WHO IPCS Framework Combined Exposure to Multiple Chemicals

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Outline

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

- Implications for Tiered Priority Setting/Assessment, Uncertainty & Sensitivity Analysis, Communication

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
  - Recommendations on terminology, assessment framework, research
- 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 – HESI workshop
  - Feb/2011 – Paris
- Contributing to several European & US initiatives

'07 Workshop Recommendations

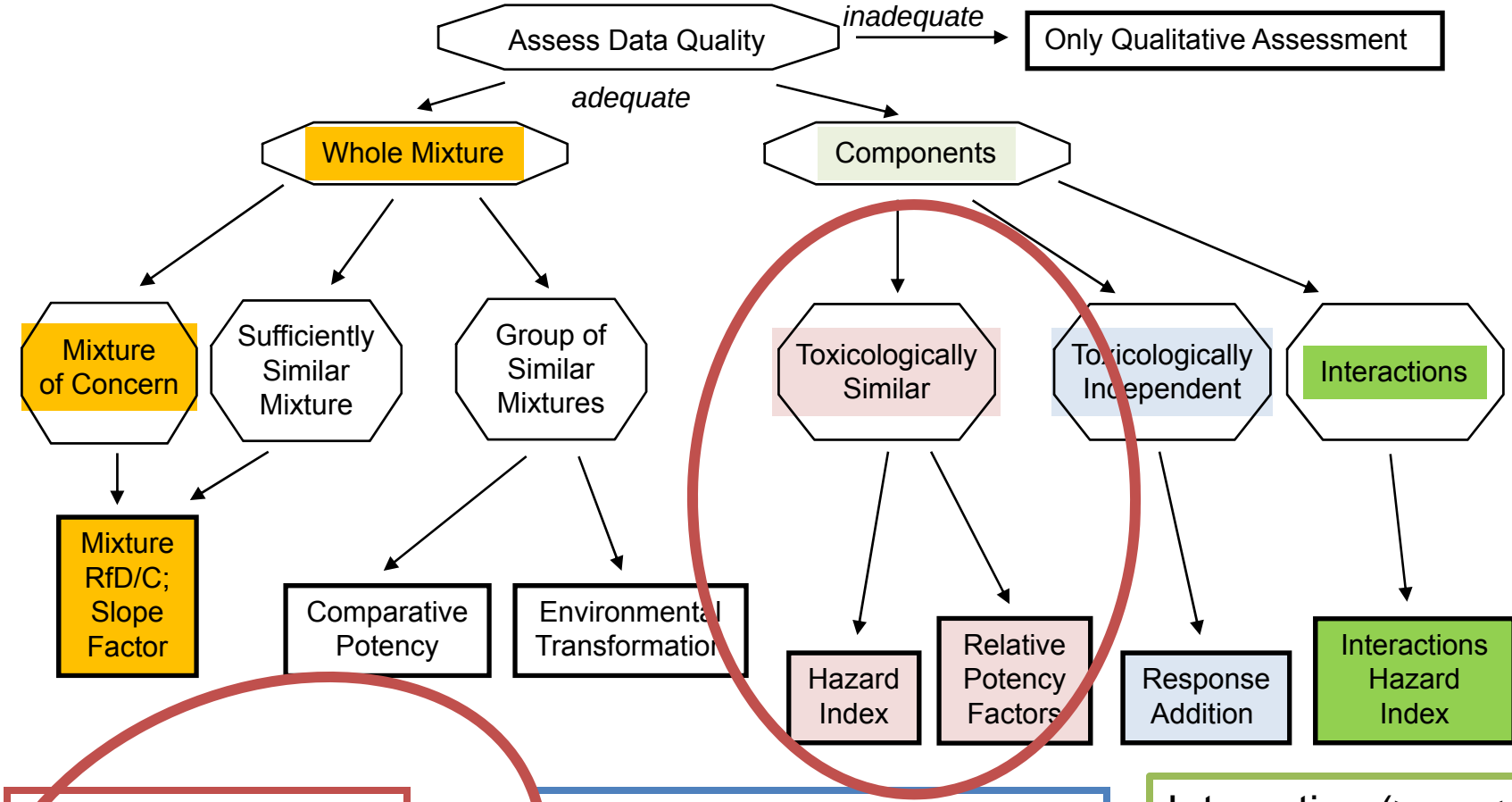
Terminology/Research:

- Avoid use of non-descriptive terms
- Avoid generic use of the term "mixtures"
- "Simple", "complex" to relate to modes of action
- ***Research***: Potential for interaction at relevant exposures

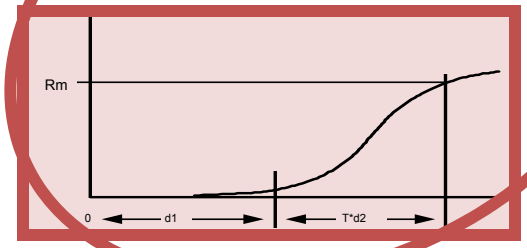
Revised Terminology:

