential risk when HI > 1

- In this case, the scaling factor \( t_i = \left( \frac{1}{RfD_i} \right) \) for each chemical i, where RfD = NOAEL / Uncertainty Factors. Other toxicity-based scaling factors can be used.
- Same mode-of-action may be relaxed to same target organ
- Similarly shaped D-R curves not required
- Use at low exposures where interaction effects are unlikely
Hazard Index Approaches

Screening-Level
Hazard Index
Target Organ Toxicity Dose

Hazard Quotient, individual chemical
HQ = Exposure / Acceptable Limit

Hazard Index, sum of HQ values
for all components
Multiple Tissues Will Respond to Insult

<table>
<thead>
<tr>
<th>Chemical</th>
<th>Developmental</th>
<th>Thyroid</th>
<th>Liver</th>
<th>Hematopoietic</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>5E-3 *</td>
<td>6E-3</td>
<td>8E-2</td>
<td>6E-3</td>
</tr>
<tr>
<td>B</td>
<td>6E-3</td>
<td>4E-3 *</td>
<td>2E-2</td>
<td>8E-3</td>
</tr>
<tr>
<td>C</td>
<td>Not Affected</td>
<td>4E-1</td>
<td>2E-3 *</td>
<td>4E-3</td>
</tr>
<tr>
<td>D</td>
<td>2E-2</td>
<td>5E-2</td>
<td>8E-3 *</td>
<td>1E-2</td>
</tr>
<tr>
<td>E</td>
<td>2E-2*</td>
<td>4E-2</td>
<td>4E-2</td>
<td>3E-2</td>
</tr>
<tr>
<td>F</td>
<td>1E-3</td>
<td>4E-3</td>
<td>6E-4*</td>
<td>8E-4</td>
</tr>
<tr>
<td>G</td>
<td>1E-1</td>
<td>4E-2 *</td>
<td>8E-2</td>
<td>6E-2</td>
</tr>
<tr>
<td>H</td>
<td>Not Affected</td>
<td>8E-3*</td>
<td>8E-2</td>
<td>2E-2</td>
</tr>
</tbody>
</table>

*Reference Dose Value, Critical effect

**Reference Values are the Oral Reference Dose for the critical effect; and Target Organ Toxicity Dose, TTD, for effects other than the critical effect.
### Screening Level Hazard Index Calculation*

<table>
<thead>
<tr>
<th>Chemical</th>
<th>Exposure**</th>
<th>RfD**</th>
<th>Organ/Tissue</th>
<th>HQ</th>
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<tbody>
<tr>
<td>A</td>
<td>3E-3</td>
<td>5E-3</td>
<td>Developmental</td>
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</tr>
<tr>
<td>B</td>
<td>2E-4</td>
<td>4E-3</td>
<td>Thyroid</td>
<td>0.05</td>
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<tr>
<td>C</td>
<td>8E-4</td>
<td>2E-3</td>
<td>Liver</td>
<td>0.40</td>
</tr>
<tr>
<td>D</td>
<td>1E-3</td>
<td>8E-3</td>
<td>Liver</td>
<td>0.125</td>
</tr>
<tr>
<td>E</td>
<td>7E-3</td>
<td>2E-2</td>
<td>Developmental</td>
<td>0.35</td>
</tr>
<tr>
<td>F</td>
<td>4E-5</td>
<td>6E-4</td>
<td>Liver</td>
<td>0.067</td>
</tr>
<tr>
<td>G</td>
<td>7E-3</td>
<td>4E-2</td>
<td>Thyroid</td>
<td>0.175</td>
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<td>H</td>
<td>4E-4</td>
<td>8E-3</td>
<td>Thyroid</td>
<td>0.05</td>
</tr>
</tbody>
</table>

