Application of the WHO Framework for Combined Exposures; Implications for Assessment

SRA DRSG Webinar
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Outline

• WHO IPCS Framework for Combined Exposures
  – Objectives
    • Building on Existing Methodology
    • Incorporating Recent Developments to Increase Efficiency

• What’s happened since

• Implications for *Tiered Priority Setting/Assessment, Uncertainty & Sensitivity* Analysis, Communication
Evolving International Mandates for Existing Chemicals

• Canada
  – “Categorization” for 23, 000 chemicals - Sept., 2006 & multi tiered assessment program
• Europe
• Japan Stepwise Assessment under the Chemical Substances Control Law (CSCL)” (2009)
• Australia Inventory Multi Tiered Assessment and Prioritization (IMAP) (2012)
• New Zealand Group Standards for Industrial Chemicals (HSNO)
• U.S.
  – Research Initiatives /Legislative Renewal?
Assessment for Combined Exposures
State of the Art (Modified from US EPA)

Assess Data Quality
- inadequate → Only Qualitative Assessment
- adequate
  - Whole Mixture
    - Mixture of Concern
      - Mixture RfD/C; Slope Factor
    - Sufficiently Similar Mixture
    - Group of Similar Mixtures
  - Components
    - Toxicologically Similar
      - Hazard Index
      - Relative Potency Factors
    - Toxicologically Independent
      - Response Addition
    - Interactions
      - Hazard Index

Dose Addition
Independent Joint Action
Interaction (> or < dose addition)
Dose Addition

Hazard Index, Reference Dose

\[
HI = \sum_{i=1}^{n} \frac{\text{estimated intake}_i}{RfD_i}
\]

Point of Departure Index

\[
PODI = \sum_{i=1}^{n} \frac{\text{estimated intake}_i}{POD_i}
\]

Toxic Equivalency

\[
TEQ = \sum_{i=1}^{n} C_i \times TEF_i
\]
Status – WHO IPCS Combined Exposures

• Overview workshop to review terminology & methodology in March/07
  – 27 invited senior experts from relevant agencies worldwide; 5 reps from partnering organizations
• Post workshop development of framework/case studies
  – WHO IPCS Drafting Group
  – ECETOC, ILSI HESI
• Framework & case studies posted for public comment & revised
  – Feb/2010 meeting – London; published 2011 (Reg. Tox. & Pharmacol. 60, S1 – S14)
• OECD/WHO/ILSI workshop
  – Feb/2011 – Paris
• Contributing to a number of international and national initiative and evolving based on case studies
Recommendations:

• Avoid use of non-descriptive terms
• Avoid generic use of the term “mixtures”
• “Simple”, “complex” to relate to modes of action, rather than numbers of components

Terminology:

• “Single Chemical, All Routes”
• “Multiple Chemicals”, “Single” or “Multiple Routes”
• (Combined) “Assessment Group”
• “Dose additive” – same mode of action
• “Independent Joint Action” - independent modes of action or different target
• “Departing from Dose Additivity”
  – Interactive effects
Contents of the WHO IPCS Framework

• When to conduct a combined assessment
  • i.e., considering several chemicals at once

• Generic description of the framework approach
  – “Fit for purpose”
  – Pragmatic tiered structure with increasingly detailed consideration of both exposure and hazard
  – Exposure influential in setting priorities

• Three case studies (examples, only)
  – Priority setting for drinking water contaminants, based on the threshold for toxicological concern
  – Screening assessment on PBDEs
  – Full assessment on carbamates
Problem Formulation for Grouping

Nature of exposure?
Is exposure likely?
Co-exposure within a relevant timeframe?
Rationale for considering compounds in an assessment group?

Uncertainty
Sensitivity

Tiered Exposure Assessments
- Tier 0: Simple semi-quantitative estimates of exposure
- Tier 1: Generic exposure scenarios using conservative point estimates
- Tier 2: Refined exposure assessment, increased use of actual measured data
- Tier 3: Probabilistic exposure estimates

Assessment
Yes, no further action required

Is the margin of exposure adequate?