- "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

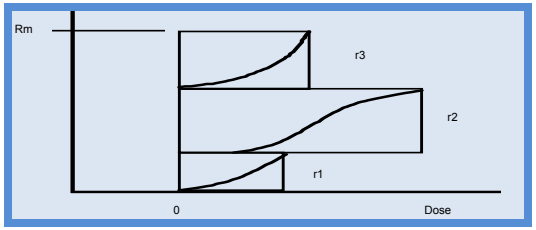
Assessment for Combined Exposures State of the Art (Modified from US EPA)



Dose Addition

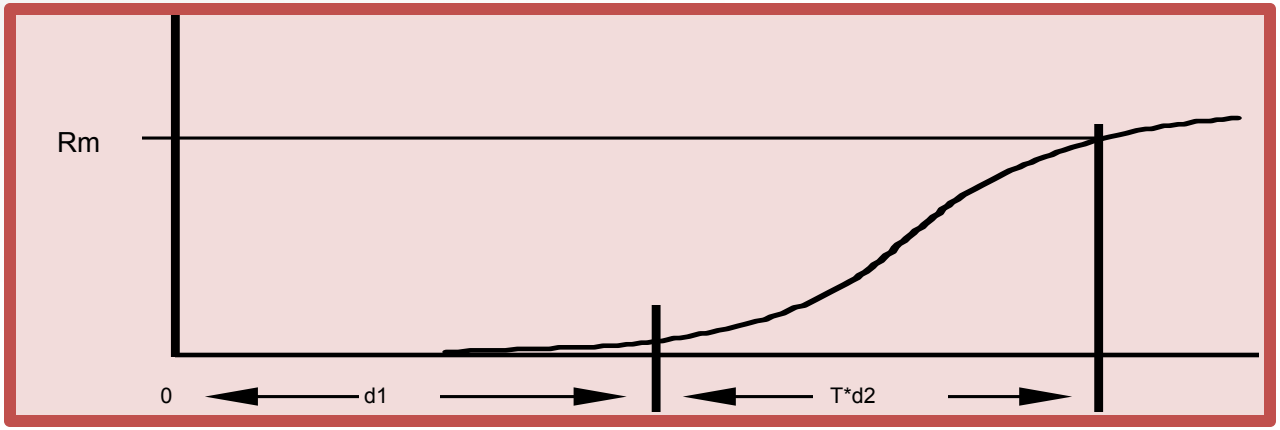


Independent Joint Action



Interaction (> or < dose addition)

Dose Addition



Hazard Index, Reference Dose

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

Point of Departure Index

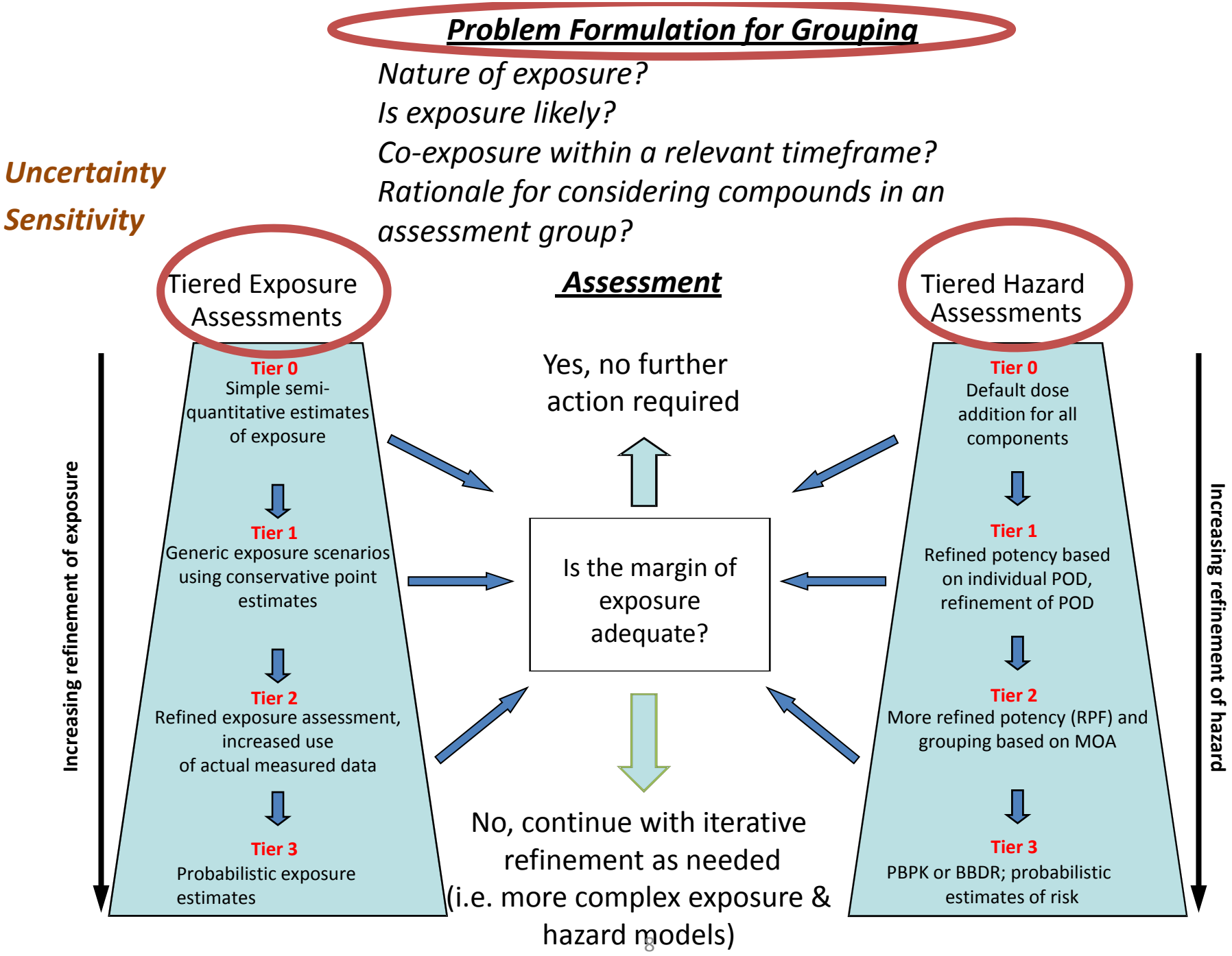
$$\mathbf{PODI} = \sum_{i=1}^{n} \frac{estimated\ intake_i}{POD_i}$$