**Screening HI= 1.82**


**Both exposure and RfD are in units of mg/kg-day
## Hazard Index Calculation

<table>
<thead>
<tr>
<th>Chemical</th>
<th>Exposure**</th>
<th>RfD**</th>
<th>Organ/Tissue HQ</th>
<th>Developmental</th>
<th>Thyroid</th>
<th>Liver</th>
<th>Hematopoietic</th>
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<tbody>
<tr>
<td>A</td>
<td>3E-3</td>
<td>5E-3</td>
<td>0.60</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>B</td>
<td>2E-4</td>
<td>4E-3</td>
<td>-</td>
<td>0.05</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>C</td>
<td>8E-4</td>
<td>2E-3</td>
<td>-</td>
<td>-</td>
<td>0.40</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>D</td>
<td>1E-3</td>
<td>8E-3</td>
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<td>-</td>
<td>0.125</td>
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<td>-</td>
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<tr>
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<tr>
<td>H</td>
<td>4E-4</td>
<td>8E-3</td>
<td>-</td>
<td>0.05</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

**HI** = 0.95

**Developmental**

**Thyroid**

**Liver**

**Hematopoietic**
### Target Organ Toxicity Dose Calculation

<table>
<thead>
<tr>
<th>Chem</th>
<th>Developmental</th>
<th>Thyroid</th>
<th>Liver</th>
<th>Hematopoietic</th>
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<tbody>
<tr>
<td></td>
<td>TTD</td>
<td>Exp.</td>
<td>HQ</td>
<td>TTD</td>
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<tr>
<td>A</td>
<td>5E-3*</td>
<td>3E-3</td>
<td>0.60</td>
<td>6E-3</td>
</tr>
<tr>
<td>B</td>
<td>6E-3</td>
<td>2E-4</td>
<td>0.033</td>
<td>4E-3*</td>
</tr>
<tr>
<td>C</td>
<td>N/A</td>
<td>8E-4</td>
<td>N.D.</td>
<td>4E-1</td>
</tr>
<tr>
<td>D</td>
<td>2E-2</td>
<td>1E-3</td>
<td>0.05</td>
<td>5E-2</td>
</tr>
<tr>
<td>E</td>
<td>2E-2*</td>
<td>7E-3</td>
<td>0.35</td>
<td>4E-2</td>
</tr>
<tr>
<td>F</td>
<td>1E-3</td>
<td>4E-5</td>
<td>0.04</td>
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<td>1E-1</td>
<td>7E-3</td>
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<tr>
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<td>N/A</td>
<td>4E-4</td>
<td>N.D.</td>
<td>8E-3*</td>
</tr>
<tr>
<td><strong>TTD</strong></td>
<td><strong>1.14</strong></td>
<td><strong>TTD= 0.98</strong></td>
<td><strong>TTD = 0.91</strong></td>
<td><strong>TTD= 1.25</strong></td>
</tr>
</tbody>
</table>

*RfD Value
N/A = developmental effects not indicated in the absence of maternal toxicity
N.D. = calculation of TTD for this chemical/endpoint not warranted, value is zero
Component Based Methods for Chemical Mixtures Risk Assessment: Apply to Integrated Exposure/Toxicity Groups

- Multiple Toxicological Effects for Each Component
  - Multivariate Statistical Models: Categorical Regression Modeling with Hazard Index & Response Addition
- Toxicological Interactions Data
  - Weight of Evidence Evaluations, Interaction Based Hazard Index
- Toxicologically Similar Components (Multi-Route Exposures)
  - Dose Addition: Hazard Index, Relative Potency Factors
- Mix of Toxicologically Similar and Independent Components Or Groups
  - Integrated Additivity Methods: Using Both Dose Addition & Response Addition
- Toxicologically Independent Components
  - Response Addition

Risk Characterization and Uncertainty Analysis
Dose Addition Theory: 
Relative Potency Factors

Assuming same mode-of-action, similarly shaped D-R curves, for exposure to a mixture of n chemicals:

\[ R_m = f_1 \left( \sum_{i=1}^{n} \left( D_1 + t_i \times D_i \right) \right) \]

Interpreted as:
mixture response = sum(doses scaled for relative potency), evaluated using the dose-response curve of the index chemical 1

Where:  
\( R_m \) = mixtures response  
\( D_i \) = exposure dose of chemical i  
\( t_i \) = potency of chemical i relative to chemical 1  
\( f_1 \) = d-r curve for the index chemical 1
Relative Potency Factor (RPF) Method

Given that mixture risk (Rm) is:

\[ R_m = f_1\left( D_1 + RPF_i \times D_i \right), \]

for a given chemical i with Dose (D_i) and Index Chemical 1 at Dose D_1, the RPF_i may be estimated as a ratio of equally toxic doses of the 2 chemicals, e.g.,

\[ RPF_i = \left( \frac{ED_{10}(\text{Index Chemical})}{ED_{10}(\text{Chemical } i)} \right) \]

Note: EDx = the “Effective Dose” at which an x% response is observed. This method can be extended to evaluate mixtures of many chemicals.