No, continue with iterative refinement as needed (i.e. more complex exposure & hazard models)

Tiered Hazard Assessments
- Tier 0: Default dose addition for all components
- Tier 1: Refined potency based on individual POD, refinement of POD
- Tier 2: More refined potency (RPF) and grouping based on MOA
- Tier 3: PBPK or BBDR; probabilistic estimates of risk

Modified from Meek et al., 2011
Exposure Based Problem Formulation

• What is the nature of combined exposure?
  – If not known: may need risk management or data on key components/mixture

• Is exposure likely taking into account the context?
  – consideration of use profile, environmental dilution/degradation, substance not absorbed

• Is there a likelihood of co-exposure within a relevant time frame?
  – Consider time related aspects, both external exposure and mode of action (toxicokinetics and dynamics)
  – If likelihood of co-exposure low, don’t assess as group
Problem Formulation (Cont’d) - Hazard

• What is the rationale for considering compounds in an assessment group?
  – Information on chemical structure (SAR, QSAR, structural alerts)
  – Hazard or other biological data (tox or efficacy)
    • Same target organs
    • Same biological outcome
    • Same intended use target of the chemical
      – (e.g. anti-oxidant use in fat, moulting inhibitors)
Case Study – TTC – Contaminants in Drinking Water

Problem Formulation

Nature of exposure?
Is exposure likely?
Co-exposure within a relevant timeframe?
Rationale for considering compounds in an assessment group?

Tiered Exposure Assessment

Yes, no further action required

Input from exposure or hazard assessments (iterative process)

Is the margin of exposure adequate?

Tiered Hazard Assessment

Tier 0
Generic thresholds

Increasing refinement of exposure

Increasing refinement of hazard

Tier 1-2
Highest measured levels in drinking water
Illustrative Case Study for Tier 0/1 – Drinking Water

- Based on Hazard Index

\[
HI = \sum_{i=1}^{n} \frac{\text{estimated intake}_i}{RfD_i}
\]

- and the Threshold of Toxicological Concern (TTC)
  - Based on chemical structure, a generic (i.e., non chemical specific) “conservative” toxicity value can be identified for many chemicals
  - 5th percentile NOEL of all compounds in the dataset for that particular class
Contaminants in Drinking Water – Tier 0 Hazard

Structural alerts for genotoxicity or no data?: TTC=0.15 µg/day

- 90 µg/day (0.15 mg/kg/d)
- 540 µg/day (0.90 mg/kg/d)
- 1800 µg/day (3 mg/kg/d)

NOEL/100 (mg/kg/day)
Illustrative case study – Tier 0/1 Exposure

• 10 substances found in surface waters
  – Assume all present simultaneously at all times, at max concentration detected
  – Assume all belong to same assessment group, i.e. act by dose addition
  – Assume 100% of drinking water is from this source

• Use maximum exposure group (in this case, 3-6 years of age)
  – Exposure (mg/kg-bw/day) = 
    \[
    \frac{\text{Surface water concentration (ppm)} \times 0.42 \text{ L consumption/ day}}{18 \text{ kg body weight}}
    \]
**Illustrative case study. Contaminants in Drinking Water**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Water conc [ppb]</th>
<th>Exposure (mg/kg/d)</th>
<th>Cramer class</th>
<th>TTC (mg/kg/d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>0.083</td>
<td>1.94E-06</td>
<td>II</td>
<td>0.0091</td>
</tr>
<tr>
<td>B</td>
<td>0.076</td>
<td>1.77E-06</td>
<td>III</td>
<td>0.0015</td>
</tr>
<tr>
<td>C</td>
<td>3.8</td>
<td>8.87E-05</td>
<td>II</td>
<td>0.0091</td>
</tr>
<tr>
<td>D</td>
<td>1.7</td>
<td>3.97E-05</td>
<td>I</td>
<td>0.0300</td>
</tr>
<tr>
<td>E</td>
<td>0.13</td>
<td>3.03E-06</td>
<td>III</td>
<td>0.0015</td>
</tr>
<tr>
<td>F</td>
<td>0.18</td>
<td>4.20E-06</td>
<td>III</td>
<td>0.0015</td>
</tr>
<tr>
<td>G</td>
<td>34</td>
<td>7.93E-04</td>
<td>II</td>
<td>0.0091</td>
</tr>
<tr>
<td>H</td>
<td>0.28</td>
<td>6.53E-06</td>
<td>I</td>
<td>0.0300</td>
</tr>
<tr>
<td>I</td>
<td>6.1</td>
<td>1.42E-04</td>
<td>III</td>
<td>0.0015</td>
</tr>
<tr>
<td>J</td>
<td>1.1</td>
<td>2.57E-05</td>
<td>I</td>
<td>0.0300</td>
</tr>
</tbody>
</table>

