Considering Risks and Uncertainties Related to Combined Exposures

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Presented by:

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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 in Combined Exposures Assessment***

Evolving Mandates for Existing Chemicals

- Canada
  - "Categorization" for 23, 000 chemicals - Sept., 2006 & multi tiered assessment program
- Europe
  - ***R***egistration, ***E***valuation and ***A***uthorization of ***C***hemicals (REACH) (2007)
- Japan Stepwise Assessment under the ***C***hemical ***S***ubstances ***C***ontrol ***L***aw (CSCL)" (2009)
- Australia ***I***nventory ***M***ulti ***T***iered ***A***ssessment and ***P***rioritization (IMAP) (2012)
- ***New Zealand Group Standards for Industrial Chemicals (HSNO)***
- U.S.
  - VoluntaryTesting/Research Initiatives /Legislative Renewal?

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 several European & US initiatives

Post Workshop Revised Terminology

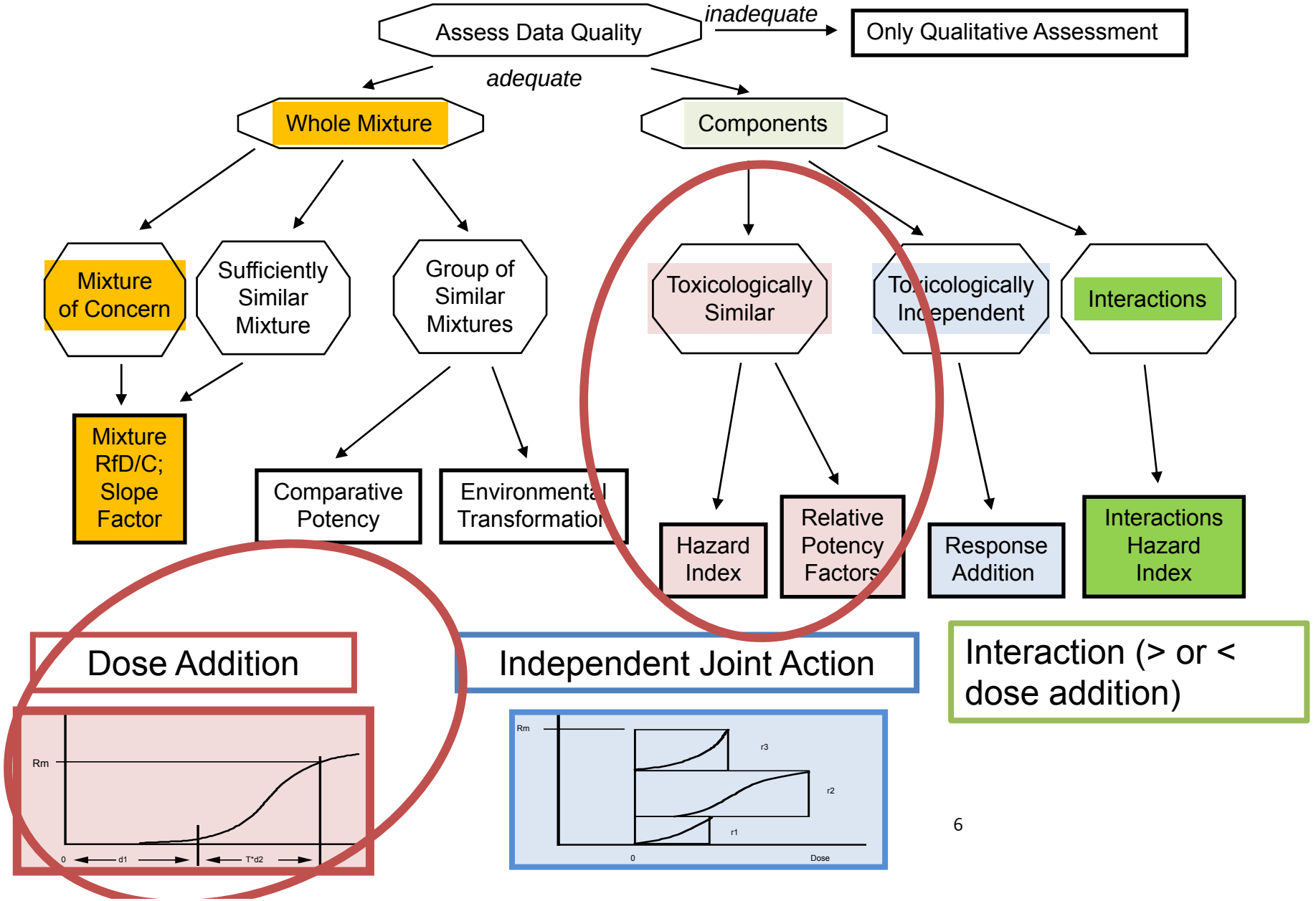
Recommendations:

- 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

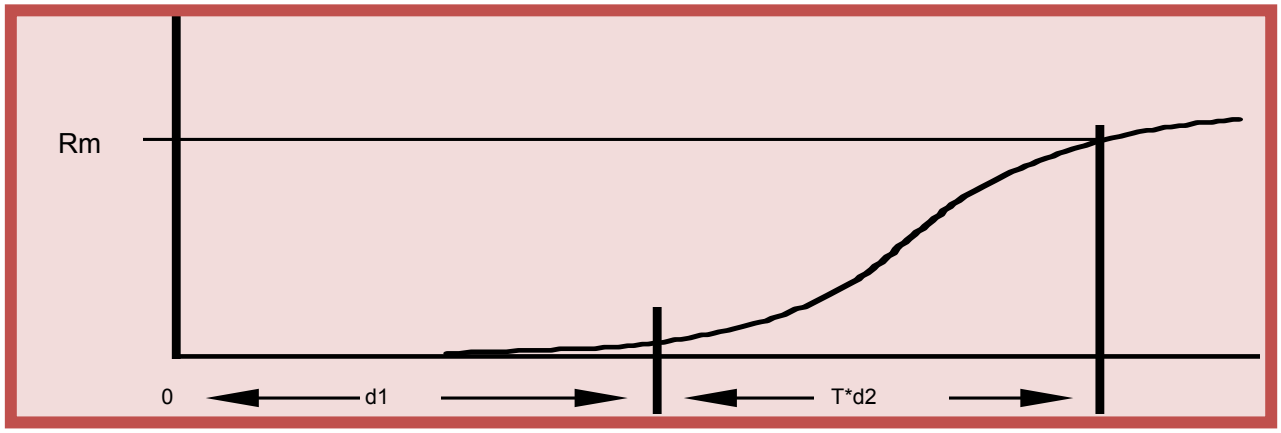
Terminology:

- "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

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



Dose Addition



Hazard Index, Reference Dose

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

Point of Departure Index

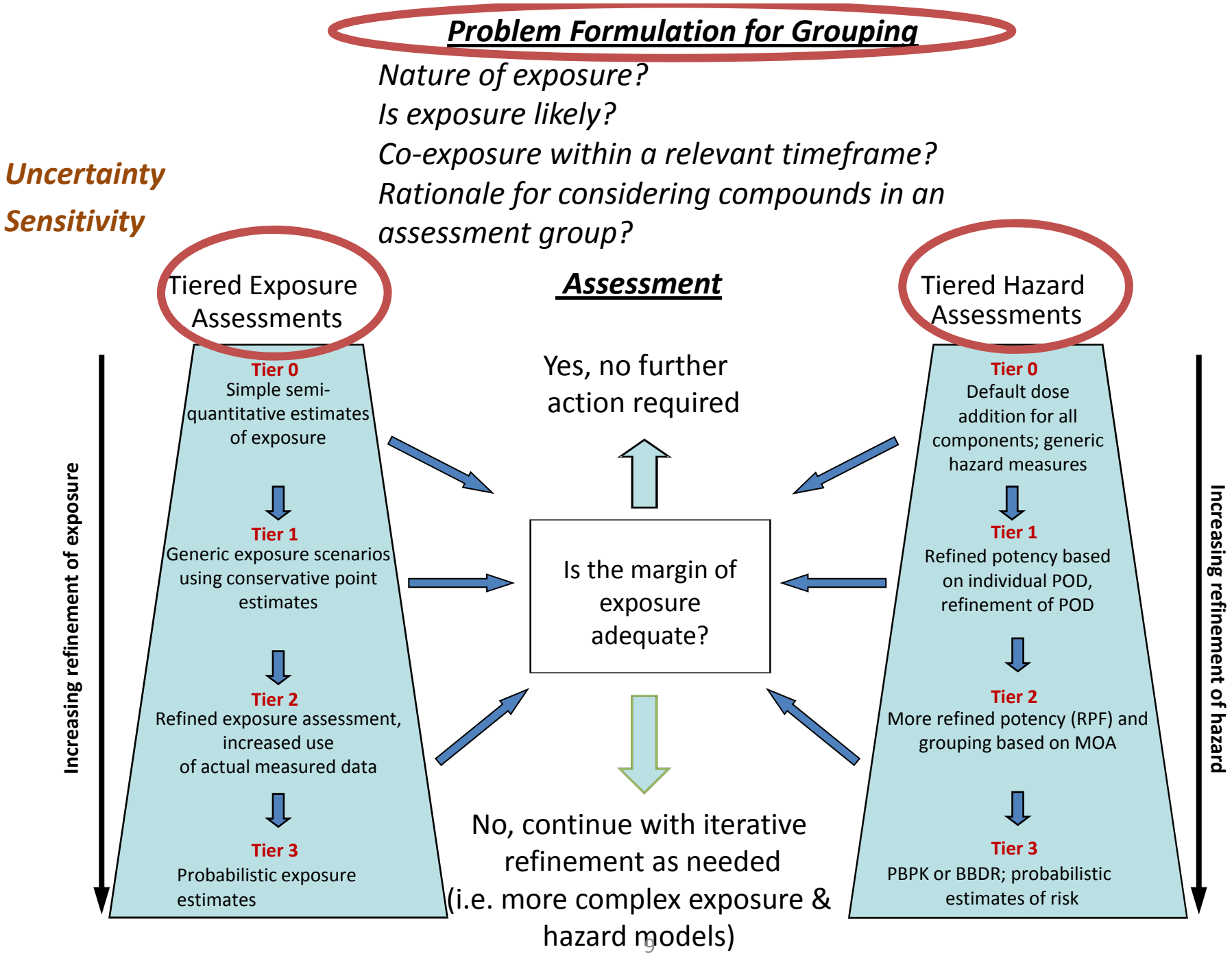
$$\mathbf{PODI} = \sum_{i=1}^{n} \frac{estimated\ intake_i}{POD_i}$$

Toxic Equivalency

$$\mathbf{TEQ} = \sum_{i=1}^{n} \mathrm{Mass}_i \times \mathrm{TEF}_i$$

Contents of the 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
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
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; generic hazard measures
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 hazard