Toxic Equivalency

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

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
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
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
Increasing refinement of exposure
Increasing refinement of hazard
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)

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

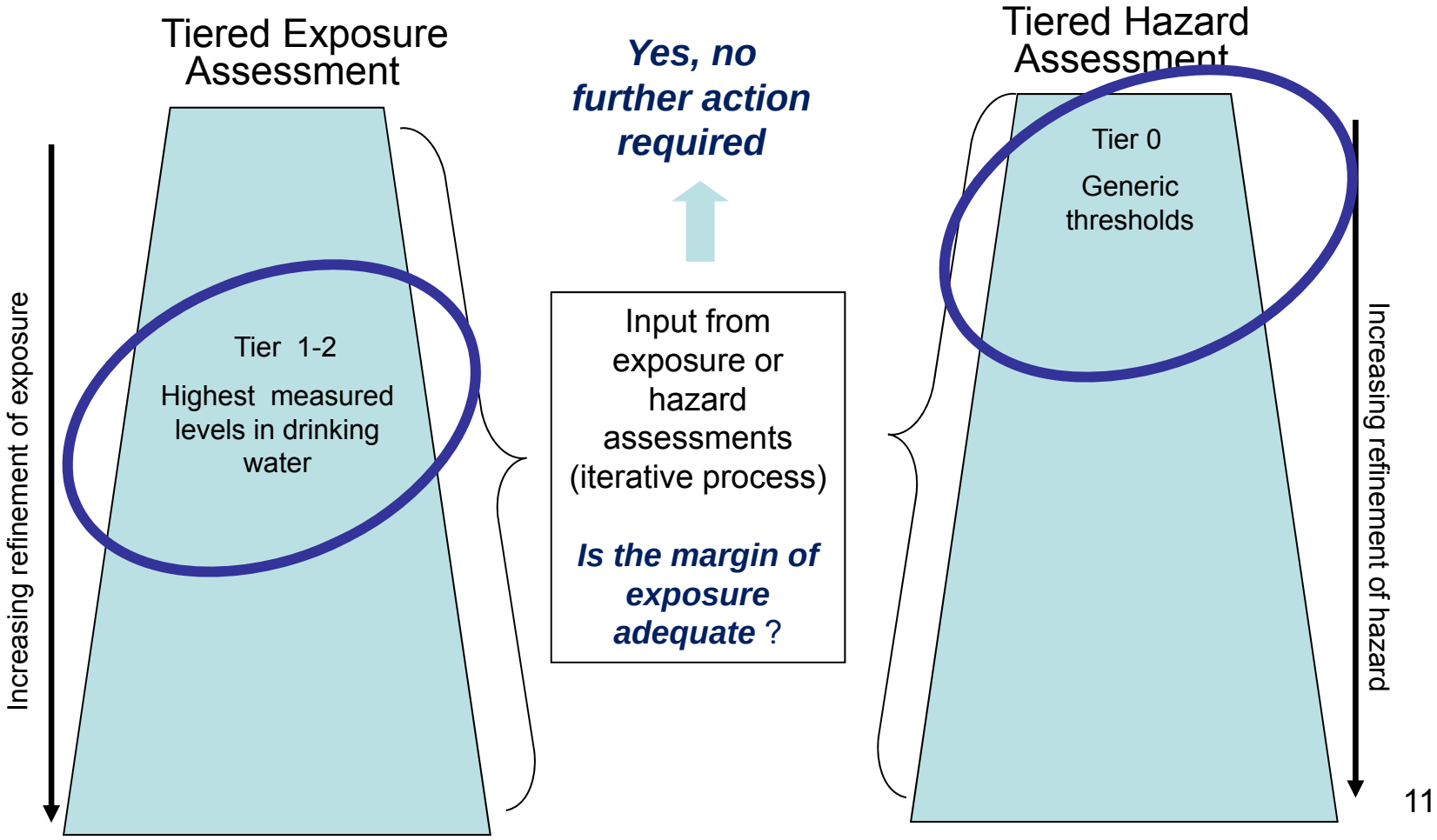
Problem Formulation (Cont'd) - Hazard

- 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

