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

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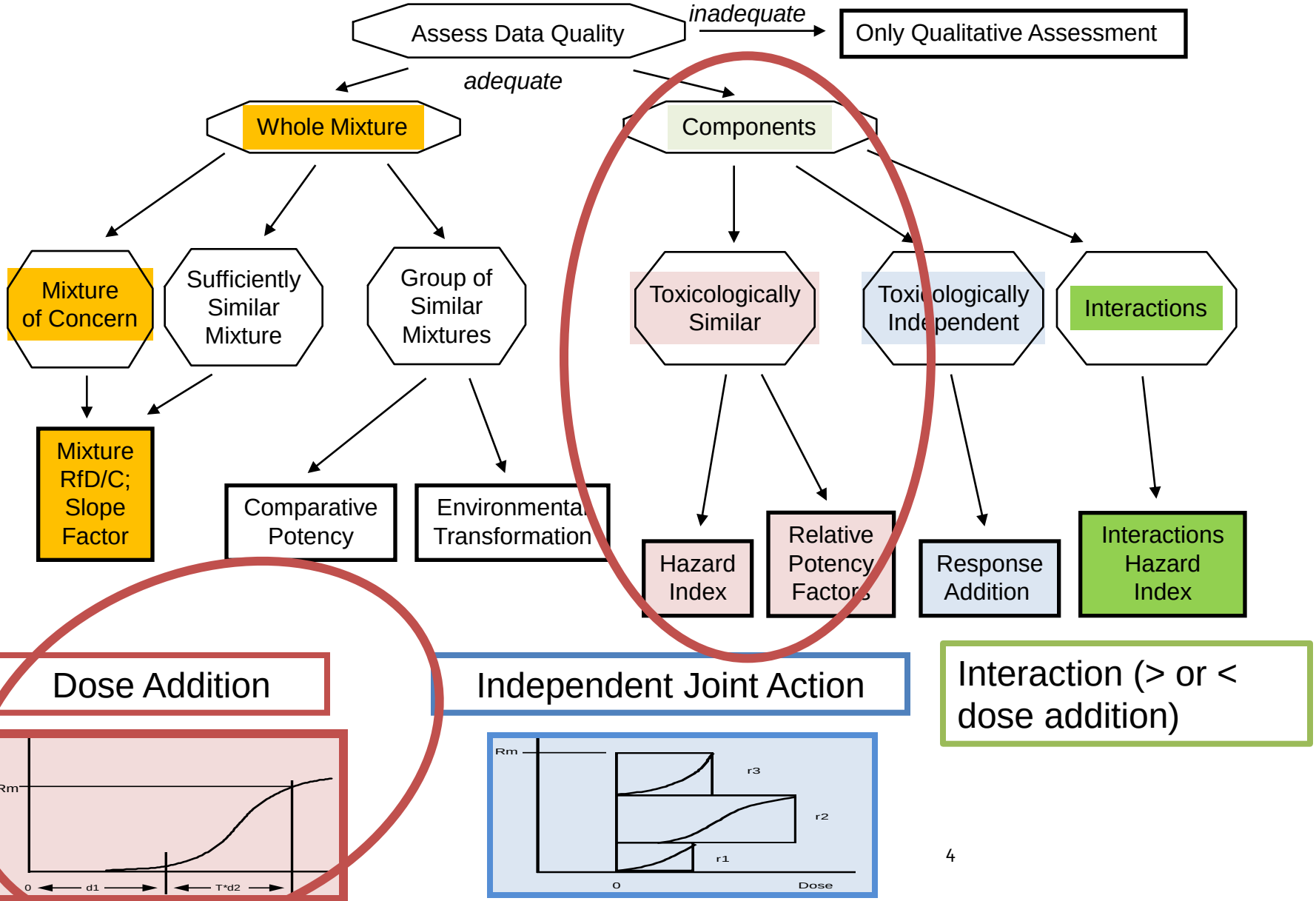
Outline

- WHO IPCS Framework for Combined Exposures
  - Objectives
    - Building on Existing Methodology
    - Incorporating Recent Developments to Increase Efficiency
- What's happened since
- Implications for ***Tiered Priority Setting/Assessment***, ***Uncertainty & Sensitivity*** Analysis, Communication

