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ENVIRONMENT 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

Ms. Anne Gourmelon
Tel: + 33 (0) 1 45 24 98 49; E-mail: Anne.Gourmelon@oecd.org

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OECD Environment, Health and Safety Publications

Series on Testing and Assessment

No. 140

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

INTER-ORGANIZATION PROGRAMME FOR THE SOUND MANAGEMENT OF CHEMICALS

A cooperative agreement among FAO, ILO, UNEP, UNIDO, UNITAR, WHO, World Bank and OECD

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Paris 2011

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The Environment, Health and Safety Division publishes free-of-charge documents in ten different series: Testing and Assessment; Good Laboratory Practice and Compliance Monitoring; Pesticides and Biocides; Risk Management; Harmonisation of Regulatory Oversight in Biotechnology; Safety of Novel Foods and Feeds; Chemical Accidents; Pollutant Release and Transfer Registers; Emission Scenario Documents; and Safety of Manufactured Nanomaterials. More information about the Environment, Health and Safety Programme and EHS publications is available on the OECD's World Wide Web site (www.oecd.org/ehs/).

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

Contents

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

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The International Programme on Chemical Safety (IPCS)

WHO ILO UNEP

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

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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

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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 how to approach (risk) questions associated with combined exposures.

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Framework

General Philosophy

Overall Approach

Points of consideration

Case Studies

Illustration of the framework

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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)

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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

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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

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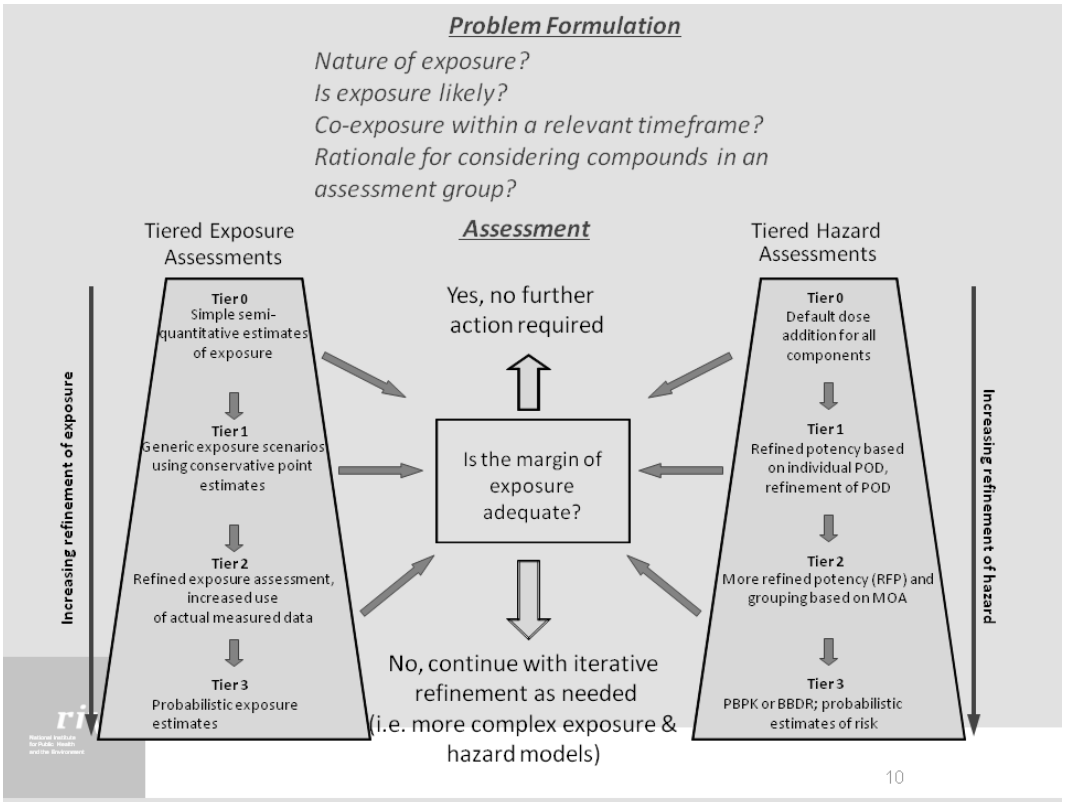
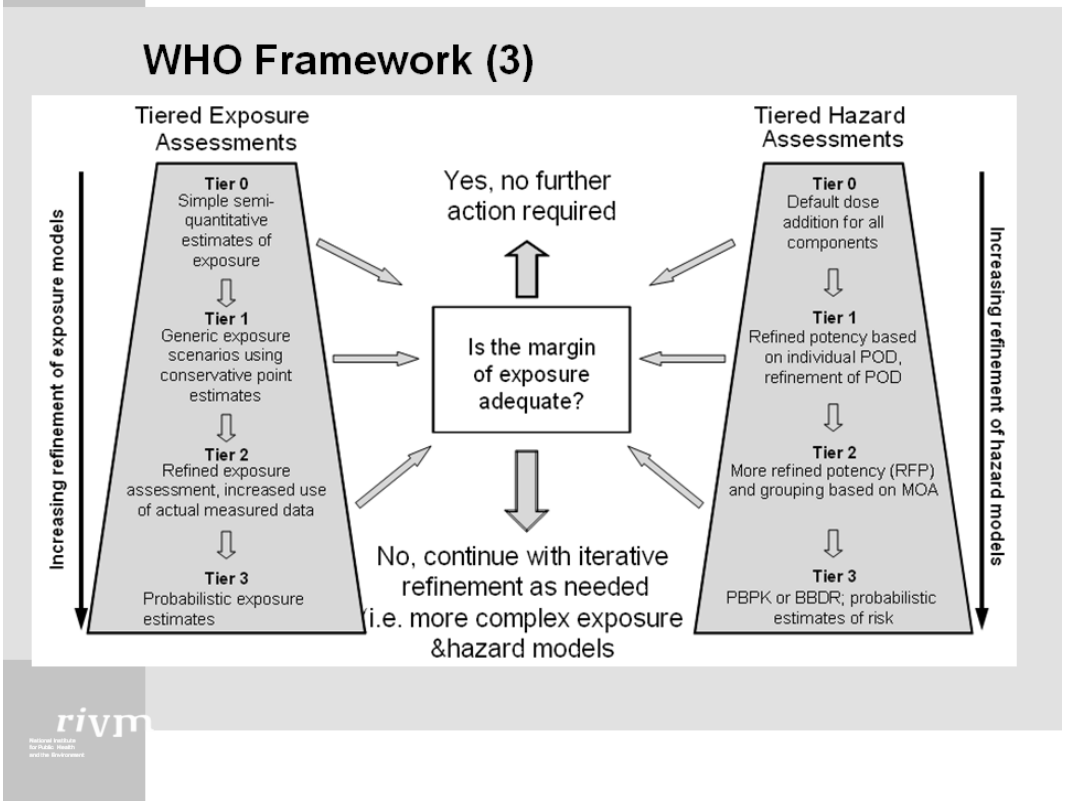

Problem Formulation
Nature of exposure?
Is exposure likely?
Co-exposure within a relevant timeframe?
Rationale for considering compounds in an assessment group?
Assessment
Tiered Exposure Assessments
Tiered Hazard Assessments
Tier 0
Simple semi-quantitative estimates of exposure
Tier 1
Generic exposure scenarios using conservative point estimates
Tier 2
Refined exposure assessment, increased use of actual measured data
Tier 3
Probabilistic exposure estimates
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)
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 BBDR; probabilistic estimates of risk
Increasing refinement of exposure
Increasing refinement of hazard
10


WHO Framework (3)
Tiered Exposure Assessments
Tiered Hazard Assessments
Tier 0
Simple semi-quantitative estimates of exposure
Tier 1
Generic exposure scenarios using conservative point estimates
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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 BBDR; probabilistic estimates of risk
Increasing refinement of exposure models
Increasing refinement of hazard models

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

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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

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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 %

$$\underbrace{300 \times 0.025 \times 0.25}_{\text{food}} + \underbrace{200 \times 0.1 \times 0.25}_{\text{drinks}} = 7 \text{ mg/kg bw/d}$$

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Example Tier 0: Hazard

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

$$\frac{\text{Exposure A}}{\text{TDI A}} + \frac{\text{Exposure B}}{\text{TDI B}} + \frac{\text{Exposure C}}{\text{TDI C}} < 1$$

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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 compenents
  - Refine relative potencies (gross toxicity outcomes, NOAEL, BMD)
    - E.g. Point Of Departure (POD) index instead of Hazard Index

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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.