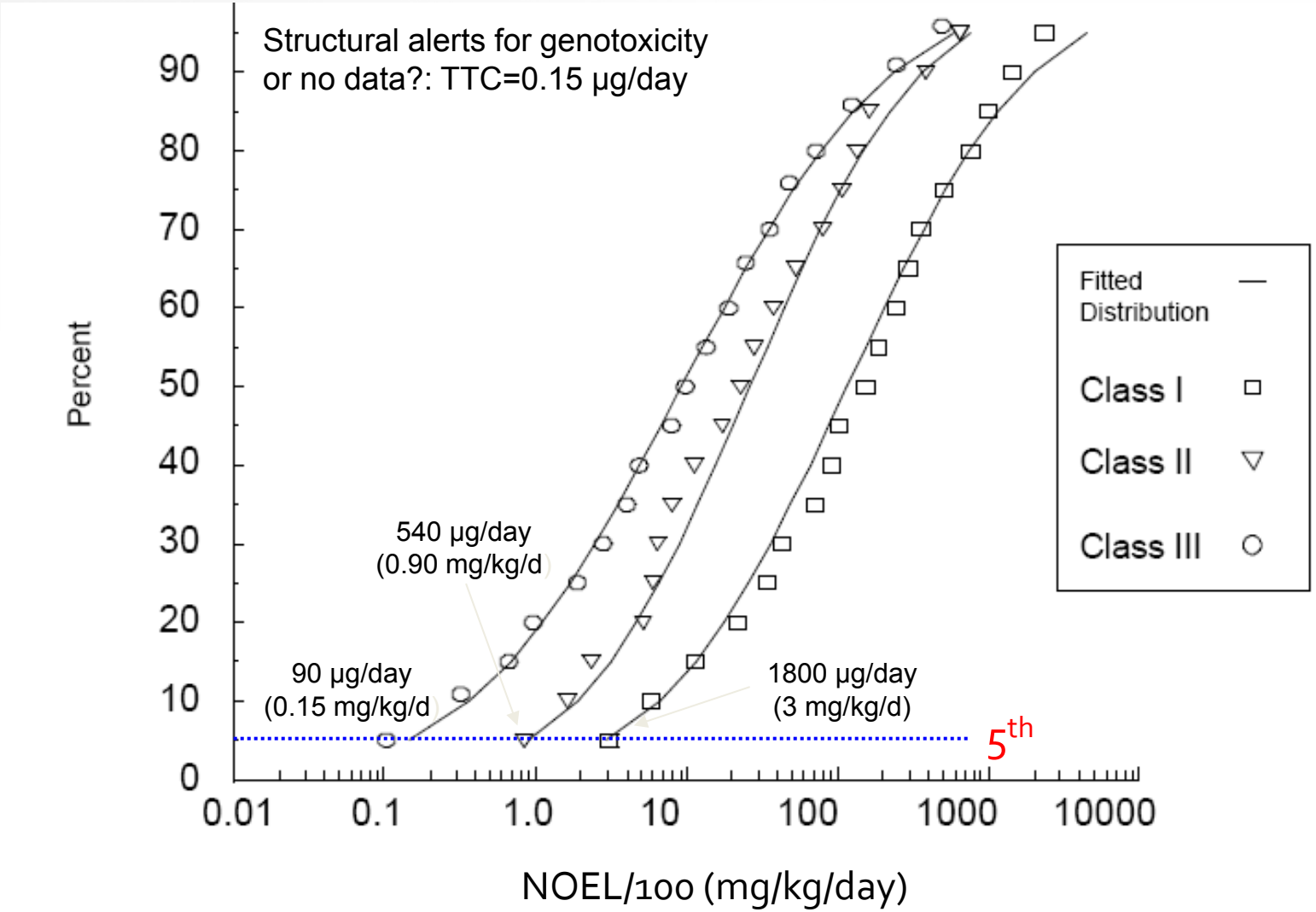
Nature of exposure?
Is exposure likely?
Co-exposure within a relevant timeframe?
Rationale for considering compounds in an assessment group?



Illustrative Case Study for Tier 0 (Hazard) – Drinking Water

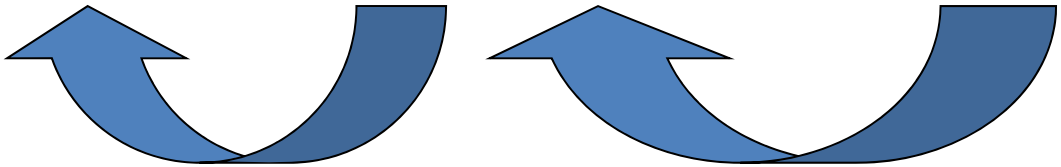
- Examines the applicability of the Threshold of Toxicological Concern (TTC) concept
  - TTC proposes that a *de minimis* value for toxicity can be identified for many chemicals
  - When structural data are available, this is used to identify relevant TTC

Threshold of Toxicological Concern (TTC)