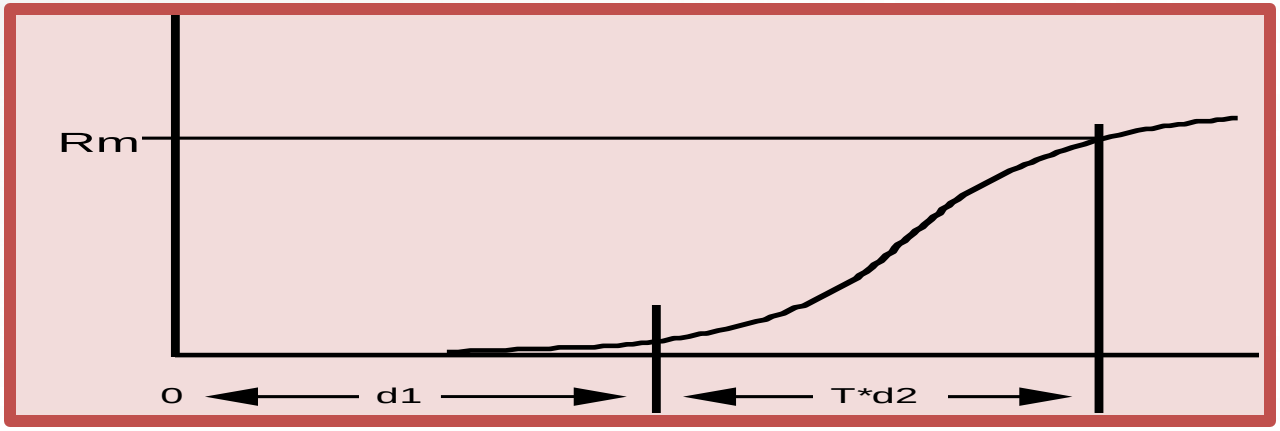
Evolving International Mandates for Existing Chemicals

- Canada
  - "Categorization" for 23, 000 chemicals - Sept., 2006 & multi tiered assessment program
- Europe
  - ***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.
  - Research Initiatives /Legislative Renewal?

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

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

Status – WHO IPCS Combined Exposures

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

Challenges in International Coordination 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

Contents of the WHO IPCS Framework


Regulatory Toxicology and Pharmacology

Risk assessment of combined exposure to multiple chemicals: A 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