HQ (each substance) = \( \frac{\text{Exposure (each substance)}}{\text{TTC value (each substance)}} \)

HI (combined exposure) = \( HQ_A + HQ_B + HQ_C + HQ_D \ldots + HQ_J \)

HI < 1, no need to go on to Tier 1
Sample Calculations (Degree of Conservatism)

- based on the highest measured concentrations of all analytes assumed to be constantly present in the water
- all drinking water assumed to be from the single source (normally not the case)
- estimate for age group with greatest consumption on a body wt basis (children)
- each TTC value represents the 5\(^{th}\) percentile (i.e., 95\% of the compounds in the class were less toxic)
- assumed dose addition for the entire group
Drinking Water Tier 0/1 Risk Characterization

• Hazard Index < 1; considered adequate in context of degree of conservatism
• No need to go to higher tier
• If the example had gone to a higher tier, could crudely quantitate the degree of conservatism of the HI, particularly in relation to the assumptions on exposure
• This would need to be balanced against limitations of the TTC in relation to the contributing database and the extent of characterization of the appropriate range of chemicals in drinking water
  – E.g., did the 10 chemicals represent those expected to be present at highest concentrations?
Case Study - Tiered Exposure and Hazard Considerations - PBDEs

Problem Formulation

Nature of exposure?
Is exposure likely?
Co-exposure within a relevant timeframe?
Rationale for considering compounds in an assessment group?

Tiered Exposure Assessment

Tier 0
Semi-quantitative estimate based on use patterns

Tier 1
Highest value for conservative point estimates from all media for 6 age groups

Yes, no further action required

Input from exposure or hazard assessments (iterative process)

Is the margin of exposure adequate?

Tiered Hazard Assessment

Tier 0 - 1
Potency for most sensitive endpoint for most toxic of 7 congeners based on LOEL
Case Study - PBDEs

Background
• Used widely as flame retardants in consumer products
• 3 main commercial mixtures/7 different isomers
• Screening assessment for general population

Problem Formulation for Grouping
• Exposure likely?
  • Direct & indirect contact with PBDE containing products
• Co-exposure?
  • Overlap in isomers within commercial mixtures; similar kinetics
• Rationale for assessment group?
  • 7 isomers with identical base structure, similar uses & common target organs. Trend in pchem properties/toxicity with ↑ bromination.
Tier 0 – Exposure – PBDEs – General Population

- Relative ranking of all Existing Substances in Canada during categorization, based on limited information provided for all:
  - quantity (estimated annual quantity of use, Q),
  - number of submitters (S)
  - use (sum of normalized expert ranked use codes, U), reflecting two workshops $\sum$ (use $\times$ PE)

- Convert to semiquantitative measure of exposure by normalizing to Priority Substances with similar use profile/phys-chem properties
**Tier 0 Hazard - PBDEs**

- Not possible to develop a hazard index, due to lack of reference doses

\[
HI = \sum_{i=1}^{n} \frac{\text{estimated intake}_i}{RfD_i}
\]

- Arrayed the data to consider lowest reported effect level for most toxic isomer
## Tier 0 – Hazard – PBDEs (cont’d)