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

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

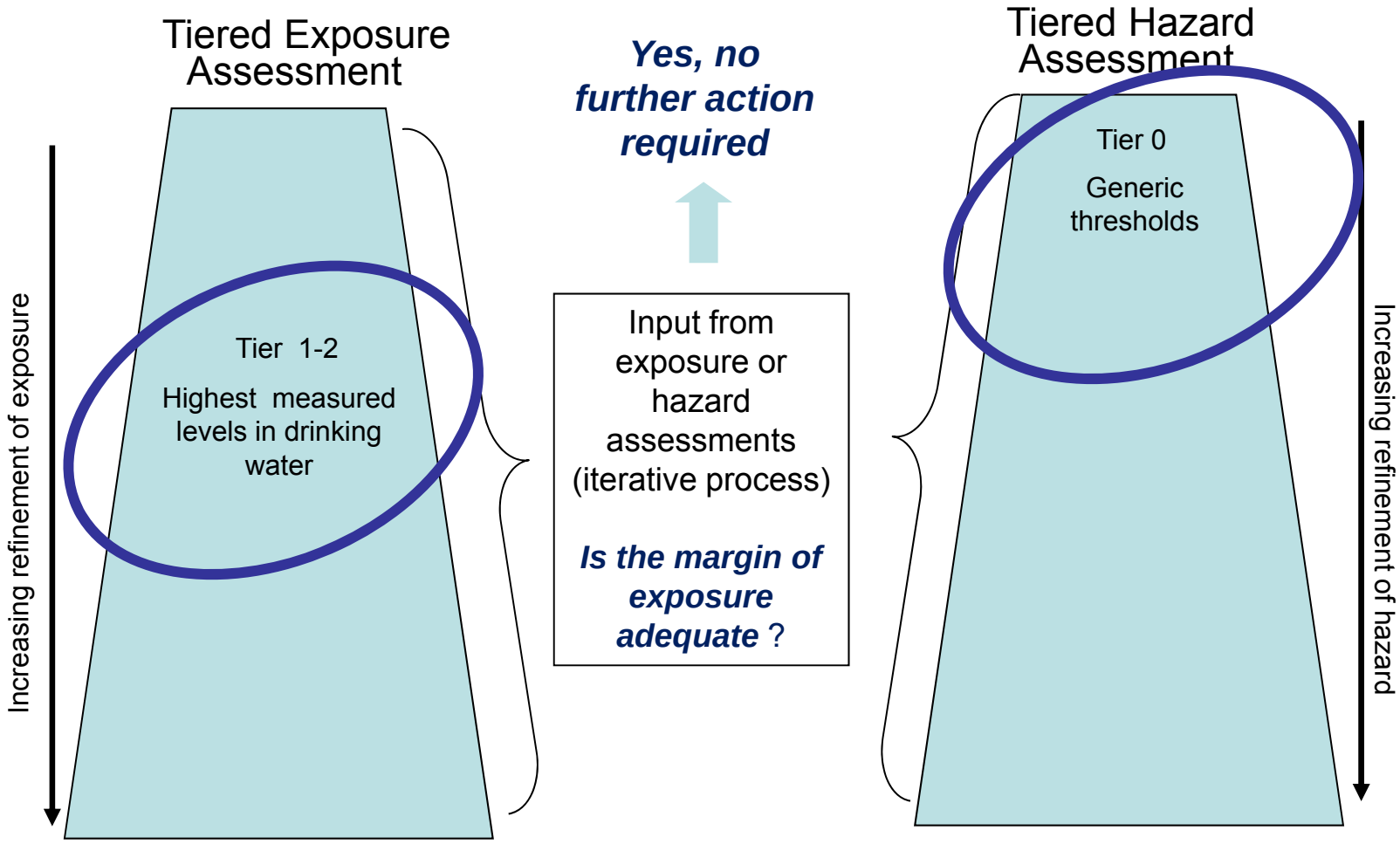
Problem Formulation (Cont'd) - Hazard

- 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)
  - 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
- Applied to 10 substances found in surface waters
  - Conservatively assumed that all present at all times at max concentration detected, 100% of drinking water from the same source, maximally exposed age group (3-6 years of age)
  - Intake (mg/kg bw/day):
    - Surface water concentration (ppm) * 0.42 L consumption/ day

      18 kg body weight

TTC case study (3)

