ENVIROMENT DIRECTORATE
JOINT MEETING OF THE CHEMICALS COMMITTEE AND
THE WORKING PARTY ON CHEMICALS, PESTICIDES AND BIOTECHNOLOGY

WHO OECD ILSI/HESI International Workshop on
Risk Assessment of Combined Exposures to Multiple Chemicals
Annex 2 to the Workshop Report

Series on Testing & Assessment
No. 140

15-16 February 2011, Paris, France

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JT03304661
WHO OECD ILSI/HESI International Workshop on Risk Assessment of Combined Exposures to Multiple Chemicals: Annex 2
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No. 128, *Validation Report of the 21-day Androgenised Female Stickleback Screening Assay (2010)*
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No.133, Peer Review Report for the H295R Cell-Based Assay for Steroidogenesis (2010)


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FOREWORD

This document is Annex 2 of a report of the WHO OECD ILSI/HESI International Workshop on Risk Assessment of Combined Exposures to Multiple Chemicals which was held on 15-16 February 2011 in Paris, France. The workshop was held following the proposal from the 45th OECD Joint Meeting of the Chemicals Committee and Working Party on Chemicals, Pesticides and Biotechnology in February 2010.

This document is published under the responsibility of the Joint Meeting of the Chemicals Committee and the Working Party on Chemicals, Pesticides and Biotechnology of the OECD.
ANNEX 2

SESSION A PRESENTATIONS

Illustration of the WHO Combined Exposures Framework: A tiered and integrative approach to exposure and hazard

Marcel T.M. van Raaij, Ph.D.
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Contents

• How the framework was created
• Basic principles of the framework
• Examples of tiered system
  - Examples for exposure
  - Examples for hazard

The International Programme on Chemical Safety (IPCS)

Harmonization of approaches to the assessment of risk from exposure to chemicals

The International Programme on Chemical Safety (IPCS) (WHO/ILO/UNEP) is leading a project to harmonize approaches to the assessment of risk from exposure to chemicals. The goal of this project is to globally harmonize approaches to risk assessment by increasing understanding and developing basic principles and guidance on specific chemical risk assessment issues.
Harmonization enables efficient use of resources and consistency among assessments.

COMBINED EXPOSURES TO MULTIPLE CHEMICALS
Workshop Washington DC, March 2007

- "Aggregate" Exposure
  - Combined exposure to a single agent from various sources

- "Cumulative" Exposure
  - Combined exposure to multiple agents with a similar working mechanism

- Combitox
  - Combined exposure to multiple agents with or without similar working mechanisms

- Complex mixtures

Public Comments

- Late 2009: draft framework has been opened for public comments
- Framework has been adapted based on comments received
- Framework is not designed to be a detailed descriptive procedure but to provide a general philosophy on how to approach (risk) questions associated with combined exposures.
WHO framework (1)

- Consideration of a common assessment group is dependent not only on potential risk but also on purpose (priority setting, screening, QRA) and focus (e.g. local, national) of the assessment

- Tailored approach in order to ensure no more resources are invested than necessary (iterative process)
WHO Framework (2)

- What is the nature of the exposure and are key components known, or are data on the hazard of the mixture available?
- Is exposure unlikely taking into account the context?
- Is there a likelihood of co-exposure within a relevant timeframe?
- What is the rationale for considering compounds in a common assessment group?

General issues

- "Aggregate" exposure is really an 'EXPOSURE' problem.
- The other issues are 'TOXICOLOGICAL' problems.

- Adequate exposure assessment is essential.

- Terminology issues:
  - Single Chemical, all routes
  - Multiple Chemical, Multiple routes
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?