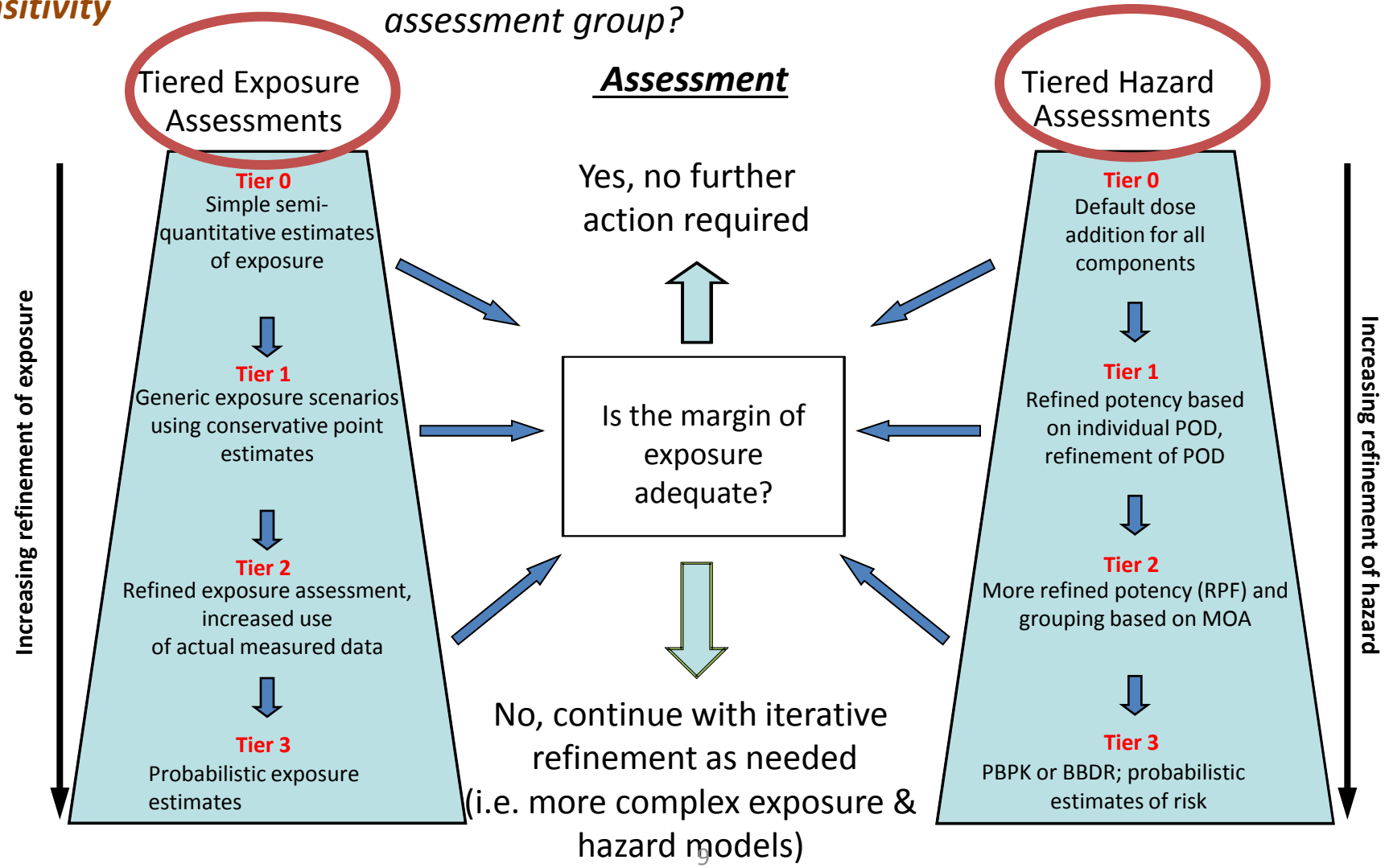
Problem Formulation for Grouping

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

Modified from Meek et al., 2011

Uncertainty

Sensitivity



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

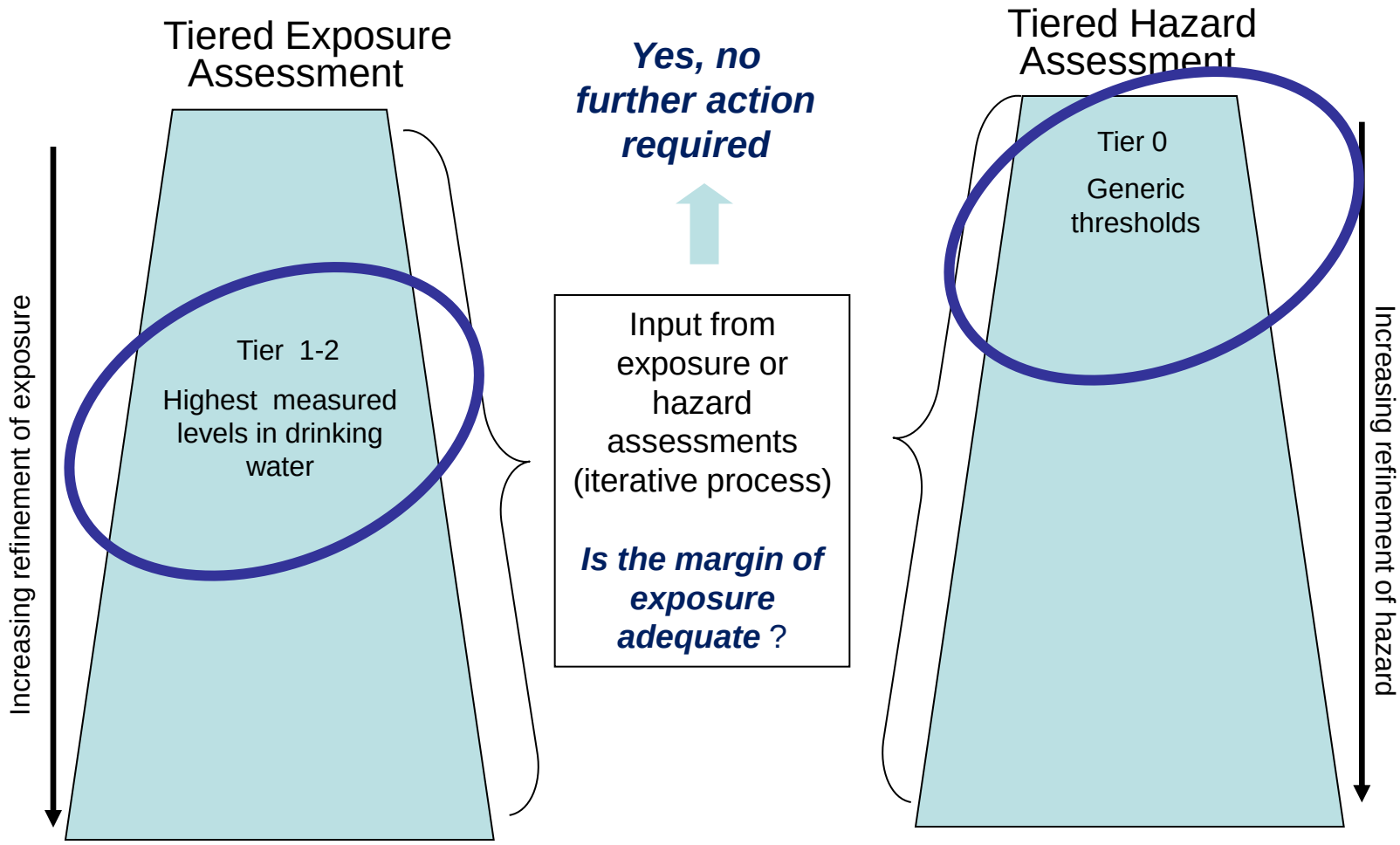
Problem Formulation (Cont'd) - Hazard

- 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 0/1 – Drinking Water

- Based on Hazard Index

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

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

Illustrative case study – Tier 0/1 Exposure

- 10 substances found in surface waters