<table>
<thead>
<tr>
<th>Congener Group</th>
<th>LOEL (mg/kg bw/day)</th>
<th>Endpoint</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>TeB</td>
<td>11</td>
<td>Developmental: behavioural (mouse)</td>
<td>E et al. (2001)</td>
</tr>
<tr>
<td>PeB</td>
<td>0.8</td>
<td>Developmental: behavioural (mouse)</td>
<td>E et al. (1998, 2001)</td>
</tr>
<tr>
<td>HxB</td>
<td>0.9</td>
<td>Developmental: behavioural (mouse)</td>
<td>V et al. (2002)</td>
</tr>
<tr>
<td>HeB</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>OcB</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>NoB</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>ComPeB</td>
<td>2</td>
<td>Liver histopathology: subchronic dietary study (rat)</td>
<td>GLCC (undated)</td>
</tr>
<tr>
<td>ComOcB</td>
<td>5</td>
<td>Liver weight: subchronic dietary study (rat)</td>
<td>GLCC (1987)</td>
</tr>
</tbody>
</table>
Risk Characterization/Uncertainties

- Summed semiquantitative benchmarked measures of exposure > lowest observed effect level for the most toxic congener

- Need for higher tier assessment
  - Very conservative estimate of exposure
    - Semi-quantitative based on very limited data
    - Very high degree of uncertainty, based on a series of very conservative choices
**Tier 1 - Exposure – PBDEs**

- Upper bound estimate of daily intake of total PBDEs by 6 age groups of the population based on:
  - Monitoring data in ambient and indoor air, water, various foodstuffs, human breast milk and dust
  - Standard reference values for intakes, body weights, etc.
  - In separate scenarios, considered also:
    - a traditional “country food diet”
    - estimated intake from dermal contact with household products
Appendix to case-study A on PBDEs: Supporting data

Table 3: Upper-bounding estimate of PBDE daily intake for the general population.

<table>
<thead>
<tr>
<th>Route of exposure</th>
<th>Estimated intake (µg/kg-bw per day) of PBDEs by various age groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Formula fed&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Ambient air&lt;sup&gt;i&lt;/sup&gt;</td>
<td>7.7 × 10&lt;sup&gt;-6&lt;/sup&gt;</td>
</tr>
<tr>
<td>Indoor air&lt;sup&gt;i&lt;/sup&gt;</td>
<td>4.4 × 10&lt;sup&gt;-4&lt;/sup&gt;</td>
</tr>
<tr>
<td>Drinking-water&lt;sup&gt;k&lt;/sup&gt;</td>
<td>1.4 × 10&lt;sup&gt;-3&lt;/sup&gt;</td>
</tr>
<tr>
<td>Food&lt;sup&gt;d&lt;/sup&gt;</td>
<td>2.3 × 10&lt;sup&gt;-3&lt;/sup&gt;</td>
</tr>
<tr>
<td>Soil/dust&lt;sup&gt;m&lt;/sup&gt;</td>
<td>2.3 × 10&lt;sup&gt;-1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Total intake&lt;sup&gt;n&lt;/sup&gt;</td>
<td>2.3 × 10&lt;sup&gt;-1&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> Assumed to weigh 7.5 kg, to breathe 2.1 m<sup>3</sup> of air per day, to drink 0.2 litres/day (not formula fed) and to ingest 30 mg of soil per day. Consumption of food groups reported in Health Canada (1998).

<sup>b</sup> Breastfed infants are assumed to have an intake rate of 0.75 kg of formula per day. TeBDE to HeBDE congeners were identified in a composite sample of baby formula at a value of 14 ng/kg (Ryan, undated). This study was the only data point for the medium.

<sup>c</sup> The sum of the maximum concentrations of TeBDE to HeBDE identified in 72 samples of human breast milk collected in 1992 in Canada was 589 ng/g fat (Ryan & Patry, 2001a, 2001b; Ryan et al., 2002a, 2002b). Breastfed children 0–6 months of age are assumed to have an intake rate of 0.75 kg of breast milk per day (Health Canada, 1998). The percent fat of human breast milk has been estimated at 4% (USEPA, 1997). No data on levels of OcBDE, NoBDE or DeBDE in human milk were identified. Data considered in the selection of critical data also included Damerud et al. (1998, 2002), Meironyte et al. (1998), Ryan & Patry (2000), Strandman et al. (2000), Atuma et al. (2001), Papke et al. (2001), Hori et al. (2002), Meironyte Guvenius et al. (2002) and Ohta et al. (2002).