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

Tiered Exposure Assessments

Tier 0
Simple semi-quantitative estimates of exposure

Tier 1
Genetic exposure scenarios using conservative point estimates

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

Tier 3
Probabilistic exposure estimates

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 (RFP) and grouping based on MOA

Tier 3
PBPK or BDOR, probabilistic estimates of risk

WHO Framework (3)
Tier 0

• Exposure
  - Simple semi quantitative estimates of summed exposure
    • E.g. ranking of Canadian Domestic Substances List
    • E.g. Budget Method for Food Additives
    • MSDI for Flavourings

• Hazard
  - Assume dose addition for all components
  - Assume equipotency
    • E.g. Hazard Index
  - TTC Concept

Example Tier 0 Exposure

“Budget Method” used for Food Additives
• Not actual exposure but conservative screening tool
• Uses a number of default assumptions, e.g.
  - Physiological needs
  - Energy density of food

• Calculation by:
  1. Maximum amount of food and drinks consumed
  2. Maximum levels in foods en drinks
  3. Proportion of food that can contain additive
Illustration: Ponceau 4R (E124)

- Max. use level food: 50-500 mg/kg
  - 500 mg/kg only in specific food category (decorations, sauces, pickles)
  - Second maximum level: 300 mg/kg

- Max. use level drinks: 200 mg/L (adults)

- Proportion of foods and beverages for adults that can contain additive: 25%

\[
300 \times 0.025 \times 0.25 + 200 \times 0.1 \times 0.25 = 7 \text{ mg/kg bw/d}
\]

Example Tier 0: Hazard

- Assume all compounds in the mixture to be equipotent (to the most potent compound known).

- Use Hazard Index

\[
\text{Exposure A} + \text{Exposure B} + \text{Exposure C} < 1
\]

\[
\text{TDI A} \quad \text{TDI B} \quad \text{TDI C}
\]
Tier 1

- Exposure
  - Generic exposure scenarios using conservative point estimates
    - E.g. Summation of deterministic estimates for all components of the common assessment group
    - E.g. default values for use of cosmetic products per day

- Hazard
  - Assume dose addition for all components
  - Refine relative potencies (gross toxicity outcomes, NOAEL, BMD)
    - E.g. Point Of Departure (POD) index instead of Hazard Index

Example Tier 1: Exposure

- Aggregate exposure to Carvone (conservative point estimates)

- Exposure through natural products (herbs, cabbage etc)
  - NFCS data: 0.0004 mg/kg bw/day
- Exposure as food additive (beverages, biscuits, candy etc)
  - Annual production/survey: 0.04 mg/kg bw/day
- Exposure through personal care products (toothpaste, soap etc)
  - Indicative data EU monograph: 0.0006 mg/kg bw/day
- Exposure as pesticide (e.g. potatoes)
  - Unpealed potatoes NFCS data: 0.012 mg/kg bw/day

- Total deterministic exposure = 0.053 mg/kg bw/day (sum)
- Because Acceptable Daily Intake (ADI) is 0.025 mg/kg bw/day
  ⇒ refinement is needed.

Example Tier 1: Hazard

- If dose additivity is still assumed
- Use refinement in hazard starting points
  - Use Point of Departure instead of TDI/ADI/RfC
- Use Point of Departure Index (PODI)
  - Use BMD or NOAEL for specific toxic endpoint
    - No Assessment Factors
    - Use the same toxicological endpoint for all compounds

\[
\text{Exposure A} + \text{Exposure B} + \text{Exposure C} < 1
\]

POD A  POD B  POD C

Tier 2

- Exposure
  - Refined deterministic exposure (not worst case; more realistic); needs more input information
  - More incorporation of measured data
  - Still use summation for total exposure
- Hazard
  - Use more specific information on Mode of Action
    - Critical evaluation of assessment group
  - Use relative potencies (RPFs), preferably by BMD analysis
  - Use index compound: express the concentrations of all compounds in equivalents of the IC
Relative Potency Factors (OPs)

Tier 3

- Exposure
  - Probabilistic exposure assessment
  - Use distributions of exposure factors / parameters
  - Use actual data as much as possible
  - Relevant populations

- Hazard
  - Mode of Action considerations
  - Possibly PBPK modelling or PBPK – PD modelling
  - Possibly probabilistic estimates of hazard
Aims (adjusted) of this study

- Is probabilistic assessment possible and can it be used at the international level addressing both acute and chronic toxicity. Are those models applicable for calculating actual exposure using monitoring data as well as potential exposure as a consequence of the process of MRL setting