  - Assume all present simultaneously at all times, at max concentration detected; all drinking water from same source (consider degree of conservatism)
  - Assume all belong to same assessment group, i.e. act by dose addition
- Use maximum exposure group (in this case, 3-6 years of age)
  - Exposure (mg/kg-bw/day) =

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

Illustrative case study. Contaminants in Drinking Water

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

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

$$HI\ (\text{combined exposure}) = HQ_A + HQ_B + HQ_C + HQ_D .... + HQ_J$$

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

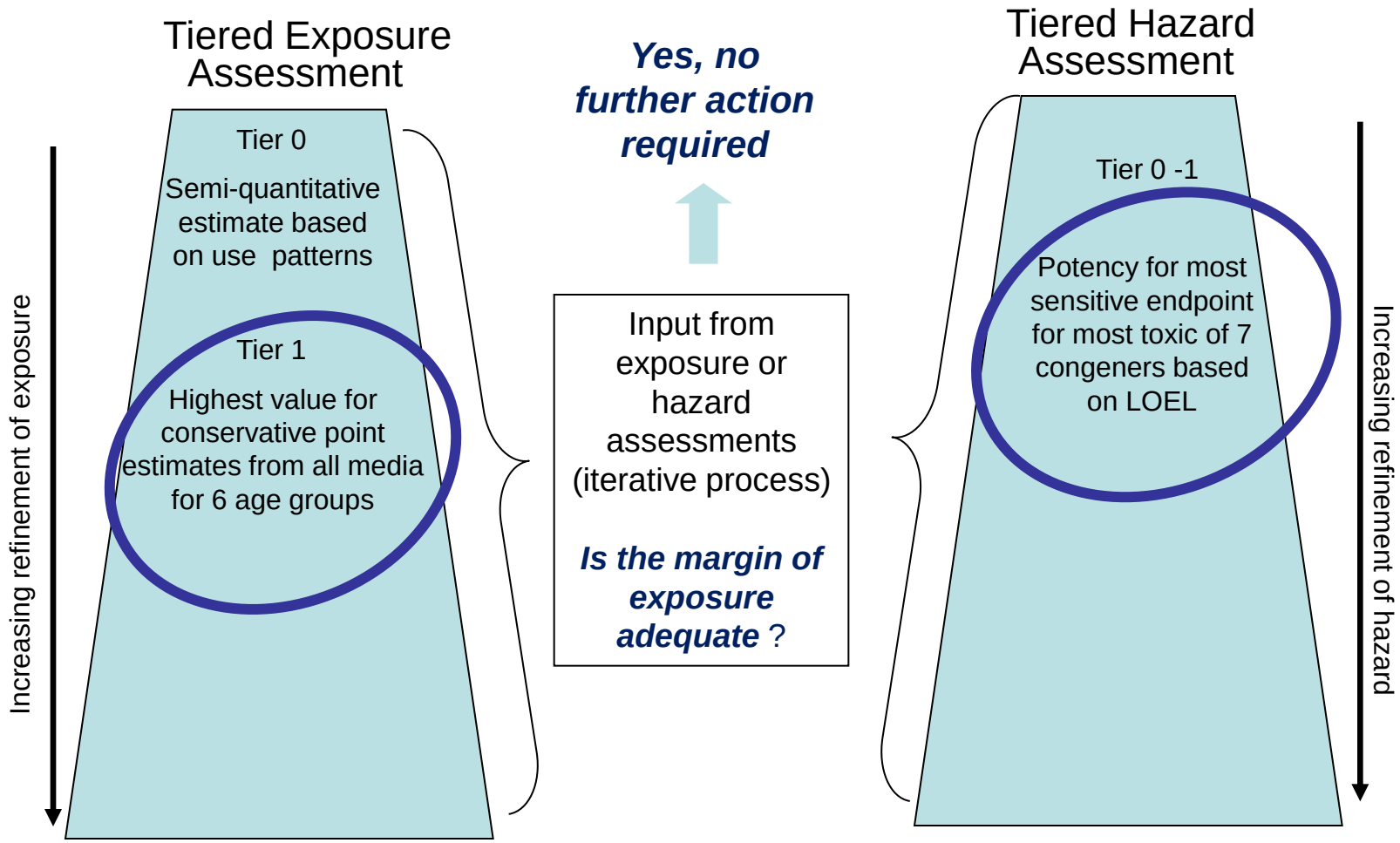
Drinking Water Tier 0/1 Risk Characterization