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

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

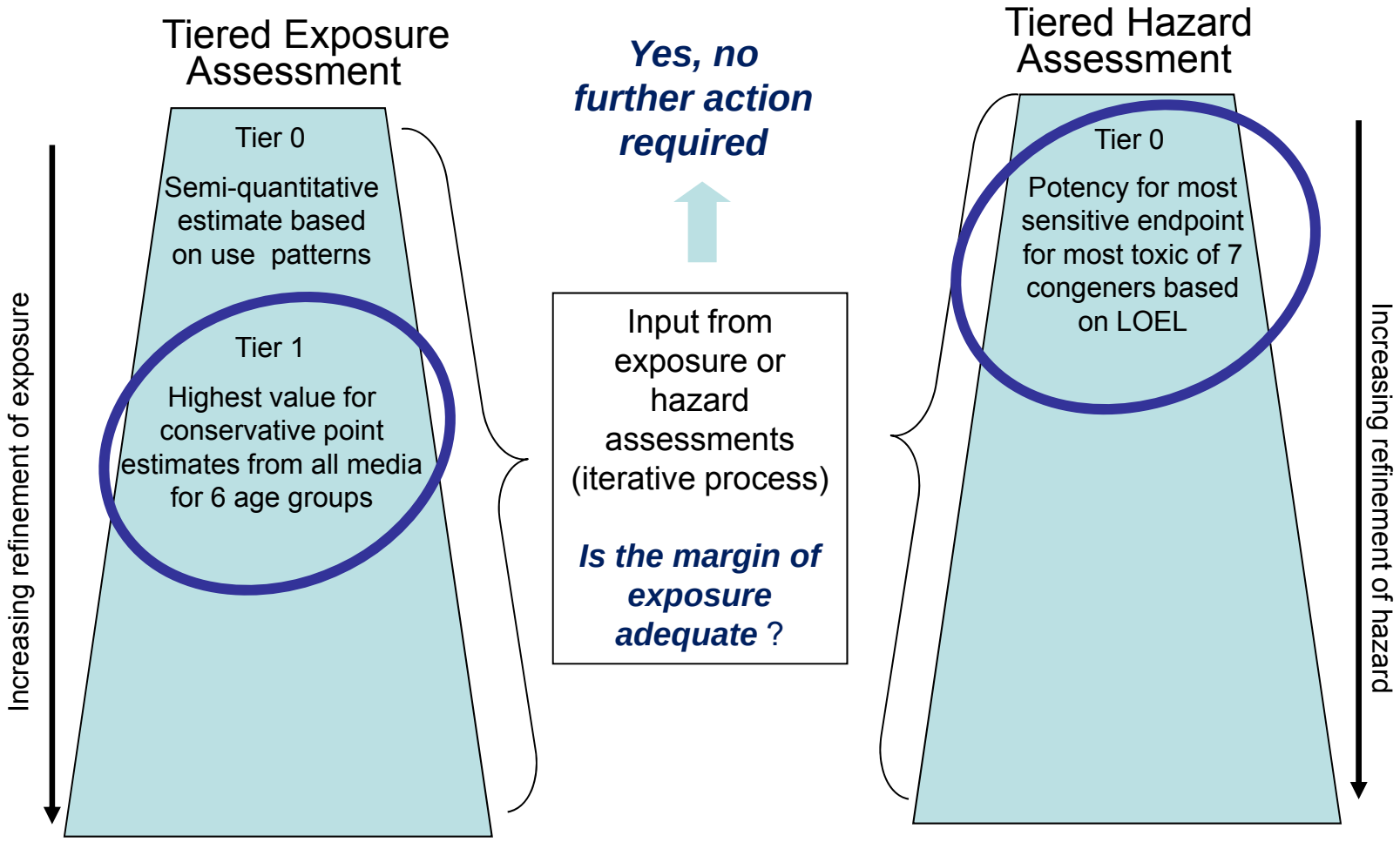
- $HI_{\text{mixture}} = HQ_A + HQ_B + HQ_C + HQ_D \ldots + HQ_J$

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?



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

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

- 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 (incl. 3 subgroups of infants)
- In separate scenarios, considered also traditional "country food diet" & dermal intake from household products

Degree of Conservatism

- 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

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[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[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

PBDEs Tier 1 Risk Characterization

- Margin between critical effect level and intake of total PBDEs for the most highly exposed subgroup of the population (breastfed infants):

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

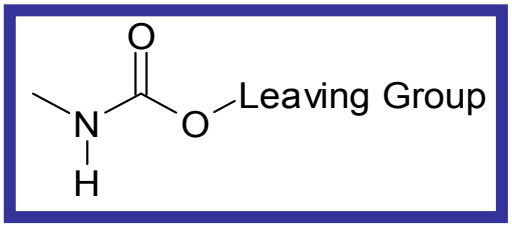
≈ 300

Need to quantitate (at least crudely) uncertainty/conservatism for critical determinants as a basis to consider adequacy of margin of exposure

- 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

Tiered Exposure Assessments

Tiered Hazard Assessments

Yes, no further action required

Is the margin of exposure adequate?