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Source: RIVM report 320108002/2009; Wolterink et al.

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

$$\frac{\text{Exposure A}}{\text{POD A}} + \frac{\text{Exposure B}}{\text{POD B}} + \frac{\text{Exposure C}}{\text{POD C}} < 1$$

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Tier 2

- Exposure
  - Refined determinstic 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

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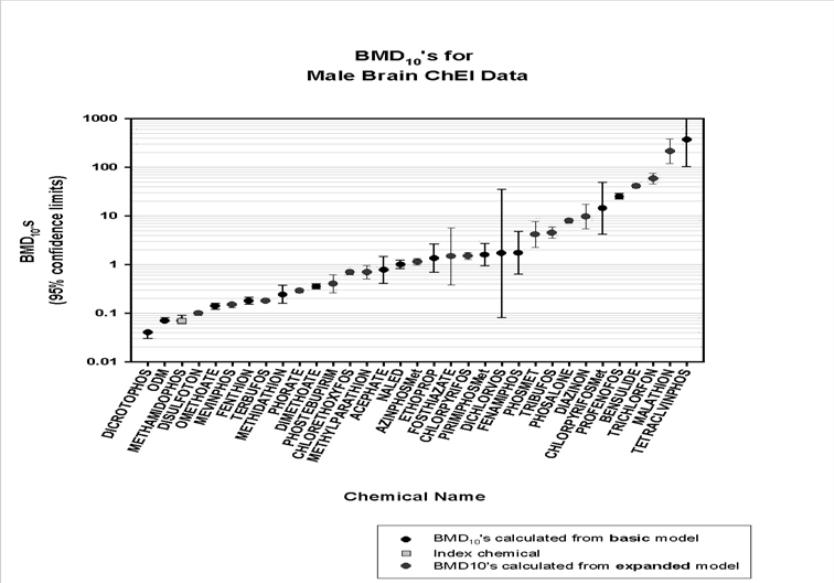
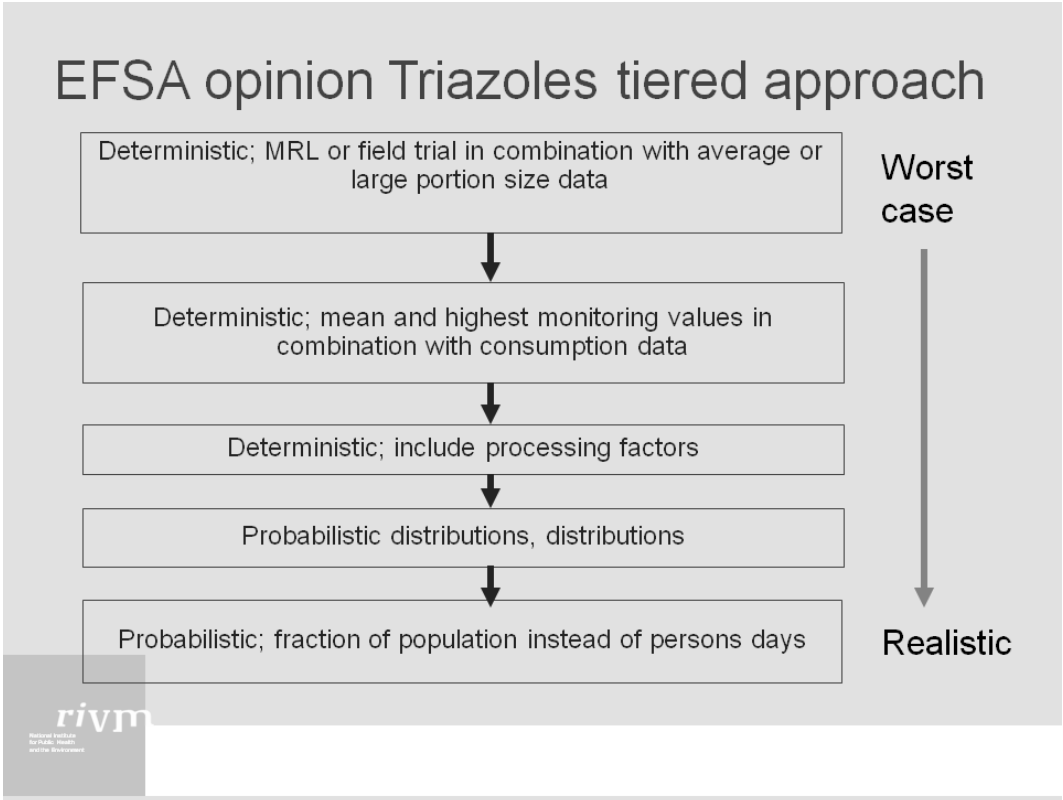
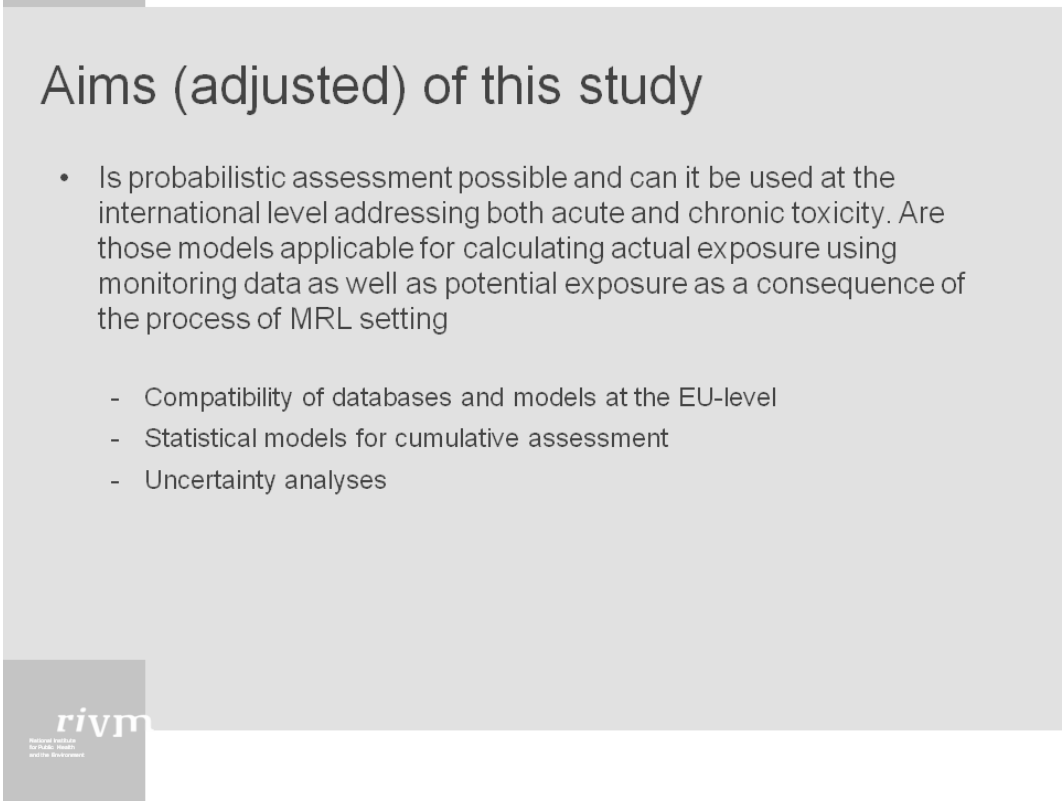
Relative Potency Factors (OPs)