<sup>d</sup> Assumed to weigh 15.5 kg, to breathe 9.3 m<sup>3</sup> of air per day, to drink 0.7 litres of water per day and to ingest 100 mg of soil per day. Consumption of food groups reported in Health Canada (1998).

<sup>e</sup> Assumed to weigh 31.0 kg, to breathe 14.5 m<sup>3</sup> of air per day, to drink 1.1 litres of water per day and to ingest 65 mg of soil per day. Consumption of food groups reported in Health Canada (1998).

<sup>f</sup> Assumed to weigh 59.4 kg, to breathe 15.8 m<sup>3</sup> of air per day, to drink 1.2 litres of water per day and to ingest 30 mg of soil per day. Consumption of food groups reported in Health Canada (1998).

<sup>g</sup> Assumed to weigh 70.9 kg, to breathe 16.2 m<sup>3</sup> of air per day, to drink 1.5 litres of water per day and to ingest 30 mg of soil per day. Consumption of food groups reported in Health Canada (1998).

<sup>h</sup> Assumed to weigh 72.0 kg, to breathe 14.3 m<sup>3</sup> of air per day, to drink 1.6 litres of water per day and to ingest 30 mg of soil per day. Consumption of food groups reported in Health Canada (1998).
Sample Calculations (Degree of Conservatism)

• In addition to the 6 age groups, 3 subsets of infants (formula fed, breast-fed, non-formula fed)
• General and likely highly exposed populations
• \textit{Sum} of the \textit{maximum} concentrations of measured congeners in human milk
• For each of 8 food groups, assumed \textit{highest} concentrations of the \textit{sum} of PBDEs in analyzed food items in that group
• \textit{Maximum} value of group (PBDEs) in surface water
• \textit{Maximum} sums of measured PBDEs in ambient, indoor air and housedust

Need to quantitate (at least crudely) uncertainty/conservatism for critical determinants as a basis to consider adequacy of margin of exposure
**PBDEs Tier 1 Risk Characterization**

- Margin between critical effect level and upper bound deterministic estimate of exposure
  - intake of total PBDEs for the most highly exposed subgroup of the population (breastfed infants):
    \[ \frac{0.8 \text{ mg/kg bw/day}}{2.6 \text{ ug/kg bw/day}} = 300 \]
  - Margin considered adequate in context of degree of conservatism
    - Critical effect level was for most sensitive effect for most toxic congener; effects in chronic studies were 100 x greater
    - Large interindividual variability in PBDEs in breast milk
      - *Mean & median levels 400 & 200 fold < than maximum levels used in estimates*

- Needs to be balanced against:
  - Increase in body burden of PBDEs over time (9x between 1992 & 2001)
Case Study - Tiered Exposure and Hazard Considerations - Carbamates

**Problem Formulation**

Nature of exposure?
Is exposure likely?
Co-exposure within a relevant timeframe?
Rationale for considering compounds in an assessment group?

**Assessment**

Yes, no further action required

Is the margin of exposure adequate?

Tier 3
Probabilistic exposure estimates

Tier 2
More refined grouping based on MOA; refinement of POD

Increasing refinement of exposure

Increasing refinement of hazard

Tiered Exposure Assessments

Tiered Hazard Assessments

Leaving Group
Carbamates Higher Tier Assessment

- **Exposure assessment** (Tier 3)
  - Probabilistic modeling of exposure using United States Dept of Agriculture Pesticide Data Program findings (pesticide residues in commodities) and food intake survey data

- **Hazard assessment** (Tier 2)
  - age-specific refinement of potency factors

- Outcome: **Margin of Exposure sufficient**
Learnings

- Limited numbers of regulatory examples
  - Legislative drivers critical
- Exposure more discriminating than hazard
- Limited use of predictive/screening methods
  - Combined assessments sometimes more complex than necessary; focussed on hazard
  - Limited use of exposure profiling to “group”
- Importance of problem formulation
  - “Fit for purpose” assessment; Communication
- Importance of “framing” output of tiers
  - Degree of conservatism, understanding the most influential parameters
Limited Progress on Combined Exposures?