The sum of the scaled doses forms the Index Chemical Equivalent Dose (ICED). The ICED is evaluated using the dose response information of the Index Chemical.
Relating Potency: Rat Toxicity Studies

Chemical A
Chemical B (Index Chemical)
Chemical C

Dose (mg/kg/day)

Fixed Response Level

5 25 125
# Computing Relative Potency

Fixed response level, same measurement technique

<table>
<thead>
<tr>
<th>Chemical</th>
<th>Rat ED 10 Oral Dose</th>
<th>RPF Oral Dose</th>
<th>Human Dose (mg/kg/day)</th>
<th>ICED*** (mg/kg/day)</th>
<th>% of Subgroup ICED</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>25</td>
<td>5/25 = 0.2</td>
<td>0.002</td>
<td>0.0004</td>
<td>5</td>
</tr>
<tr>
<td>B</td>
<td>5</td>
<td>5/5 = 1</td>
<td>0.005</td>
<td>0.005</td>
<td>67</td>
</tr>
<tr>
<td>C</td>
<td>150</td>
<td>5/150 = 0.03</td>
<td>0.07</td>
<td>0.0021</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Total ICED</td>
<td>0.0075</td>
</tr>
</tbody>
</table>

**Total ICED**
Estimate Mixture Response

Chemical B (Index Chemical)

![Graph showing dose-response relationship for Chemical B]

- Dose (mg/kg/day) vs. Response Level
- ICED: 0.0075

- B

- 0.01
- 0.005
- 0.001
- 0.005
- 0.01
Response Addition Method

\[ R_m = \sum_{i=1}^{n} r_i \]

Where:
- \( R_m \) = mixtures risk
- \( n \) = number of components
- \( r_i \) = component risks

Assumes biological and statistical independence of action.
Use is appropriate at low doses where
- interaction effects are less likely, and
- risks are small, so cross-products are negligible.
Response Addition: How to Estimate Response?

Response Addition:

Independence of Action

\[ R_m = f_1(D_1) + f_2(D_2) + f_3(D_3) = R_1 + R_2 + R_3 \]
Cumulative RPF Analysis - Sum MOA Groups A and B Risks

Component ICED for Index Chemical A1 = DoseA1*1

Component ICED for Chemical A2 = DoseA2*RPFA2

Component ICED for Chemical A3 = DoseA3*RPFA3

Component ICED for Chemical B1 = DoseB1*RPFB1

Component ICED for Chemical B2 = DoseB2*RPFB2

Component ICED for Index Chemical Chemical B3 = DoseB3*1

Dose Addition for Chemicals in MOA Group A

Dose Addition for Chemicals in MOA Group B

ICED for MOA Group A

ICED for MOA Group B

MOA Group A ICED

MOA Group B ICED

Response Addition for Total Mixture Risk

Risk for MOA Group A Evaluated at Group A ICED \((r_1)\)

Risk for MOA Group B Evaluated at Group B ICED \((r_2)\)

Total Mixture Risk as Sum of Risks for MOA Groups A and B \((r_1 + r_2)\)

Response Addition for Total Mixture Risk

In Conclusion, CRA ......

• Is solidly based on Mixtures Toxicology concepts and practice,
• Is established and the practice is codified,
• Addresses population (community) -based risk,
• Requires exposure assessment and dose-response data,
• Optimally includes information on mode of action,
• Can characterize or confirm susceptibility,
• Can identify major agents or sources for remediation, and
• Can be an effective tool to prioritize community-based health improvement activities.
Some References


Special Thanks to....

Linda Teuschler
Glenn Rice
Jason Lambert
Michael Wright
Moiz Mumtaz
Jane Ellen Simmons