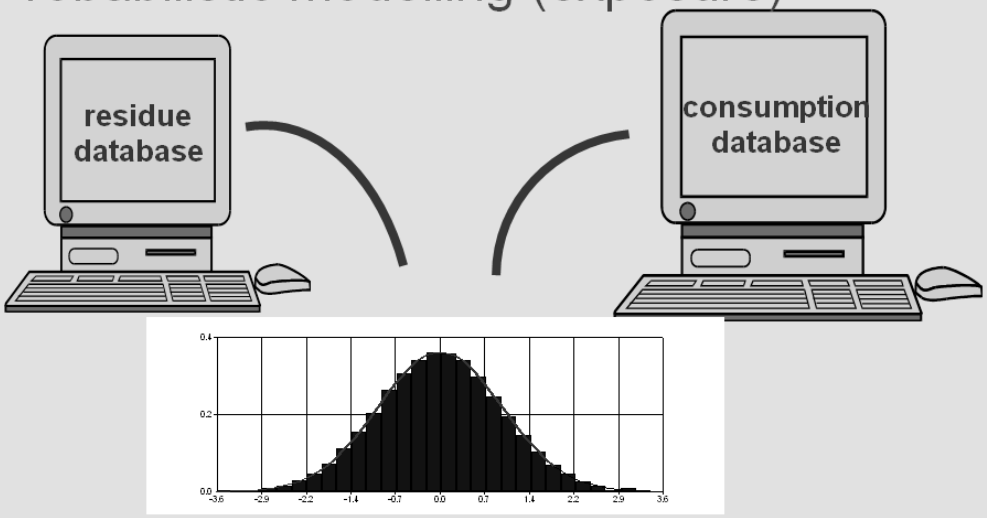
Tier 3

- Exposure
  - Probilistic 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


EFSA opinion Triazoles tiered approach
Deterministic; MRL or field trial in combination with average or large portion size data
Deterministic; mean and highest monitoring values in combination with consumption data
Deterministic; include processing factors
Probabilistic distributions, distributions
Probabilistic; fraction of population instead of persons days
Worst case
Realistic
rivm


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
rivm

Probabilistic modelling (exposure)



99, 99.9, and/or 99.99 percentile

MCRA Software platform

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Converting toxicity into RPFs (1)

Acute toxic effects

- Common effect is cranio-facial malformations
- Index compound flusilazole

Chronic toxic effects

- Common effect is hepatoxicity
- Index compound cyproconazole

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Converting toxicity into RPFs acute (2)

Compound	BMD RPF	NO(A)EL (RPF)
Flusilazole	1.0	1.0
Bitertanol	2.1	1.7
Cyproconazole	2.2	4.2
Diniconazole	1.0	0.6
Epoxiconazole	1.5	0.8
Propiconazole	0.1	1.7
Triadimefon	1.2	1

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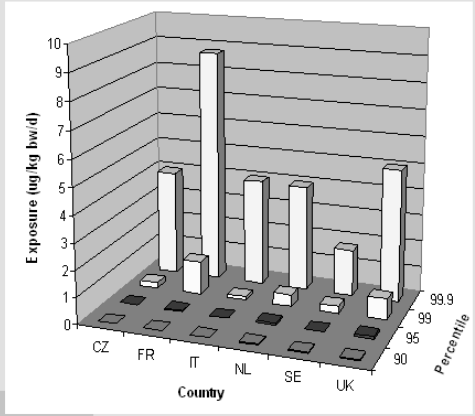
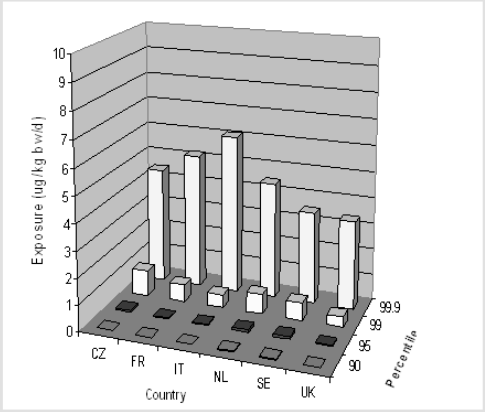
Calculations possible in different countries

Residue per country



All residues pooled



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Example Tier 3

- Integrated Probabilistic Risk Assessment (IPRA) model
- Combined probabilistic assessment for both exposure and Hazard

  - Van der Voet el al. (2009); Fd Chem Tox 47

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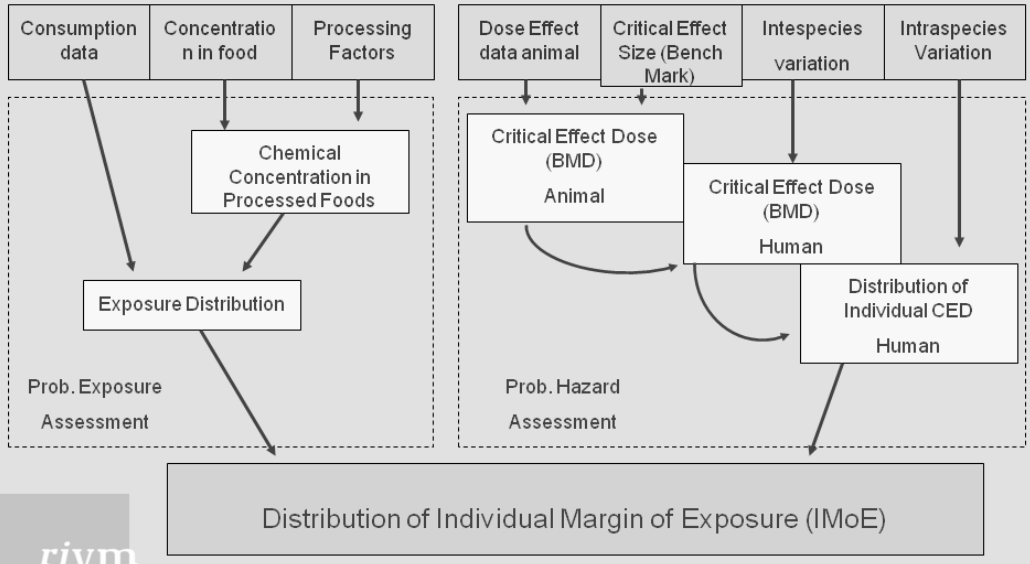
IPRA Model overview (food example)