TTC Exposure Based Limits

TTC Tier (ug/d)	Equivalent (mg/kg/d)	Basis
0.15	0.0000025	Structural alerts for genetox
1.5	0.000025	
18	0.0003	Organophosphate
90	0.0015	CC III: 5th %ile NOEL = 0.15 mg/kg/day
540	0.009	CC II: 5th %ile NOEL = 0.9 mg/kg/day
1800	0.03	CC I: 5th %ile NOEL = 3 mg/kg/day



Convert from mg to ug; multiply by bw of 60 kg

Divide by UF of 100

TTC case study - (1)

- 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) =

$$\frac{\text{Surface water concentration (ppm)} * 0.42 \text{ L consumption/ day}}{18 \text{ kg body weight}}$$

TTC case study (2)

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

TTC case study (3)

- $HQ_{\text{individual substance}} =$

$$\frac{\text{Exposure}_{\text{individual substance}}\ (\text{mg/kg-bw/day})}{\text{TTC value}_{\text{individual substance}}\ (\text{mg/kg-bw/day})}$$

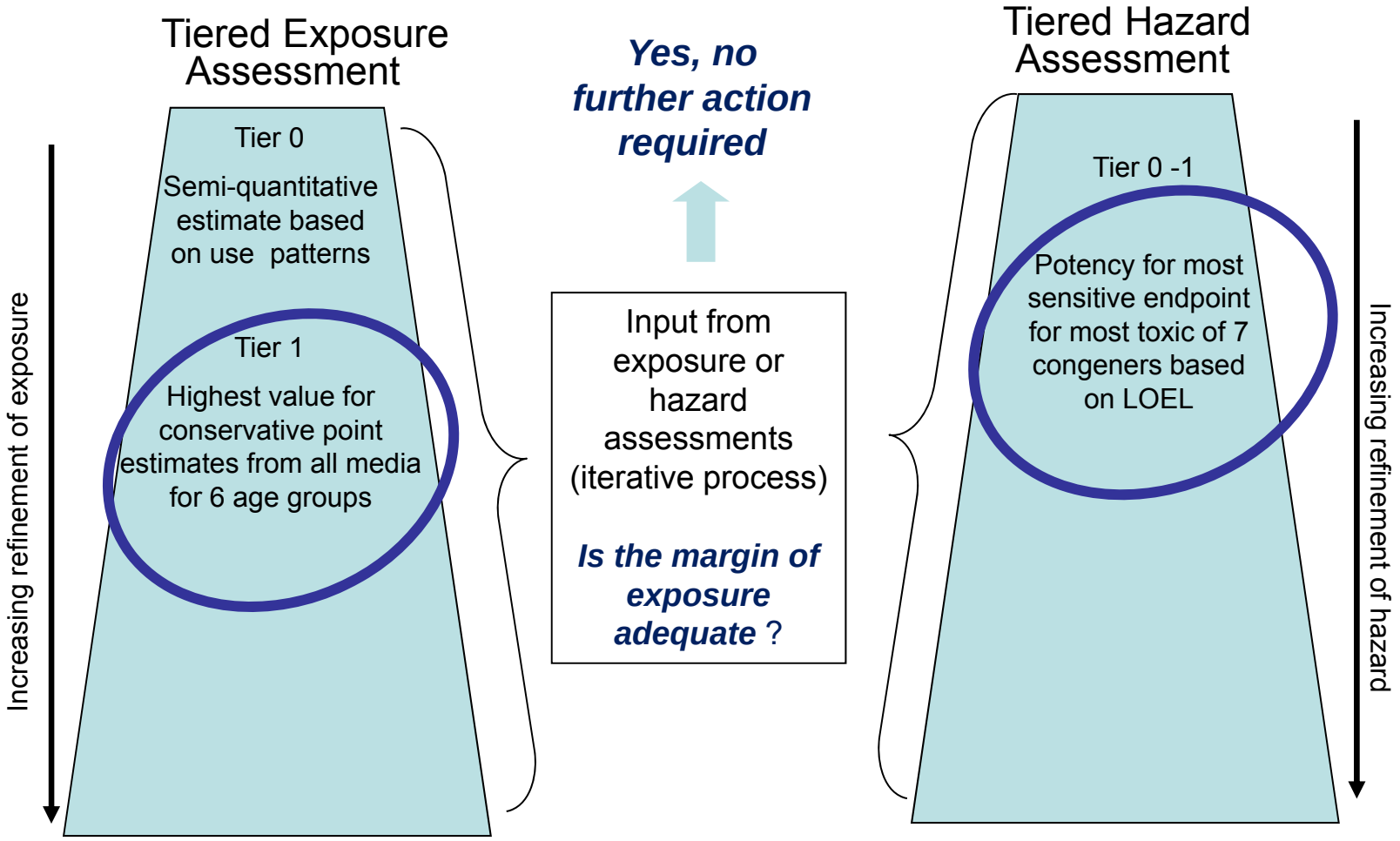
- $HI_{\text{mixture}} = HQ_A + HQ_B + HQ_C + HQ_D \ldots + HQ_J$

HI < 1, no need to go on to Tier 1

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?