Increasing refinement of exposure

Increasing refinement of hazard

Tier 3

Probabilistic exposure estimates

Tier 2

More refined grouping based on MOA ; refinement of POD

Learnings - Experience on Combined Exposures

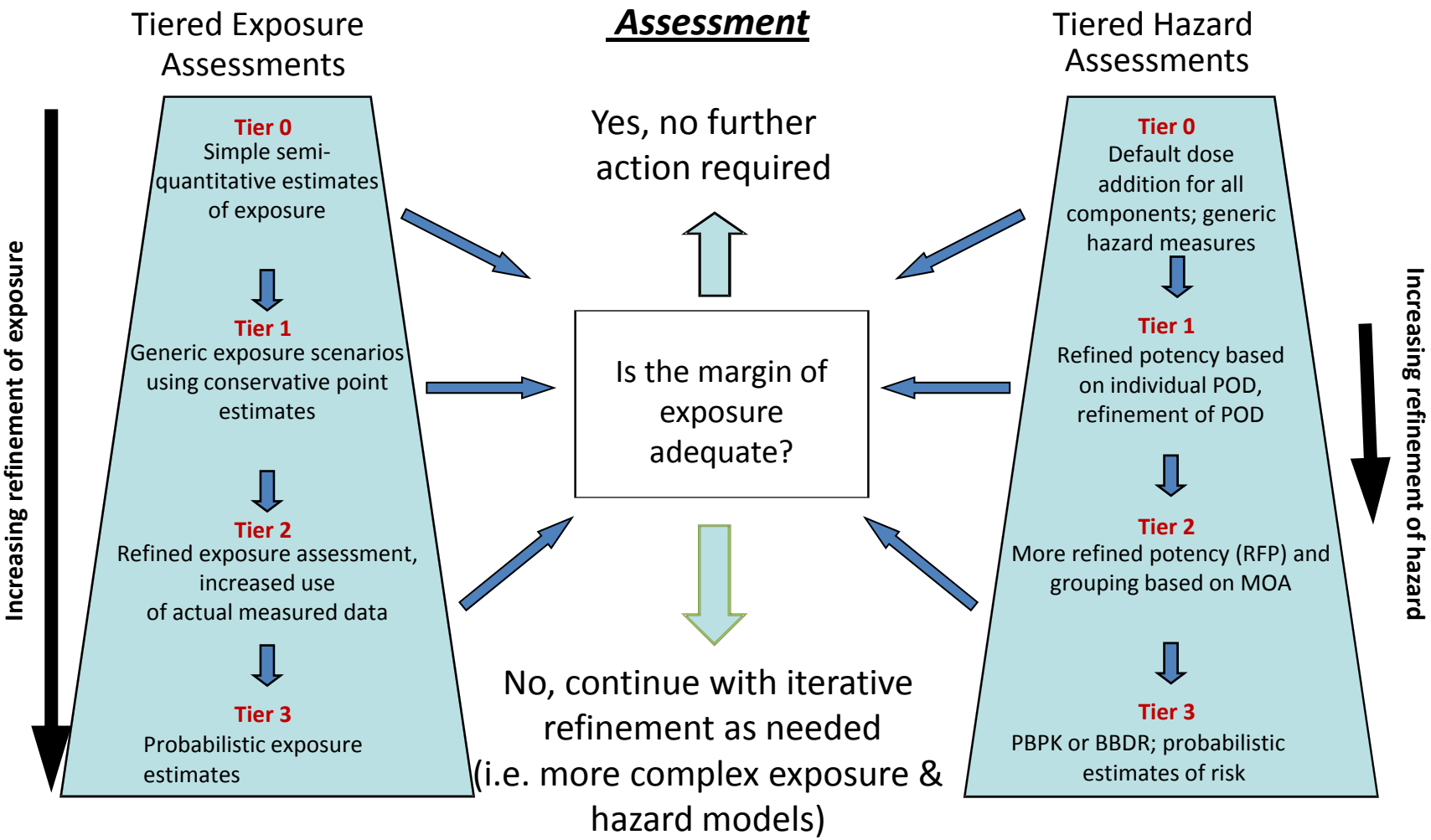
- Limited numbers of examples of combined assessments from regulatory programs
- Combined assessments sometimes more complex than necessary
  - "Have data, must use"
- Exposure more discriminating than hazard