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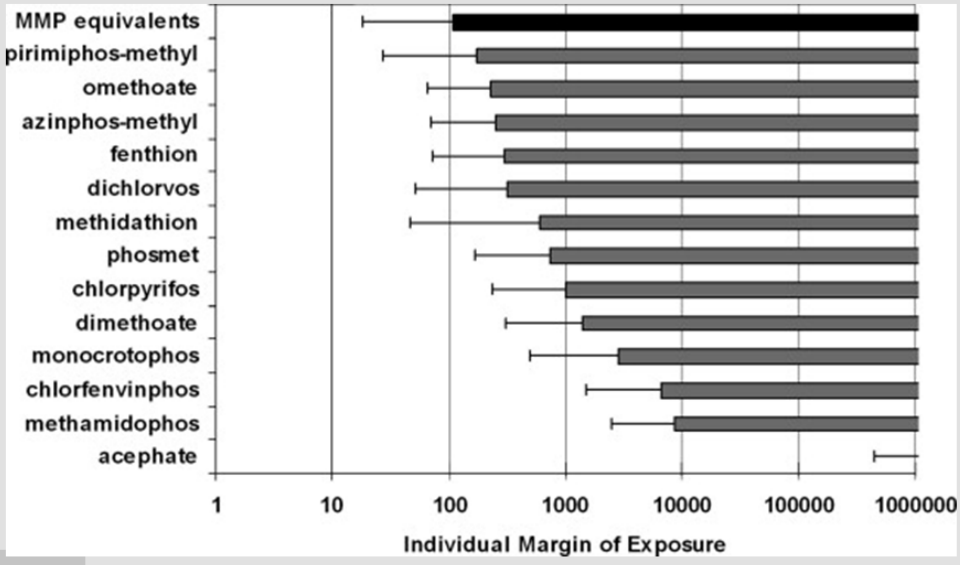
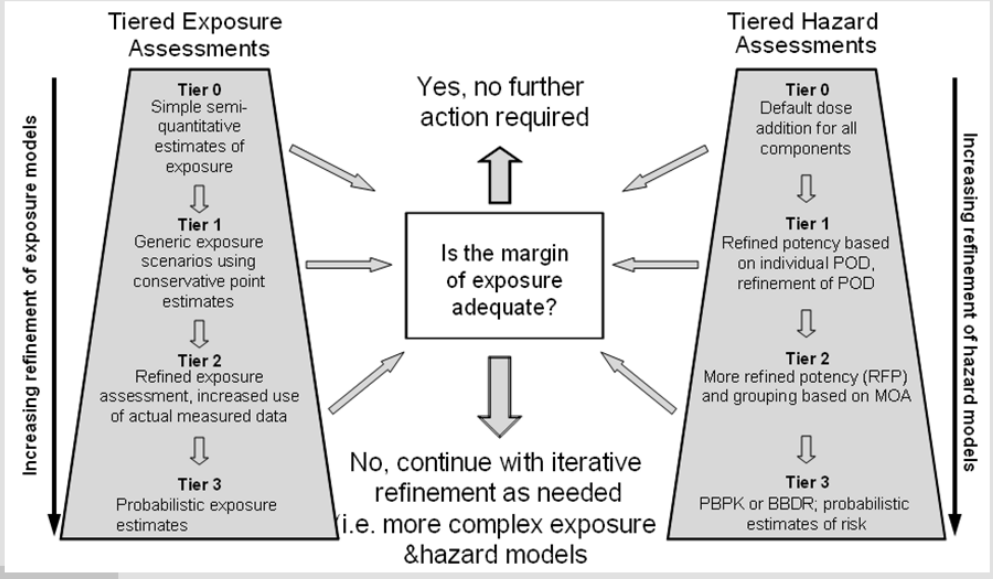
IPRA example OPs: IMoE results



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