Illustrative 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 o Hazard - PBDEs

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

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

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

Tier 0 – Hazard – PBDEs (cont'd)

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)

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

Tier 1 –Exposure – PBDEs (cont'd)

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[d]	5–11 years[e]	12–19 years[f]	20–59 years[g]	60+ years[h]
	Formula fed[b]	Breastfed[c]	Not formula fed					
Ambient air[j]	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[j]	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

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
- ***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

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

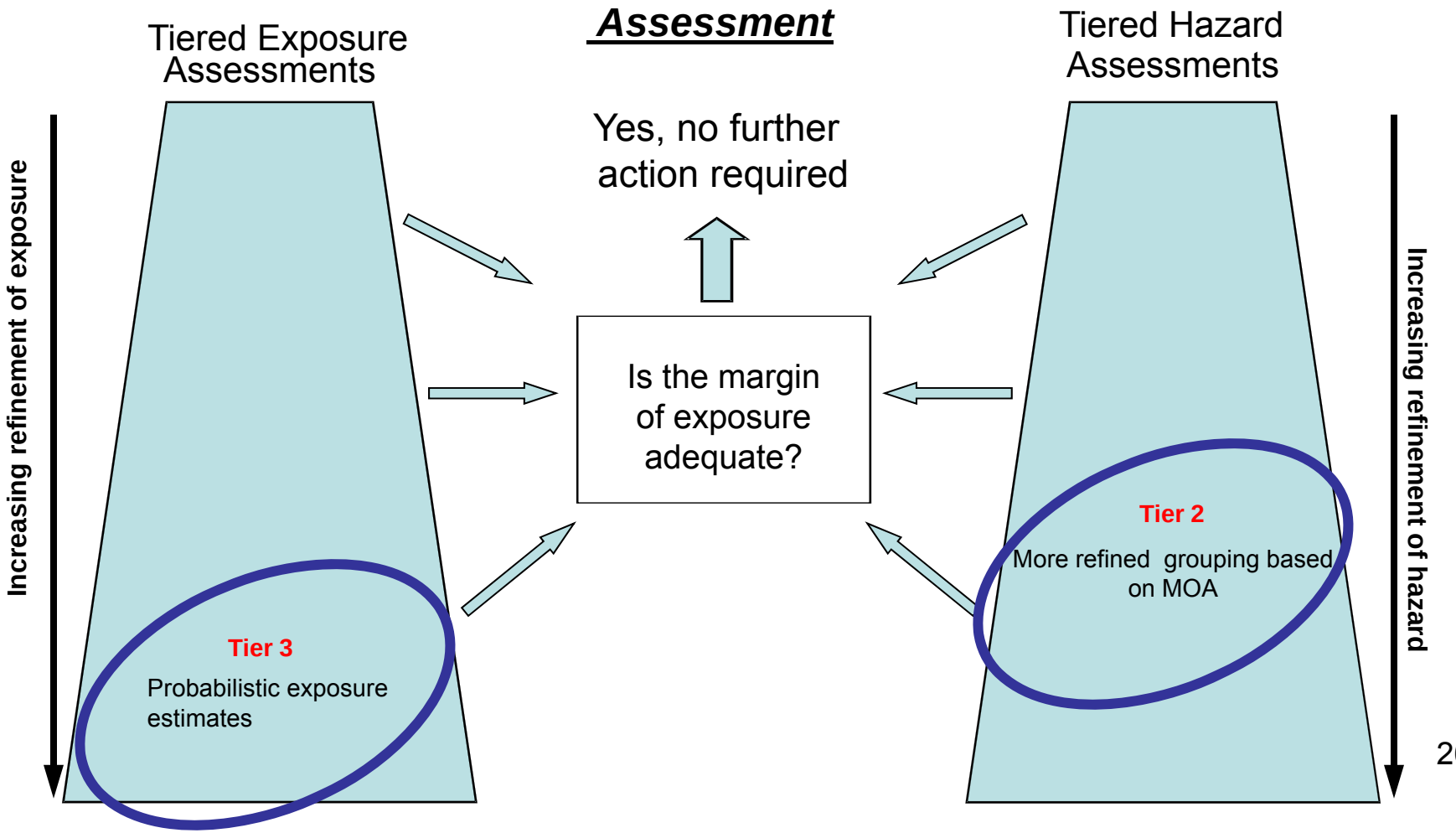
- Margin considered adequate in context of degree of conservatism (i.e., uncertainty)
  - Critical effect level was for most sensitive effect for most toxic congener; effects in chronic studies were 100 x greater
  - Large interindividual variability in PBDEs in breast milk
    - ***Mean& median levels 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 - Carbamates

Problem Formulation

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

Assessment



Illustrative Case Study - Carbamates

Background

- US EPA (2007) assessment of N-methyl carbamates (NMC)
  - aldicarb, carbaryl, carbofuran, methomyl, other related compounds

Problem Formulation for Grouping

- Exposure likely?
  - dietary (including drinking water), occupational, and / or residential
- Co-exposure?
  - Some food samples every year in the US contain multiple NMC residues
- Rationale for assessment group?
  - All inhibit AChE in a similar, rapidly reversible manner

Tier 0 - Carbamates

- Exposure:
  - Assume exposure to residues of each NMC singly at 95th or 99th percentile
  - Exposure estimates ranged up to 0.15 mg/kg bw/day
- Hazard:
  - Assume all compounds in (most conservative) Cramer Class 3 with TTC value of 0.0015 mg/kg bw/day