- We’ve been challenged to consider combined exposures for some time, though most of our regulatory mandates have been chemical specific.
- Limited application of consideration of combined exposures.
  - Exception has been contaminated sites and more recently, pesticides.
    - Both were driven by legislated mandates.
- The legislated mandates worldwide to assess more chemicals more efficiently should also contribute.
  - Need to consider more chemicals efficiently.
    - Necessarily in groups.
Principles – Facilitating Regulatory Change

1. transitioning in a familiar context,
2. tiering to acquire experience and increase confidence,
3. contextual knowledge transfer to facilitate interpretation and communication in application,
4. coordination and development of expertise and
5. the importance of continuing challenge

Meek, M.E. & Lipscomb., J. Toxicol. (submitted)
Learnings

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  – Legislative drivers critical
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• Importance of problem formulation
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**Problem Formulation for Grouping**

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**Uncertainty**

**Sensitivity**

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**Tiered Exposure Assessments**

- **Tier 0**
  - Simple semi-quantitative estimates of exposure

- **Tier 1**
  - Generic exposure scenarios using conservative point estimates

- **Tier 2**
  - Refined exposure assessment, increased use of actual measured data

- **Tier 3**
  - Probabilistic exposure estimates

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**Assessment**

Yes, no further action required

Is the margin of exposure adequate?

No, continue with iterative refinement as needed (i.e. more complex exposure & hazard models)

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**Tiered Hazard Assessments**

- **Tier 0**
  - Default dose addition for all components; generic hazard measures

- **Tier 1**
  - Refined potency based on individual POD, refinement of POD

- **Tier 2**
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Modified from Meek et al., 2011
Learnings

• Limited numbers of regulatory examples
  – Legislative drivers critical
• Exposure more discriminating than hazard
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  – Limited use of exposure profiling to “group”
• Importance of problem formulation
  • “Fit for purpose” assessment; Communication
• Importance of “framing” output of tiers
  – Degree of conservatism, understanding the most influential parameters
Example Tier 0 Exposure

- Budget method for food additives
- Calculation by:
  - Maximum amount of food and drinks consumed
  - Maximum levels in foods and drinks
    - 300 mg/kg in specific food categories (decorations, sauces, pickles)
    - 200 mg/L in drinks
  - Proportion of food that can contain additive
    - 25%

Intake = \(300 \times 0.025 \times 0.25 + 200 \times 0.1 \times 0.25 = 7 \text{ mg/kg bw/d} \)
The Challenge to the Exposure Community

• Broadly drawing upon the assessment experience on (relatively limited numbers of) (data rich) chemicals, to develop first order estimates of exposure:
  – Identification of a limited number of key parameters as exposure determinants (n = ?),
  – And their relevant information sources,
    • Which could include data generation
• But recognizing: that readily accessible information not necessarily the most informative
Screening of Hazard

• While hazard appears to be less discerning than exposure, identified need for simpler and more predictive measures of potency to increase efficiency in combined exposures assessment

• For example, even though an early tier tool, the hazard index is fairly data intensive
  – requires a sufficiently full database to characterize RfDs for component compounds

• Some progress in this area
  – Mechanistic groupings
New developments in the evolution and application of the WHO/IPCS framework on mode of action/species concordance analysis†