WHO Framework



Thank you for your attention

Merci

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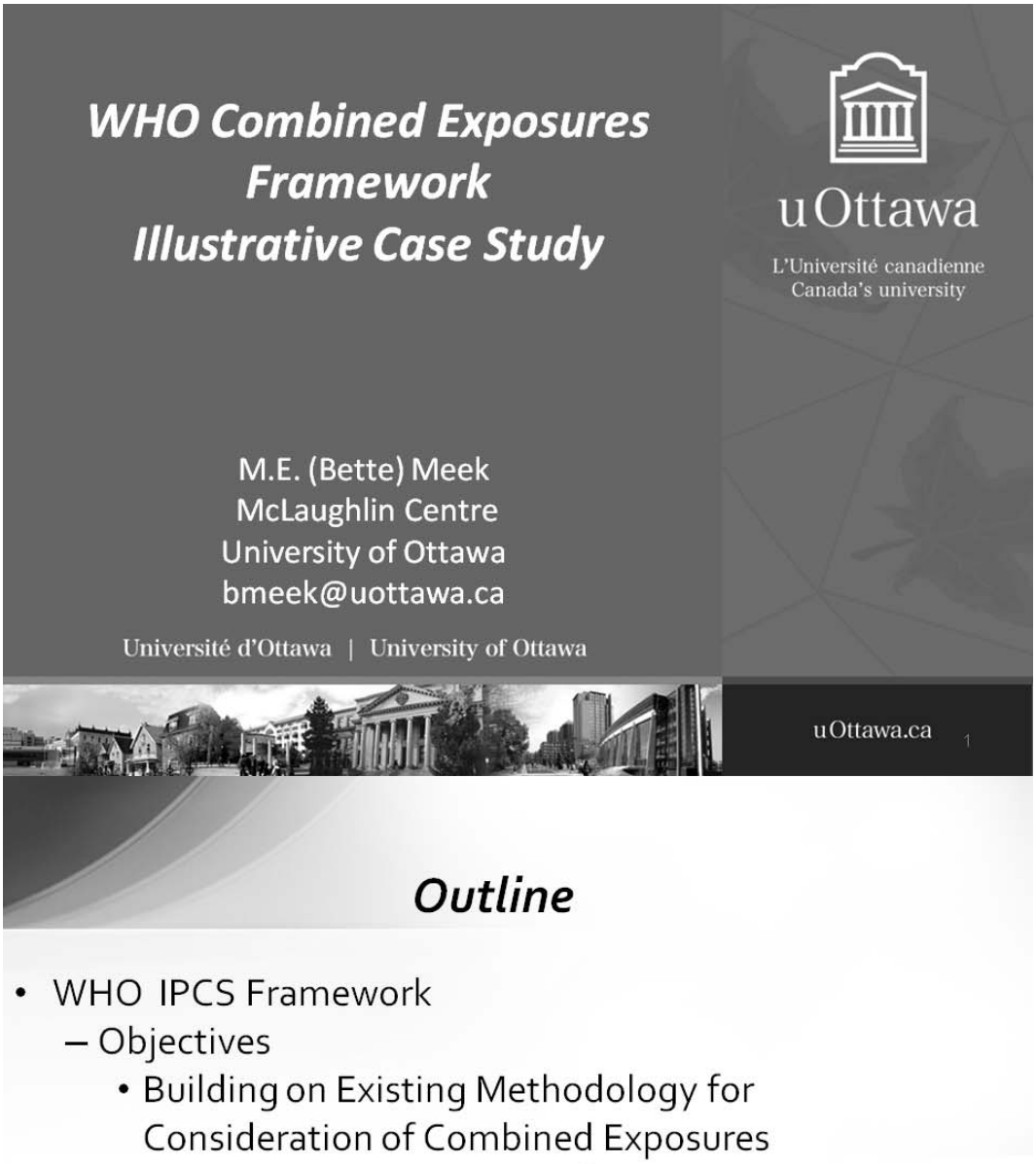
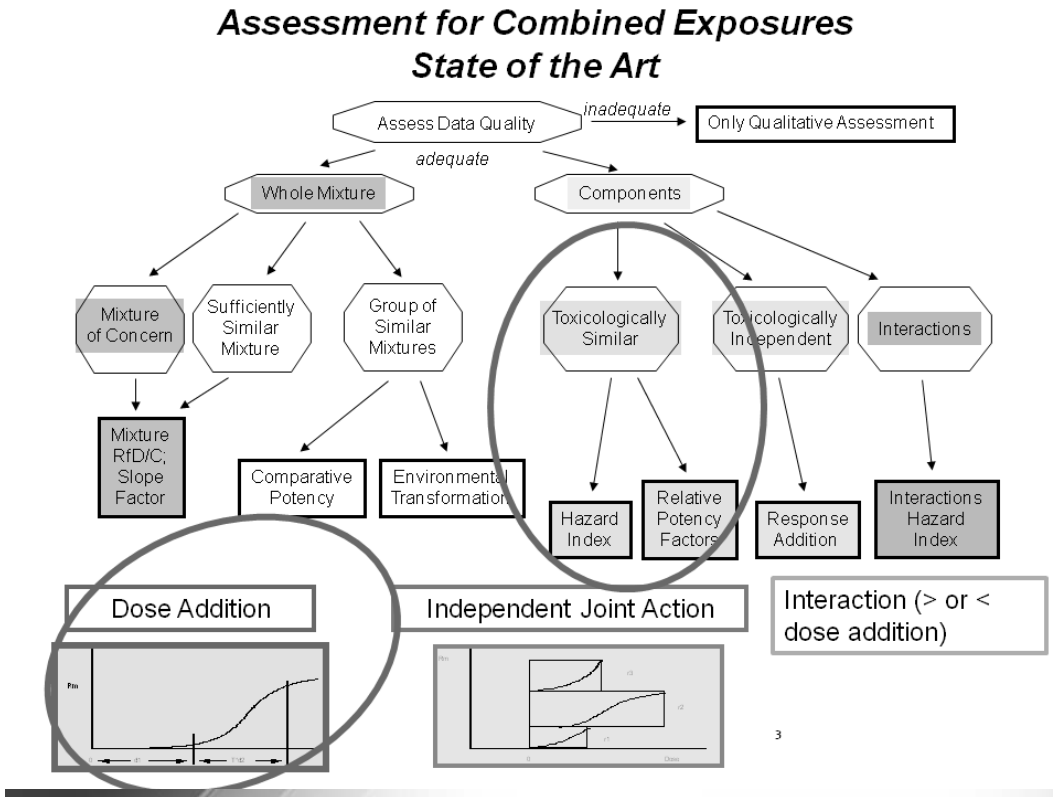
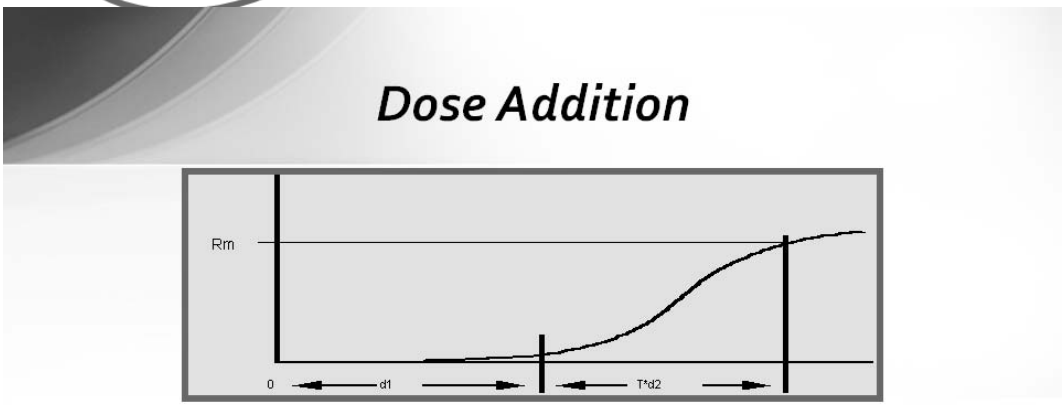