Tier 0 – Risk Characterization - Carbamates

			95th Percentile			99th Percentile		
Component	Cramer Class for Component	TTC, mg/kg bw/day	Estimated Exposure, mg/kg bw/day	Dose, mg/kg bw/day	Hazard Quotient TTC	Estimated Exposure, mg/kg bw/day	Dose, mg/kg bw/day	Hazard Quotient TTC
Aldicarb	3	0.0015	0.00029	0.000029	0.0193	0.000136	0.0000136	0.0091
Carbaryl	3	0.0015	0.000706	0.0000706	0.0471	0.001919	0.0001919	0.1279
Carbofuran	3	0.0015	0.000041	0.0000041	0.0027	0.000091	0.0000091	0.0061
Formetanate HCl	3	0.0015	0.089488	0.0089488	5.9659	0.146534	0.0146534	9.7689
Methiocarb[a]	3	0.0015	0	0	0	0	0	0
Methomyl	3	0.0015	0.000307	0.0000307	0.0205	0.000573	0.0000573	0.0382
Oxamyl	3	0.0015	0.00229	0.0000229	0.1527	0.00839	0.000839	0.5593
Pirimicarb	3	0.0015	0.002215	0.0002215	0.1477	0.003945	0.0003945	0.2630
Propoxur[a]	3	0.0015	0	0	0	0	0	0
Thiodicarb[a]	3	0.0015	0	0	0	0	0	0

[a] For methiocarb, propoxur, and thiodicarb, there was no food use or minimal use resulting in no exposure

Cumulative Hazard Index TTC	Cumulative Hazard Index TTC
6.36	10.77

- hazard index of 6.4 (95th percentile) or 10.8 (99th percentile)
- Need to go to next tier

Tier 1 - Carbamates

- Exposure:
  - Single-compound exposure assessments suggest that % ARfD exposure is fairly high for some compounds
  - Project exposure to high percentage of Reference Dose for multiple compounds at once

Compound	Reference Value	Source study	Endpoint	Safety Factors	Age group	% Reference value
Aldicarb	0.001 mg/kg bw/day	Human volunteer	AChE inhibition	100	Children, 1-6 years old	19%
Carbaryl	0.01 mg/kg bw/day	Rat devel. neurotox	FOB changes	100	General population	43%
					Children, 1-2 years old	68%
Formetanate HCl	0.00065 mg/kg bw/day	Comparative AChE study	AChE inhibition	100	Adults, 20-49 years old	16%
					Infants	56%
Methomyl	0.02 mg/kg bw/day	Rabbit teratology	Maternal / fetal tox	300	Infants < 1 year old	27%
					Children 1-6 years old	72%
Oxamyl	0.001 mg/kg bw/day	Rat acute neurotox	AChE inhibition	100	Children, 1-6 years old	81%
Pirimicarb	0.01 mg/kg bw/day	Rat neurotox	Clinical signs	1000	General population	10%
					Children, 1-2 years old	10%
					Children, 1-6 years old	7%
Thiodicarb	0.01 mg/kg bw/day	Rat teratology	Body weight gain	1000	Children, 1-6 years old	31%
					Infants	60%

Tier 1 -2 Carbamates

- Hazard:
  - Hazard data available for NMCs
  - Develop relative potency factors based on an index compound (including age specific)

	Brain		
Compound	**BMD_{10}, mg/kg bw**	**$BMDL_{10}$, mg/kg bw**	**RPF**
Aldicarb[1]	Female = 0.05 Male = 0.06	Female = 0.03 Male = 0.03	4
Carbaryl	Registrant female = 1.60 Registrant male = 1.21 NHEERL male = 5.46 Combined male = 1.58 Moser = 2.63	Registrant female = 1.35 Registrant male = 0.99 NHEERL male = 4.15 Combined male = 1.11 Moser = 2.03	0.15
Formetanate HCl	0.11	0.06	2.18
Methiocarb	1.31	0.56	0.18
Methomyl	0.36	0.2677	0.67
Oxamyl	0.24	0.18	1.00
Pirimicarb	11.96	6.98	0.02
Thiodicarb	0.27	0.23	0.89

Higher Tier - Carbamates

- Exposure (Tier 3):
  - Probabilistic modeling of exposure using USDA Pesticide Data Program data (residues in commodities) and food intake survey data
- Hazard (Tier 1-2):
  - Develop relative potency factors based on an index compound (including age specific)