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



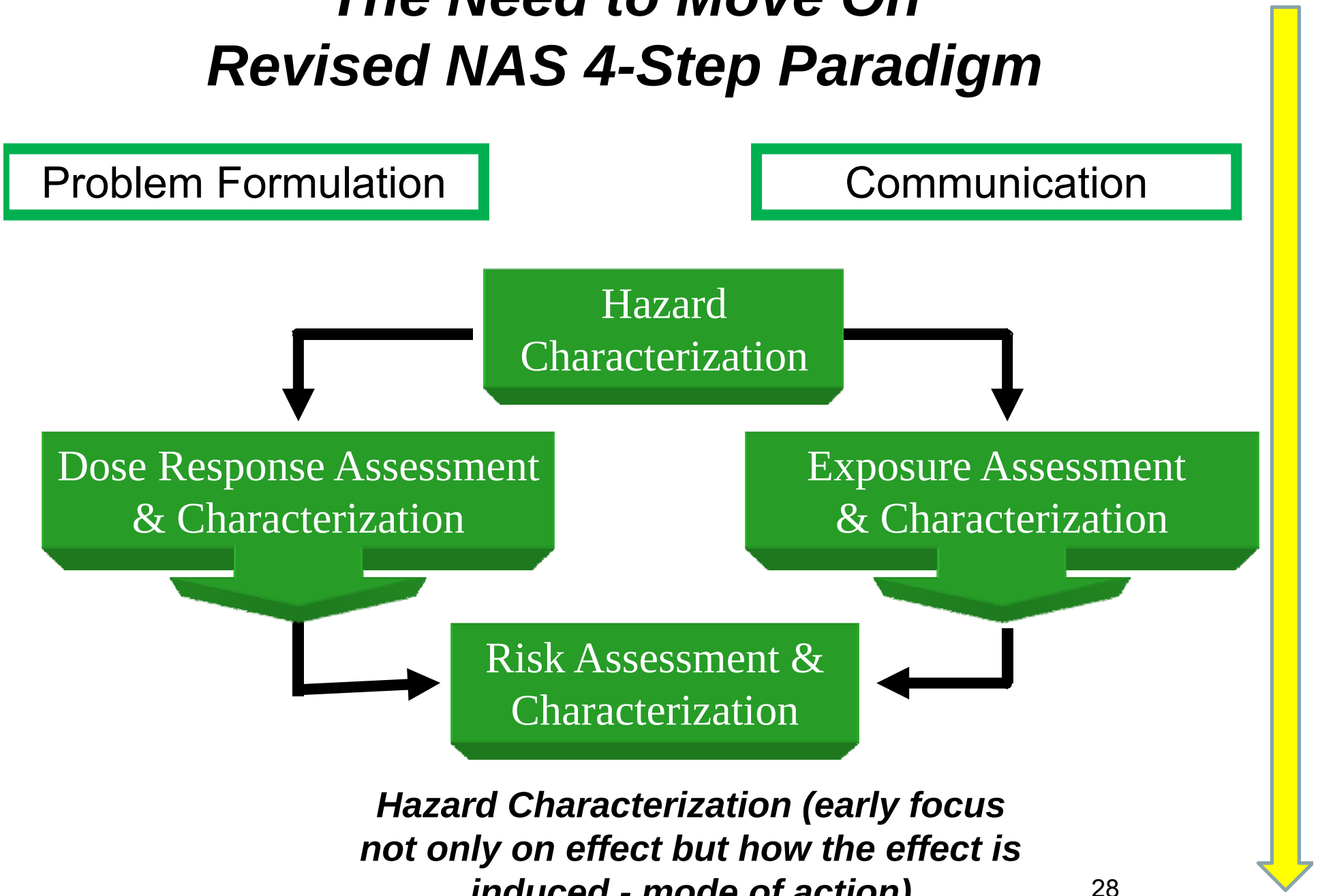
Learnings - Exposure

- 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

The Need to Move On
Revised NAS 4-Step Paradigm



Hazard Characterization (early focus not only on effect but how the effect is induced - mode of action)

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 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 IPCS/OECD/ILSI Workshop

http://www.oecd.org/document/24/0,3746,en_2649_34377_47858904_1_1_1_1,00.html