WHO Combined Exposures Framework Illustrative Case Study
uOttawa
L'Université canadienne
Canada's university
M.E. (Bette) Meek
McLaughlin Centre
University of Ottawa
bmeek@uottawa.ca
Université d'Ottawa | University of Ottawa
uOttawa.ca
1
Outline
• WHO IPCS Framework
– Objectives
• Building on Existing 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
2





Hazard Index, Reference Dose

$$HI = \sum_{i=1}^{n} \frac{estimated\ intake_i}{RfDi}$$

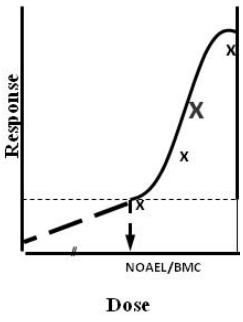
Point of Departure Index

$$PODI = \sum_{i=1}^{n} \frac{estimated\ intake_i}{PODi}$$

Toxic Equivalency

$$TEQ = \sum_{i=1}^{n} C_i \times TEF_i$$

4



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

5

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

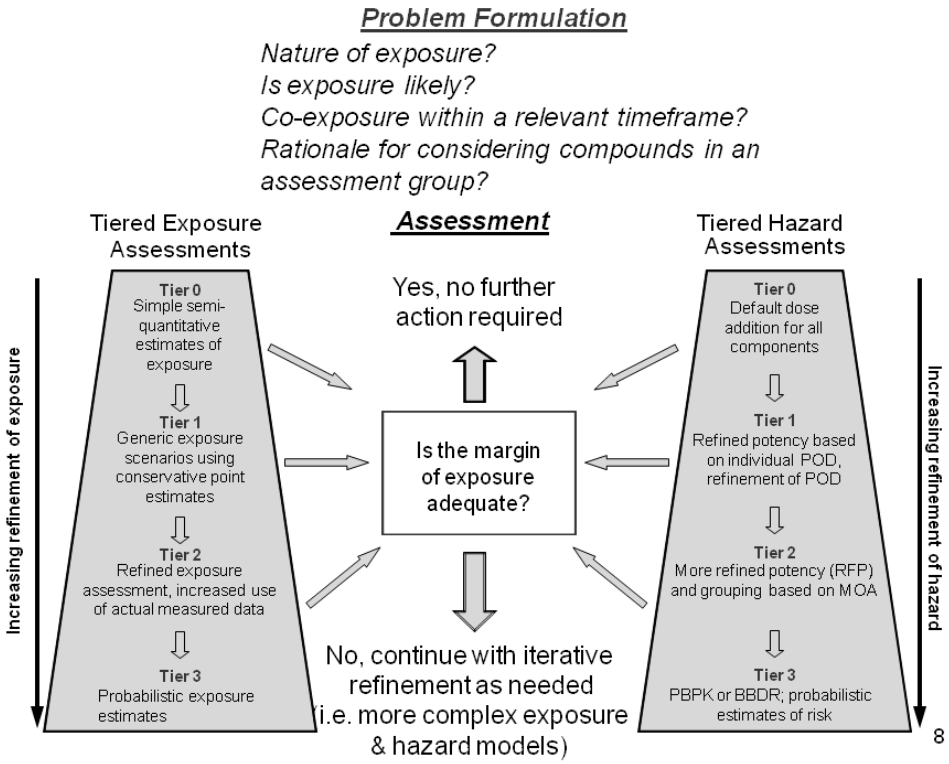
6

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

7

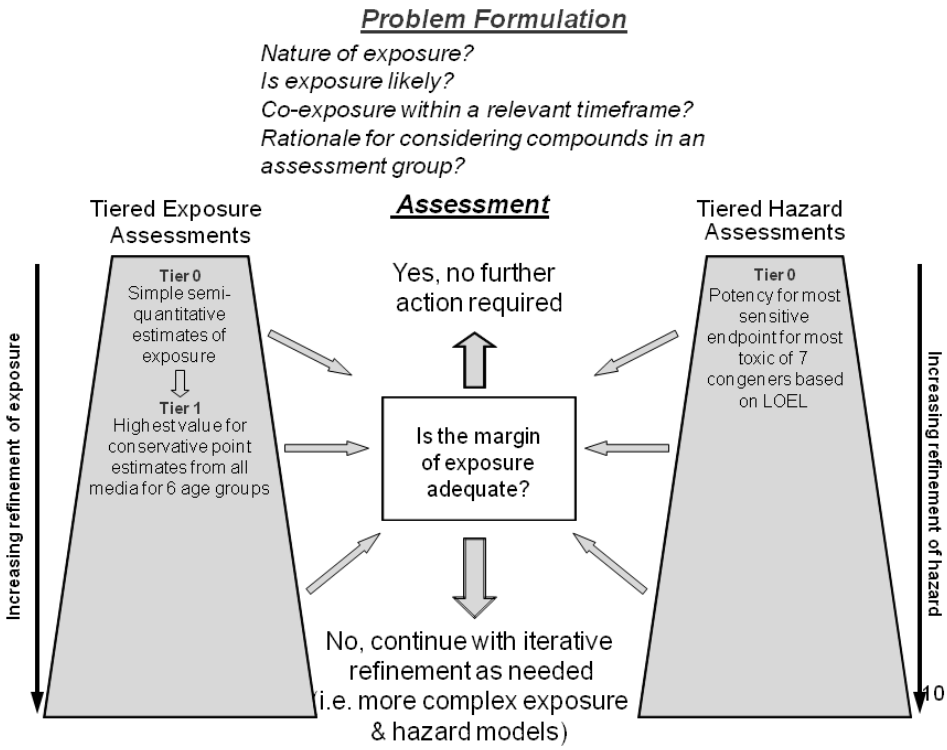


Background – Case Study

- 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)

9

Case Study -Tiered Exposure and Hazard Considerations - PBDEs



10

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/degradation, substance not absorbed?)

Yes. General population exposed through direct contact with PBDE containing products

- Is there a likelihood of co-exposure within a relevant time frame?
  - 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.

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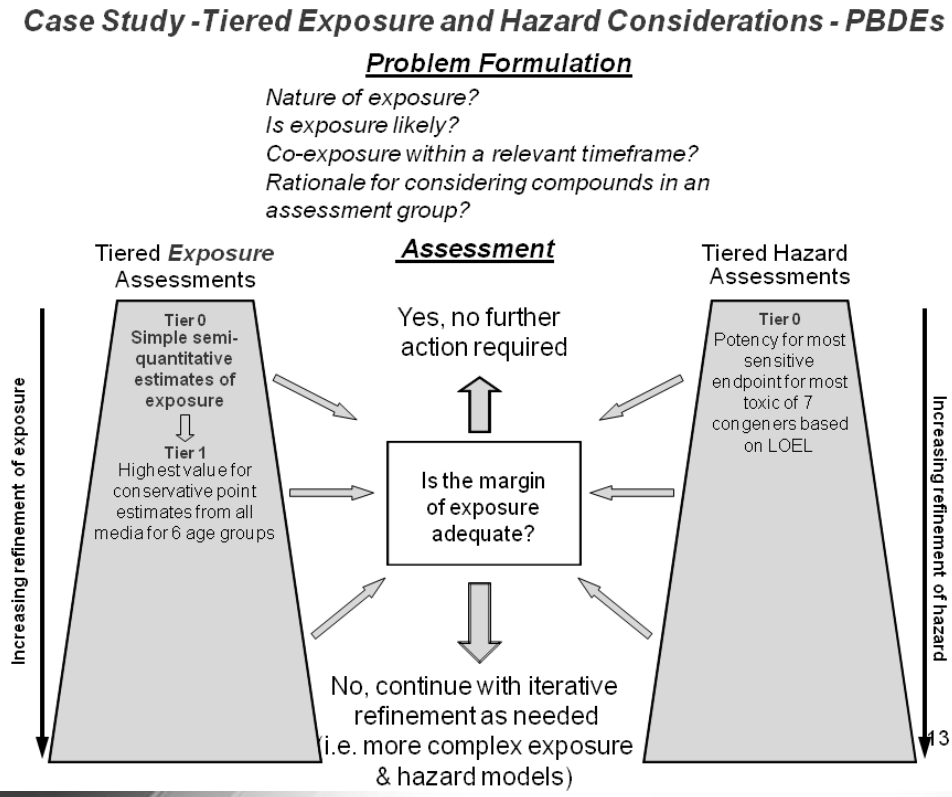
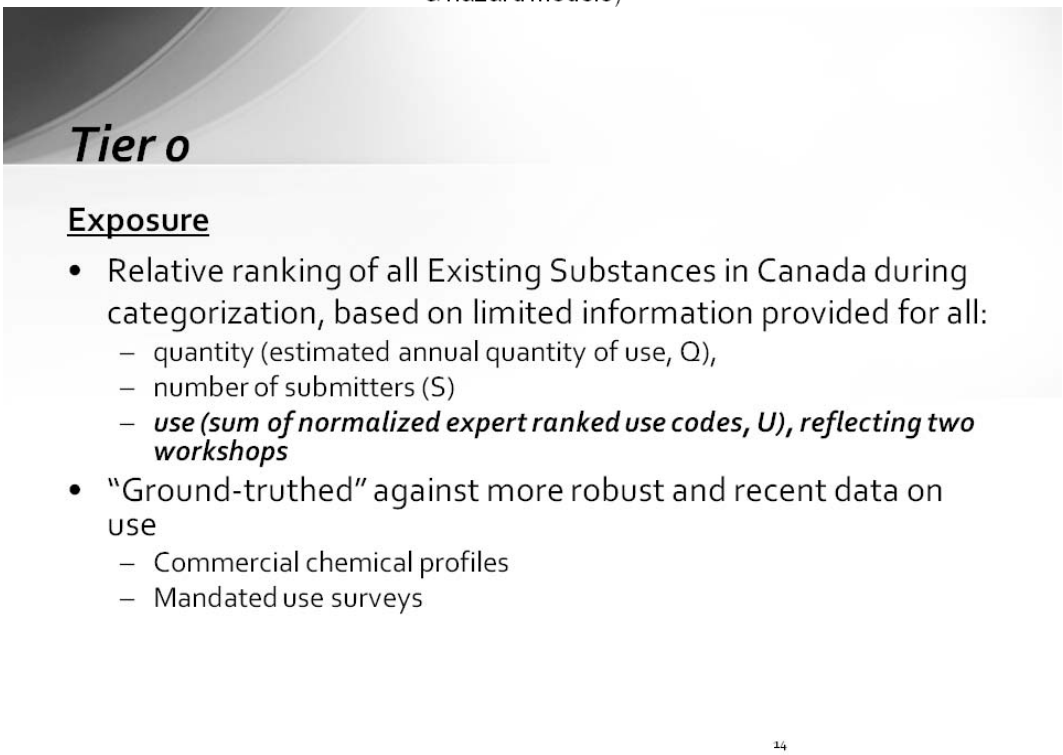
Problem Formulation: Considering a Framework Analysis for a Combined Assessment Group (Cont'd)

- 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 target 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. Physicochemical properties and toxicity vary in predicted fashion with increasing degree of bromination.