M. E. Meek*, A. Boobis†, I. Cote*, V. Dellarco*, G. Fotakis*, S. Munn*, J. Seed* and C. Vickers*

ABSTRACT: The World Health Organization/International Programme on Chemical Safety mode of action/human relevance framework has been updated to reflect the experience acquired in its application and extend its utility to emerging areas in toxicity testing and non-testing methods. The underlying principles have not changed, but the framework’s scope has been extended to enable integration of information at different levels of biological organization and reflect evolving experience in a much broader range of potential applications. Mode of action/species concordance analysis can also inform hypothesis-based data generation and research priorities in support of risk assessment. The modified framework is incorporated within a roadmap, with feedback loops encouraging continuous refinement of fit-for-purpose testing strategies and risk assessment. Important in this construct is consideration of dose-response relationships and species concordance analysis in weight of evidence. The modified Bradford Hill considerations have been updated and additionally articulated to reflect increasing experience in application for cases where the toxicological outcome of chemical exposure is known. The modified framework can be used as originally intended, where the toxicological effects of chemical exposure are known, or in hypothesizing effects resulting from chemical exposure, using information on putative key events in established modes of action from appropriate in vitro or in vivo systems and other lines of evidence. This modified mode of action framework and accompanying roadmap and case examples are expected to contribute to improving transparency in explicitly addressing weight of evidence considerations in mode of action/species concordance analysis based on both conventional data sources and evolving methods. Copyright © 2013 John Wiley & Sons, Ltd. The World Health Organization retains copyright and all other rights in the manuscript of this article as submitted for publication.

Keywords: key events; mode of action; adverse outcome pathway; human relevance framework; modified Bradford Hill considerations; weight of evidence approach; species concordance analysis; cellular response; tissue response; molecular target

Introduction

The mode of action/human relevance framework was developed in initiatives of the International Programme on Chemical Safety (IPCS) of the World Health Organization (WHO) (Boobis et al., 2006, 2008; Sonich-Mullin et al., 2001) and the International Life Sciences Institute Risk Sciences Institute (ILSIRSII) (Meek et al., 2003; Seed et al., 2005). It derives from earlier work [mode of action in animals by the US Environmental Protection Agency (US EPA, 1996, 2005a)] and has involved large numbers of scientists internationally.

Previous development of the mode of action/human relevance framework is described in the publications mentioned above and summarized more recently in Meek and Klauning (2010). The framework has been illustrated by an increasing number of case studies (more than 30 currently) demonstrating the value of mode of action in evaluating human relevance and life stage susceptibility and guiding dose-response assessment. Documented examples are presented in Table 1. The contribution of the framework has been recognized by the Society of Toxicology, and the framework has been adopted by several international and national organizations and agencies to increase transparency in the assessment of weight of evidence and identification of critical data needs (Meek, 2008, 2009; Meek et al., 2008).

The framework continues to evolve as experience increases in its application to consider systematically the weight of evidence


- Roadmap for fit-for-purpose testing strategies and risk assessment, to:
  - Integrate information from evolving technologies in more predictive context
  - Updated framework
  - Updated Supporting templates
  - Case Examples illustrating use of MOA analysis in more predictive context (i.e., earlier tiers of assessment)
Case example 6: Mode of action in grouping and potency estimates for combined exposures

Anchoring the results of (new) in vitro approaches to relevant outcomes based on existing knowledge and concepts:

• Class of pesticides, same well established mode of action and insecticidal effects
  – reversible neurotoxicity through interaction with neuronal sodium channels

• Members of the class expected to share key events
  – Interaction with sodium channels

• Consider grouping and rank for potency for broader group of compounds in suitable \textit{in vitro} system for this key event
Learnings

- Limited numbers of regulatory examples
  - Legislative drivers critical
- Exposure more discriminating than hazard
- Limited use of predictive/screening methods
  - Combined assessments sometimes more complex than necessary; focussed on hazard
  - Limited use of exposure profiling to “group”
- Importance of problem formulation
  - “Fit for purpose” assessment: Communication
  - Importance of “framing” output of tiers
    - Degree of conservatism, understanding the most influential parameters
Importance of “Framing” of the Tiers Considering Uncertainty, Variability and Sensitivity in Hazard Values

• Tiered assessment strategies necessitate consideration of factors relevant to both exposure and effect that impact most
  – Sensitivity analysis
  – Essential to be efficiency in refinement of assessments in tiered strategy and as basis for data generation

• Evaluation of the adequacy of MOEs promotes consideration of important sources of uncertainty and variability and their weighting for hazard
  – Not necessarily those considered in “uncertainty factors” for reference doses
RfD Components
- “Sensitivity” Analysis