  - Compatibility of databases and models at the EU-level
  - Statistical models for cumulative assessment
  - Uncertainty analyses
Probabilistic modelling (exposure)

- residue database
- consumption database

99, 99.9, and/or 99.99 percentile

MCRA Software platform

Converting toxicity into RPFs (1)

Acute toxic effects
- Common effect is cranio-facial malformations
- Index compound flusilazole

Chronic toxic effects
- Common effect is hepatotoxicity
- Index compound cyproconazole
Converting toxicity into RPFs acute (2)

<table>
<thead>
<tr>
<th>Compound</th>
<th>BMD RPF</th>
<th>NO(A)EL (RPF)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Flusilazole</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Bitertanol</td>
<td>2.1</td>
<td>1.7</td>
</tr>
<tr>
<td>Cyproconazole</td>
<td>2.2</td>
<td>4.2</td>
</tr>
<tr>
<td>Diniconazole</td>
<td>1.0</td>
<td>0.6</td>
</tr>
<tr>
<td>Epoxiconazole</td>
<td>1.5</td>
<td>0.8</td>
</tr>
<tr>
<td>Propiconazole</td>
<td>0.1</td>
<td>1.7</td>
</tr>
<tr>
<td>Triadimefon</td>
<td>1.2</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Calculations possible in different countries

Residue per country  All residues pooled
Example Tier 3

- Integrated Probabilistic Risk Assessment (IPRA) model
- Combined probabilistic assessment for both exposure and Hazard
  - Van der Voet et al. (2009); Fd Chem Tox 47
**IPRA example OPs: IMoE results**

Bosgra et al. (2009); Reg. Tox. Pharm. 54

**WHO Framework**

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

Increasing refinement of exposure 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 (RFP) and grouping based on MOA
- Tier 3: PBPK or BBOR, probabilistic estimates of risk

Increasing refinement of hazard models

Is the margin of exposure adequate?

Yes, no further action required

No, continue with iterative refinement as needed, i.e., more complex exposure & hazard models
Thank you for your attention

Merci
WHO Combined Exposures Framework
Illustrative Case Study

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McLaughlin Centre
University of Ottawa
bmeek@uottawa.ca

Outline

- WHO IPCS Framework
  - Objectives
    • Building on Existing Methodology for Consideration of Combined Exposures
    • Incorporating Recent Developments in Assessment to Increase Efficiency
  - Illustration of Generic Aspects of the Framework by Detailed Case Study
Assessment for Combined Exposures
State of the Art

Whole Mixture
- Mixture of Concern
  - Mixture RDIC, Slope Factor
- Sufficiently Similar Mixture
  - Comparative Potency
- Group of Similar Mixtures
  - Environmental Transformation

Components
- Toxicologically Similar
  - Hazard Index
  - Relative Potency Factor
- Toxicologically Independent
  - Response Addition
- Interactions
  - Interactions Hazard Index

Dose Addition

Interaction (≥ or ≤ dose addition)

Hazard Index, Reference Dose
\[ HI = \sum_{i=1}^{n} \frac{\text{estimated intake}_i}{RfD_i} \]
Point of Departure Index
\[ PODI = \sum_{i=1}^{n} \frac{\text{estimated intake}_i}{PODi} \]
Toxic Equivalency
\[ TEQ = \sum_{i=1}^{n} C_i \times TEF_i \]
Revised 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
    - Synergy/antagonism

Objectives of the WHO IPCS “Combined Exposures” Framework

- Provides overview harmonizing construct
  - Builds upon other related initiatives and methodologies
- Consideration of an assessment group based on:
  - purpose
  - focus (e.g., local, national)
- Designed to maximize efficiency in the consideration and generation of information, depending on:
  - the potential risk and objective of the assessment
  - conservative less data dependent initial tiers; more data and labour intensive subsequent tiers
  - interpretation based on explicit delineation of uncertainty
Contents of the Framework