12


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?
Assessment
Tiered Exposure Assessments
Tiered Hazard Assessments
Tier 0
Simple semi-quantitative estimates of exposure
Tier 1
Highest value for conservative point estimates from all media for 6 age groups
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)
Tier 0
Potency for most sensitive endpoint for most toxic of 7 congeners based on LOEL
Increasing refinement of exposure
Increasing refinement of hazard
13


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
14

Potential for Exposure (Greatest, Intermediate & Lowest)

	Quantity (kg/year)	Number of Submitters	***Sum of Expert Ranked Use Codes***
GPE	> 100 000	Top 10%	Top 10%
IPE	> 10 000	n.a.	Top 30%
LPE	All	All	All

$$\sum_{i=1}^{n} Use \; x \; PE$$

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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
  - ∑ (use x relative ranking for PE) normalized to quantitative estimates for Priority Substances with similar profiles

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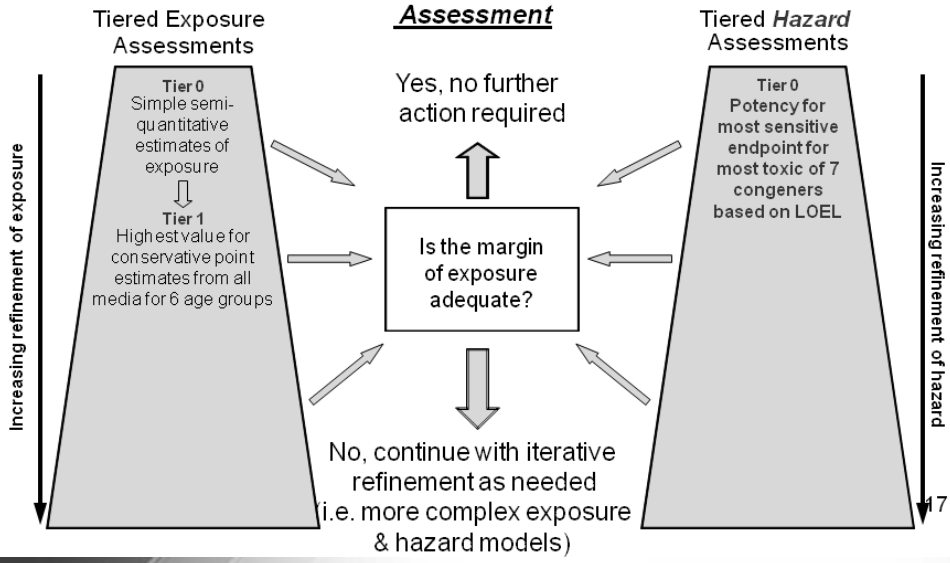
Case Study -Tiered Exposure and Hazard Considerations - PBDEs

Problem Formulation

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



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Tier 0

Hazard

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

$$HI = \sum_{i=1}^{n} \frac{estimated\ intake_i}{RfDi}$$

- Arrayed the data to consider lowest reported effect level for most toxic congener

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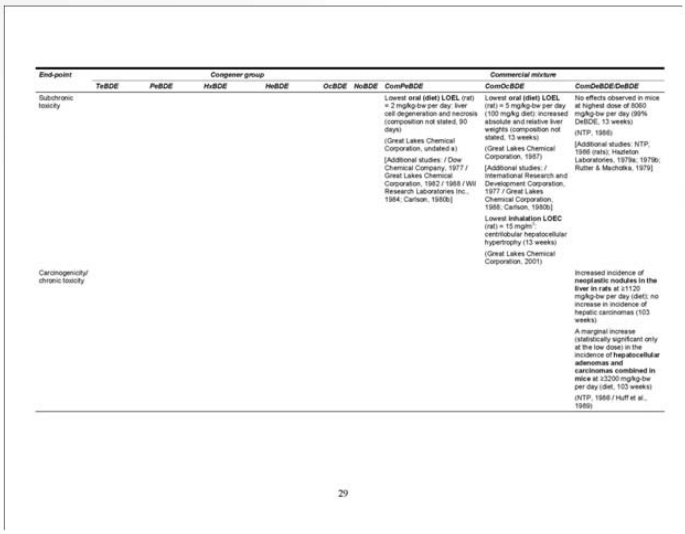
Tier o –Identifying Lowest Effect Levels – Sample of Supporting Data



End-point	Congener group						Commercial mixture		
	TeBDE	PeBDE	HxBDE	HeBDE	OcBDE	NoBDE	ComPeBDE	ComOcBDE	ComOeBDE:DeBDE
Subchronic toxicity							Lowest **oral (diet) LOEL** (rat) = 2 mg/kg-bw per day: liver cell degeneration and necrosis (composition not stated, 90 days) (Great Lakes Chemical Corporation, undated a) [Additional studies: / Dow Chemical Company. 1977 / Great Lakes Chemical Corporation. 1982 / 1988 / Wil Research Laboratories Inc., 1984, Carlson, 1980b]	Lowest **oral (diet) LOEL** (rat) = 5 mg/kg-bw per day (100 mg/kg diet): increased absolute and relative liver weights (composition not stated, 13 weeks) (Great Lakes Chemical Corporation, 1987) [Additional studies: / International Research and Development Corporation, 1977 / Great Lakes Chemical Corporation, 1988, Carlson, 1980b] Lowest **inhalation LOEC** (rat) = 15 mg/m³: centrilobular hepatocellular hypertrophy (13 weeks) (Great Lakes Chemical Corporation, 2001)	No effects observed in mice at highest dose of 8060 mg/kg-bw per day (99% DeBDE, 13 weeks) (NTP, 1986) [Additional studies: NTP, 1986 (rats); Hazleton Laboratories, 1979a, 1979b; Ruttar & Machotka, 1979]
Carcinogenicity/ chronic toxicity									Increased incidence of **neoplastic nodules in the liver in rats** at ≥1120 mg/kg-bw per day (diet); no increase in incidence of hepatic carcinomas (103 weeks) A marginal increase (statistically significant only at the low dose) in the incidence of **hepatocellular adenomas and carcinomas combined in mice** at ≥3200 mg/kg-bw per day (diet, 103 weeks) (NTP, 1986 / Huff et al., 1989)

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Tier 0 – Conservative Estimate of Hazard – Summary of Lowest Effect Levels

Congener Group	LOEL (mg/kg bw/day)	Endpoint	Reference
TeB	11	Developmental: behavioural (mouse)	E et al. (2001)
PeB	0.8	Developmental: behavioural (mouse)	E et al. (1998, 2001)
HxB	0.9	Developmental: behavioural (mouse)	V et al. (2002)
HeB	—	—	—
OcB	—	—	—
NoB	—	—	—
ComPeB	2	Liver histopathology: subchronic dietary study (rat)	GLCC (undated)
ComOcB	5	Liver weight: subchronic dietary study (rat)	GLCC (1987)
ComDeB, DeB	2.2	Developmental: behavioural (mouse)	V et al. (2001a,b, 2003); V (2002)

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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

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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