• Animal model for selected effect relevant/predictive in humans? (MOA) (uncertainty)
• Interspecies differences (principally variability)
• Human variability
• Benchmark dose response rate selection
• Uncertainty factors for limitations of the database (uncertainty)
  – E.g., lack of chronic, reproductive or other study; reliance on a LOAEL, etc.
• Dose-response model selection
Learnings – Efficiency of Assessment

• Assessment needs to be “fit for purpose”
  – Dependent on early problem formulation/issue identification
    • Objective? Resources? Deadlines? Efficiency
  – Taking into account:
    • current data availability; likelihood of successfully generating data in required timeframe
    • understanding of the most influential parameters
      – What is the “value” of the information?
• Problem formulation is important, even where a combined assessment is not a priority
  – Facilitates communication
  – Clear delineation of basis for grouping
Next Steps
Recommendations from Feb./11 WHO-OECD-ILSI-HESI Workshop

• Coordination/Harmonization
  – multi-sector, multi-stakeholder, global coordinating/working group
  – Repository of case studies

• Additional Case Studies
  – e.g., additional data rich, data poor, effects based, including non-chemical stressors, prospective; environmental effects

• Development/Refinement of Tools and Approaches
  – e.g., problem formulation “triggers”; “drivers”; uncertainty analysis

• Communication
  – e.g., lower tiers; training
More Recent Developments

- OECD Task Force on Hazard Assessment
  - June, 2014 Task Force meeting
  - Workplan building on the WHO framework/2011 OECD/WHO/ILSI workshop
    - To develop additional guidance on: problem formulation, hazard characterization, co-exposure characterization, risk assessment
      » Substances with limited data for hazard
      » Estimated daily intake from biomonitoring
      » Risk based criteria for moving to higher tiers
    - Canada co-lead with OECD Secretariat; US to co-lead with Canada and the Secretariat on problem formulation
WHO Drinking Water Guidelines

• Developing toolbox of methodologies to address combined exposures to relevant contaminants in drinking water, framed in the context of tiers of the WHO framework

• Several case studies in development
  – Pharmaceuticals in drinking water (Statins, Non-Steroidal Anti-Inflammatories)
  – Pesticides in drinking water
  – Microcystins
  – Estrogens
More Recent Developments (Cont’d)

• European Union
  – June, 2012 Communication
    • Establishment of an ad hoc working group (EFSA, ECHA, EMEA and EEA)
    • Development of technical guidelines
    • Creation of a platform for chemical monitoring data to link exposure and epidemiological data
    • Addressing gaps (Horizon 2020)
    • Promoting consistency internationally
Developments at the European Food Safety Agency (EFSA) (Cont’d)

- Participated actively in the WHO framework drafting group; adopted tiered approach and prepared case study on triazoles

- More recent developments:
  - (2012) Guidance on probabilistic for modelling dietary exposure to pesticide residues
  - (2013) Scientific opinion on pesticides to be included in cumulative assessment groups on the basis of their toxicological profile
  - (2013) Scientific opinion on the relevance of dissimilar mode of action and its appropriate application for cumulative risk assessment of pesticide residues in food
  - (2013) International frameworks dealing with human risk assessment of combined exposure to multiple chemicals

- Developing common assessment groups for hazard:
  - the nervous system and thyroid
Implications for Combined Exposure Assessment

• Consider exposure at outset in problem formulation
  – Do use profiles indicate likely co-exposure?

• The value of hierarchically addressing combined exposures to gain efficiency in assessment and management

• Maximizing understanding and availability of context specific tools for both exposure and hazard
  – E.g., potential for increasingly early, efficient refined grouping of compounds, based on e.g., use & tox profiling, documented MOA & measures of early key events for related compounds
More Information


IPCS Harmonization Website
Report of the 2007 Workshop
Case study on carbamates

Publication
Meek, Boobis, Crofton, Heinemeyer, Van Raaij & Vickers (2011) Reg. Tox. & Pharmacol. 60, Issue 2, Supplement 1, Pages S1-S14,
Including: Framework & Case Studies (TTC – Boobis et al., 2011; PBDEs – Meek)

Report of the WHO/OECD/ILSI - HESI Workshop
http://www.oecd.org/document/24/0,3746,en_2649_34377_47858904_1_1_1_1,00.html