- When to conduct a combined assessment
- Generic description of the framework approach
  - Hierarchical structure with iterative consideration of exposure and hazard
  - Initial tiers are conservative and less data dependent; later tiers require more data and are labour intensive
- Three case studies (examples, only)
  - Priority setting for drinking water contaminants
  - Full assessment on conazoles

Screening assessment on 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 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 (PPP) and grouping based on MOA
- Tier 3: PBPK or BBDD, probabilistic estimates of risk
**Background – Case Study**

- PBDEs used as:
  - Flame retardants in consumer products
  - Internal electrical/electronic components and casings in household appliances/electronics, furniture upholstery, wire and cable insulation

- 3 main commercial mixtures containing 7 isomers used in Canada
  - ComPeBDE (mixture, 4 – 6 bromines)
  - ComOCBDE (mixture, 6-9 bromines)
  - ComDeBDE (mixture, 9-10 bromines)

- Considering risk to population in the general environment & consumer products (screening)

**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 Assessments**

- Tier 0: Simple semi-quantitative estimates of exposure
- Tier 1: Highest value for conservative point estimates from all media for 6 age groups

**Assessment**

- Yes, no further action required
- No, continue with iterative refinement as needed (i.e., more complex exposure & hazard models)

**Tiered Hazard Assessments**

- Tier 0: Potency of most sensitive endpoint for most toxic of 7 congeners based on LOEL
Problem Formulation:
Considering a Framework Analysis for a Combined Assessment Group

- Is exposure likely taking into account the context?
  - E.g., based on consideration of use profile, environmental dilution/degredation, substance not absorbed?)
    Yes. General population exposed through direct contact with PBDE containing products

- Is there a likelihood of co-exposure within a relevant timeframe?
  - E.g., based on temporal aspects, both external exp. and toxicokinetics and –dynamics
    Yes. There is overlap in congeners with commercial mixtures and reason to believe that their kinetics will be similar, based on similarity in physiochemical properties.

Problem Formulation: Considering a Framework Analysis for a Combined Assessment Group (Cont’d)

- What is the rationale for considering compounds in an assessment group?
  - E.g., based on 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 of the chemical
      (e.g. anti-oxidant use in fat, moulting inhibitors)

The assessment group contains 7 isomers with identical base structure, overlap in congeners with the commercial mixtures, similarities in uses and common target organs. Physiochemical properties and toxicity vary in predicted fashion with increasing degree of bromination.
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 Assessments
- Tier 0: Simple semi-quantitative estimates of exposure
- Tier 1: Highest value for conservative point estimates from all media for age groups

Increasing refinement of exposure

Assessment
- Yes, no further action required
- No, continue with iterative refinement as needed (i.e. more complex exposure & hazard models)

Tiered Hazard Assessments
- Tier 0: Potency for most sensitive endpoint for most toxic of 7 congeners based on LOEL

Tier 0

Exposure
- 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
- “Ground-truthed” against more robust and recent data on use
  - Commercial chemical profiles
  - Mandated use surveys
Potential for Exposure (Greatest, Intermediate & Lowest)

<table>
<thead>
<tr>
<th></th>
<th>Quantity (kg/year)</th>
<th>Number of Submitters</th>
<th>Sum of Expert Ranked Use Codes</th>
</tr>
</thead>
<tbody>
<tr>
<td>GPE</td>
<td>&gt; 100 000</td>
<td>Top 10%</td>
<td>Top 10%</td>
</tr>
<tr>
<td>IPE</td>
<td>&gt; 10 000</td>
<td>n.a.</td>
<td>Top 30%</td>
</tr>
<tr>
<td>LPE</td>
<td>All</td>
<td>All</td>
<td>All</td>
</tr>
</tbody>
</table>

\[ \sum_{i=1}^{n} \text{Use} \times \text{PE} \]

Tier o

Exposure

- Four congeners considered to present “lowest potential for exposure” of the general population (TeBDE; PeBDE; HxBDE; HeBDE)
- Three congeners considered to present “intermediate potential for exposure” of the general population (OcBDE; NoBDE; DeBDE)
- Summed semiquantitative benchmarked measures of exposure
  - \( \sum \) (use \times relative ranking for PE) normalized to quantitative estimates for Priority Substances with similar profiles
**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?