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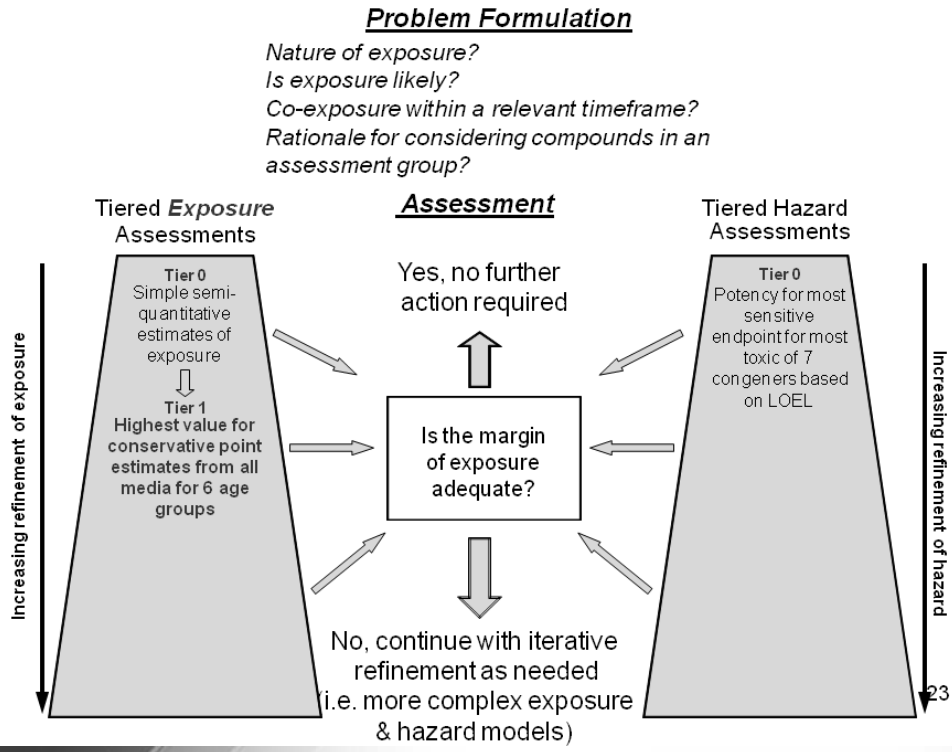
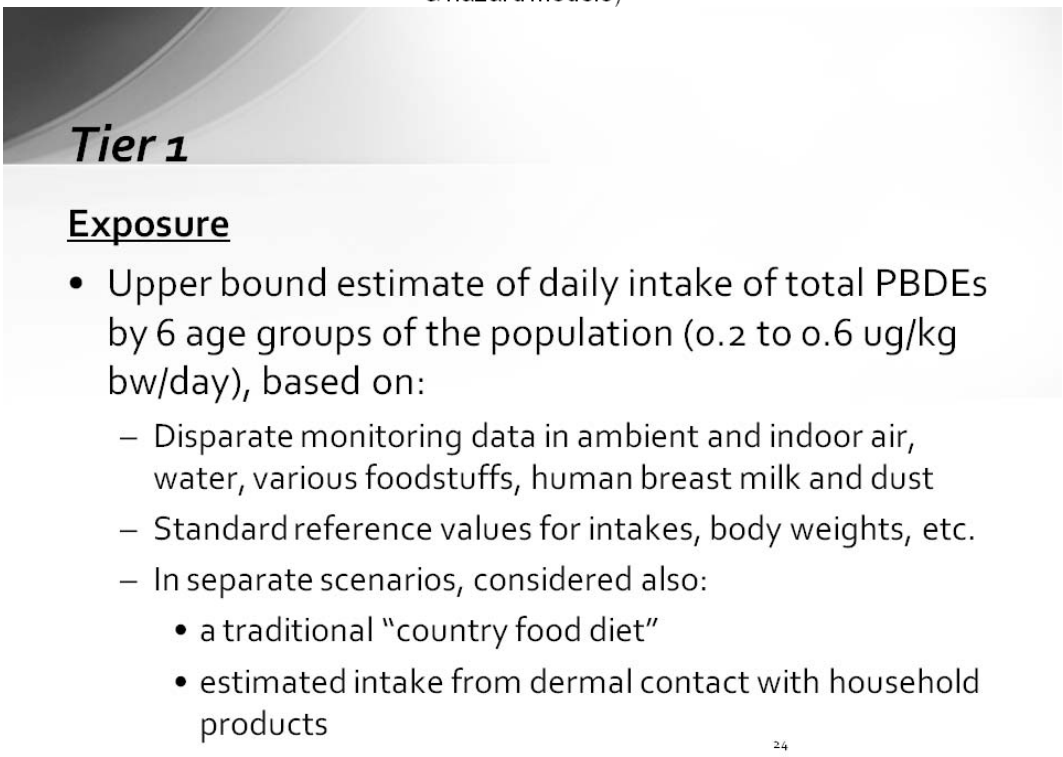
Case Study -Tiered Exposure and Hazard Considerations - PBDEs





Tier 1 - Upper Bound Estimate of Exposure

Appendix to case-study A on PBDEs: Supporting data

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

Route of exposure	Estimated intake (µg/kg-bw per day) of PBDEs by various age groups							
	0–6 months[a]			0.5–4 years[a]	5–11 years[a]	12–19 years[f]	20–59 years[g]	60+ years[h]
	Formula fed[b]	Breastfed[c]	Not formula fed					
Ambient air[i]	7.7×10^{-5}	7.7×10^{-5}	7.7×10^{-5}	1.7×10^{-4}	1.3×10^{-4}	7.3×10^{-5}	6.3×10^{-5}	5.5×10^{-5}
Indoor air[i]	4.4×10^{-4}	4.4×10^{-4}	4.4×10^{-4}	9.3×10^{-4}	7.3×10^{-4}	4.1×10^{-4}	3.6×10^{-4}	3.1×10^{-4}
Drinking-water[k]	1.4×10^{-3}	2.4	5.2×10^{-7}	5.9×10^{-7}	4.6×10^{-7}	2.6×10^{-7}	2.8×10^{-7}	2.9×10^{-7}
Food[l]			2.0×10^{-2}	5.8×10^{-1}	4.8×10^{-1}	2.7×10^{-1}	2.6×10^{-1}	1.7×10^{-1}
Soil/dust[m]	2.3×10^{-1}	2.3×10^{-1}	2.3×10^{-1}	3.6×10^{-1}	1.2×10^{-1}	2.8×10^{-2}	2.4×10^{-2}	2.3×10^{-2}
Total intake	2.3×10^{-1}	2.6	2.5×10^{-1}	9.5×10^{-1}	6.0×10^{-1}	3.0×10^{-1}	2.8×10^{-1}	1.9×10^{-1}

[a] Assumed to weigh 7.5 kg, to breathe 2.1 m^3 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).

[b] Formula-fed 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.

[c] 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 Darnerud 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).

[d] Assumed to weigh 15.5 kg, to breathe 9.3 m^3 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).

[e] Assumed to weigh 31.0 kg, to breathe 14.5 m^3 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).

[f] Assumed to weigh 59.4 kg, to breathe 15.8 m^3 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).

[g] Assumed to weigh 70.9 kg, to breathe 16.2 m^3 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).

[h] Assumed to weigh 72.0 kg, to breathe 14.3 m^3 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

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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 housedust

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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):

$$= \frac{0.8 \text{ mg/kg bw/day}}{2.6 \text{ ug/kg bw/day}}$$

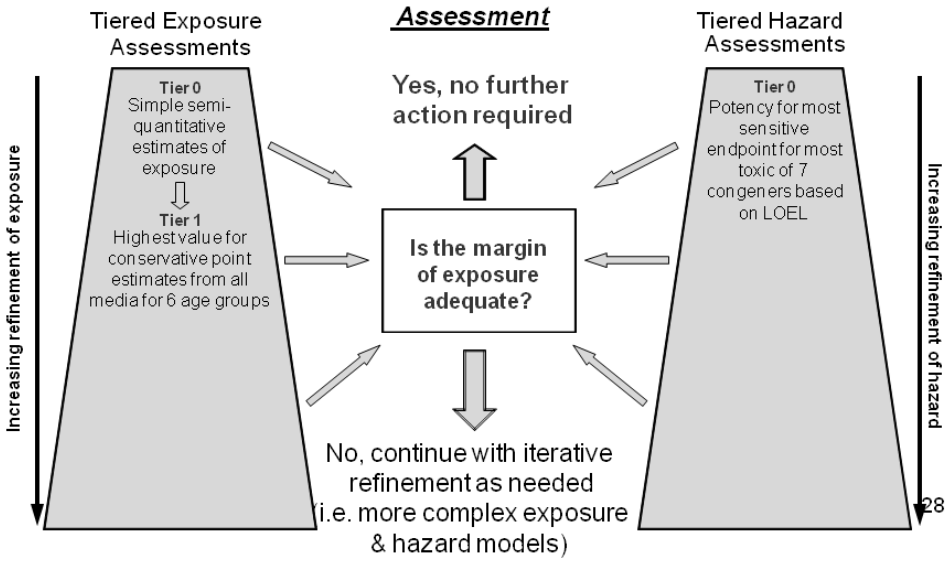
$$= 300$$

- Margin considered adequate in context of degree of conservatism (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) 27

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?



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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

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More Information

IPCS Harmonization Website

- http://www.who.int/ipcs/methods/harmonization/ar ea s/aggregate/en/index.html

Includes:

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

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