Learnings - Experience on Combined Exposures

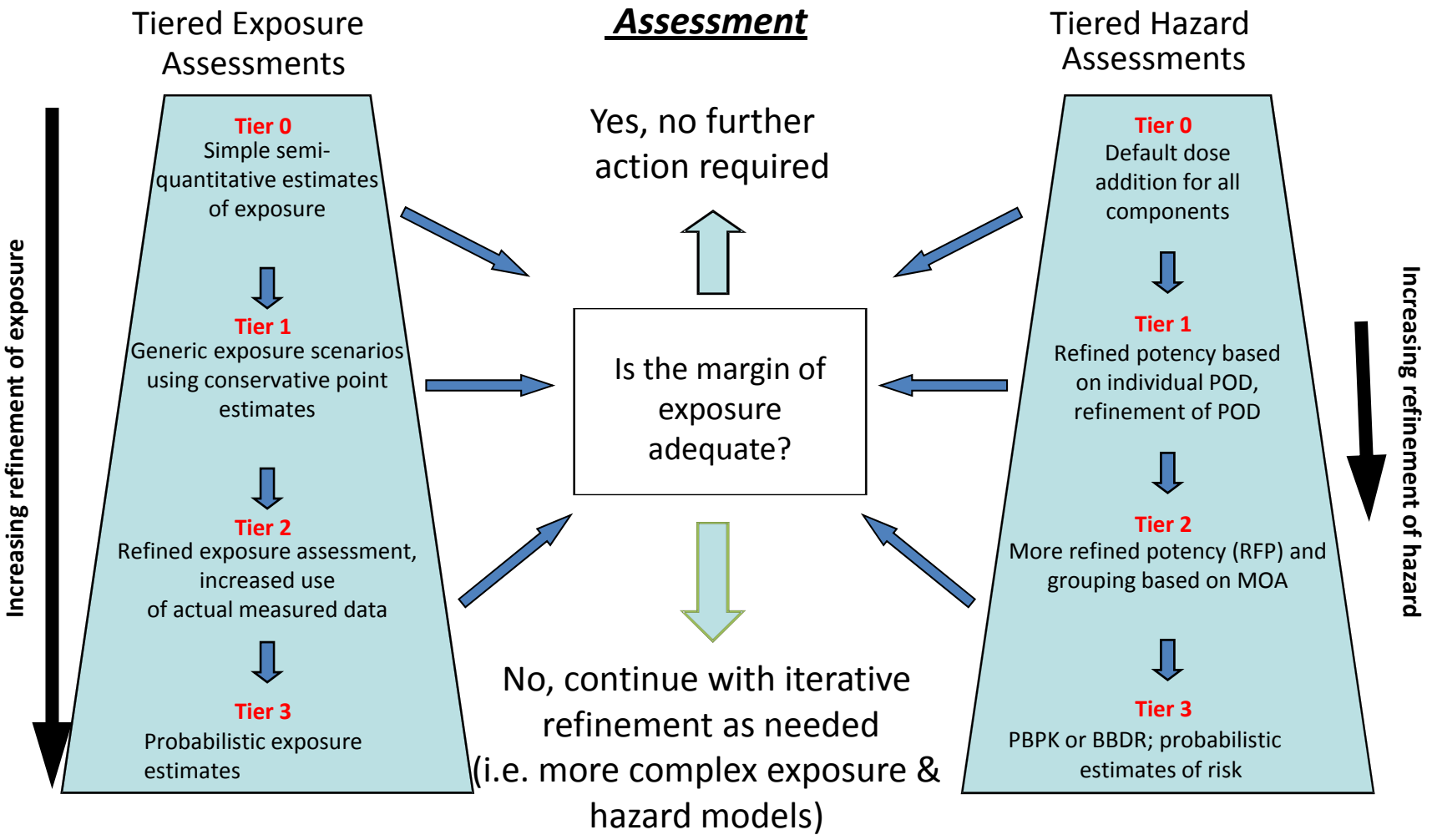
- Limited numbers of examples of combined assessments from regulatory programs
- Combined assessments sometimes more complex than necessary
  - "Have data, must use"
- Exposure more discriminating than hazard

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



Learnings - Exposure

- Importance of "framing" estimates
  - Tiering – Degree of conservatism
  - Requires a "crude" sensitivity analysis even in early tiers
    - i.e., confidence in the "driver" of the outcome?
- Limited use of predictive/screening methods
  - Need for development of simple exposure surrogates
  - Need to target monitoring to verify estimates from predictive tools

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

Next Steps
Recommendations from Feb./11 WHO-OECD-ILSI-HESI Workshop

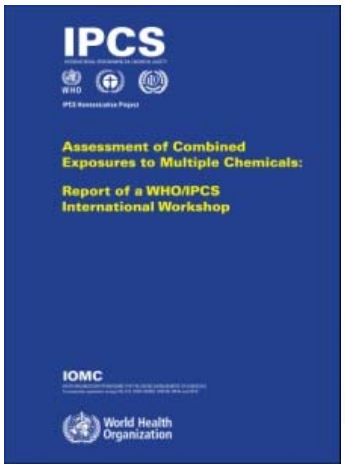
- ***Coordination/Harmonization***
  - multi-sector, multi-stakeholder, global coordinating/working group
  - Respository of case studies
- ***Additional Case Studies***
  - e.g., additional data rich, data poor, effects based, including non-chemical stressors, prospective; environmental effects
- ***Development/Refinement of Tools and Approaches***
  - e.g., problem formulation "triggers"; "drivers"; uncertainty analysis
- ***Communication***
  - e.g., lower tiers; training

More Information

IPCS Harmonization Website
http://www.who.int/ipcs/methods/harmonization/areas/aggregate/en/index.html :
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




Regulatory Toxicology and Pharmacology
Risk assessment of combined exposure to multiple chemicals: A WHO/IPCS framework