**Tier 0**

**Hazard**

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

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

- Arrayed the data to consider lowest reported effect level for most toxic congener
## Tier 0 – Conservative Estimate of Hazard – Summary of Lowest Effect Levels

<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>OoB</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>ComOoB</td>
<td>5</td>
<td>Liver weight: subchronic dietary study (rat)</td>
<td>GLCC (1987)</td>
</tr>
</tbody>
</table>
**Tier 0**

**Hazard**
- Critical Effect Level – conservative value for lowest effect level for most toxic congener (PeBDE) (0.8 mg/kg bw/day)
  - Neurobehavioural effects in neonatal mice (single oral dose postnatal day 10)
  - Supported by evidence of similar effects in mice exposed by maternal administration and neonatal mice administered tetra, hexa or deca congeners by the same investigators
  - Lower effect level (0.44 mg/kg bw/day) for ComPeBDE for alterations in hepatic enzyme activities not confirmed by histopathological changes at this or higher doses

**Tier 0 (Continued)**

**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 exposure based on limited data
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 Assessments

Tier 0
Simple semi-quantitative estimates of exposure

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

Increasing refinement of exposure

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
Potency for most sensitive endpoint for most toxic of 7 congeners based on LOEL

Increasing refinement of hazard

Tier 1

Exposure

- Upper bound estimate of daily intake of total PBDEs by 6 age groups of the population (0.2 to 0.6 ug/kg bw/day), based on:

  - Disparate 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
### Tier 1 - Upper Bound Estimate of Exposure

**Appendix to case-study A on PBDEs: Supporting data**

Table 5: Upper-bounding estimate of PBDE daily intake for the general population.

<table>
<thead>
<tr>
<th>Route of Exposure</th>
<th>Estimated intake (ng/kg bw per day of PBDE by various age groups)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.0-4 months</td>
</tr>
<tr>
<td>Formula</td>
<td>4.3 x 10^-7</td>
</tr>
<tr>
<td>Breast milk</td>
<td>4.3 x 10^-7</td>
</tr>
<tr>
<td>Food</td>
<td>1.6 x 10^-5</td>
</tr>
</tbody>
</table>

Assumed to have 375 mg of PBDEs per day, to drink 32 litres of PBDEs per day, to ingest 66 mg of PBDEs per day. Consumption of milk assumed to be 0.75 litres of milk per day.

### Sample Calculations (Degree of Conservatism)

- 6 age groups of the population including 3 subsets of infants (formula fed, breast-fed, non-formula fed)
- General and likely highly exposed populations
- Sum of the maximum concentrations of measured congeners in human milk
- For each of 8 food groups, assumed highest concentrations of the sum of PBDEs in analyzed food items in that group
- Maximum value of group (PBDEs) in surface water
- Maximum sums of measured PBDEs in ambient, indoor air and hosedust
**Tier 1**

**Risk Characterization/Uncertainties**

- 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):
    
    \[
    0.8 \text{ mg/kg bw/day} \\
    2.6 \text{ ug/kg bw/day} \\
    = 300
    \]

- Margin considered adequate in context of degree of conservatism (i.e., uncertainty)
  - 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
  - Increase in body burden of PBDEs over time (9x between 1992 & 2001)

**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 Assessments**

- Tier 0: Simple semi-quantitative estimates of exposure
- Tier 1: Highest value for conservative point estimates from all media for age groups

**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: Potency of most sensitive endpoint for most toxic of 7 congeners based on LOEL
Learnings from the WHO IPCS “Combined Exposures” Framework

- Combined assessments sometimes more complex than necessary
- Limited numbers of examples of combined assessments from regulatory programs
  - Most are component based
- Framework evolves through application
  - the European Food Safety Agency
  - Stockholm Convention Persistent Organic Pollutants Review Committee
  - Joint OECD/WHO IPCS Workshop

More Information

IPCS Harmonization Website
  Includes:
  - Draft Framework & Case Studies
  - Report of the 2007 Workshop
    - including extended abstracts on methodology used in various agencies