- Hazard Index < 1; considered adequate based on degree of conservatism
  - Needs to be specified
- Degree of conservatism needs to be balanced against (e.g.,)
  - limitations of the TTC
  - the extent of characterization of the appropriate range of chemicals in drinking water
- For a higher tier
  - i.e., what would values be, if data-based assumptions used?

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?



Problem Formulation – PBDEs – General Population

Problem Formulation for Grouping

- 3 main commercial mixtures/7 different isomers used widely as flame retardants in consumer products
- Exposure likely?
  - Direct & indirect contact with PBDE containing products
- Co-exposure?
  - Overlap in isomers within commercial mixtures; similar kinetics
- Hazard
  - common target organs; trend in pchem properties/ toxicity with ↑ bromination

Tiers – Exposure – PBDEs – General Population

Tier 0

- Relative ranking of all Existing Substances in Canada during categorization, based on limited information provided for all:
  - quantity (estimated annual quantity of use, Q),
  - number of submitters (S)
  - ***use (sum of normalized expert ranked use codes, U), reflecting two workshops*** $\sum$ (use x PE)
- Convert to semiquantitative measure of exposure by normalizing to Priority Substances with similar use profile/phys-chem properties

Tier 1

- Upper bound estimate of daily intake of total PBDEs by 6 age groups of the population based on monitoring data in ambient/indoor air, water, foodstuffs, breast milk & dust

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

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

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 (cont'd)

Modified from Health Canada, 2006

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

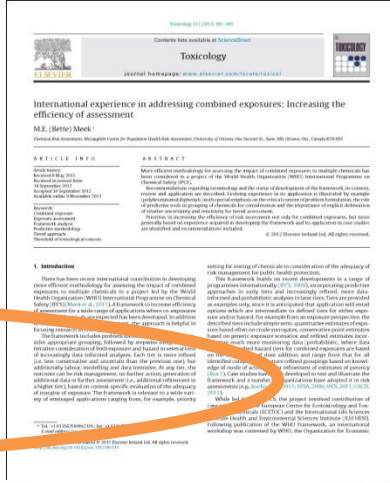
- Margin between critical effect level and upper bound deterministic estimate of exposure
  - intake of total PBDEs for the most highly exposed subgroup of the population (breastfed infants):

$$= \frac{0.8 \text{ mg/kg bw/day}}{2.6 \text{ ug/kg bw/day}} = 300$$

- Margin considered adequate in context of degree of conservatism
  - Critical effect level was for most sensitive effect for most toxic congener; effects in chronic studies were 100 x greater
  - Large interindividual variability in PBDEs in breast milk
    - ***Mean& median levels 400 & 200 fold < than maximum levels used in estimates***
- Needs to be balanced against:
  - Increase in body burden of PBDEs over time (9x between 1992 & 2001)

Learnings

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


Toxicology

International experience in addressing combined exposures: Increasing the efficiency of assessment

M.E. (Bette) Meek

Limited Progress on Combined Exposures? Principles – Facilitating Regulatory Change

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

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

Exposure More Discriminating than Hazard

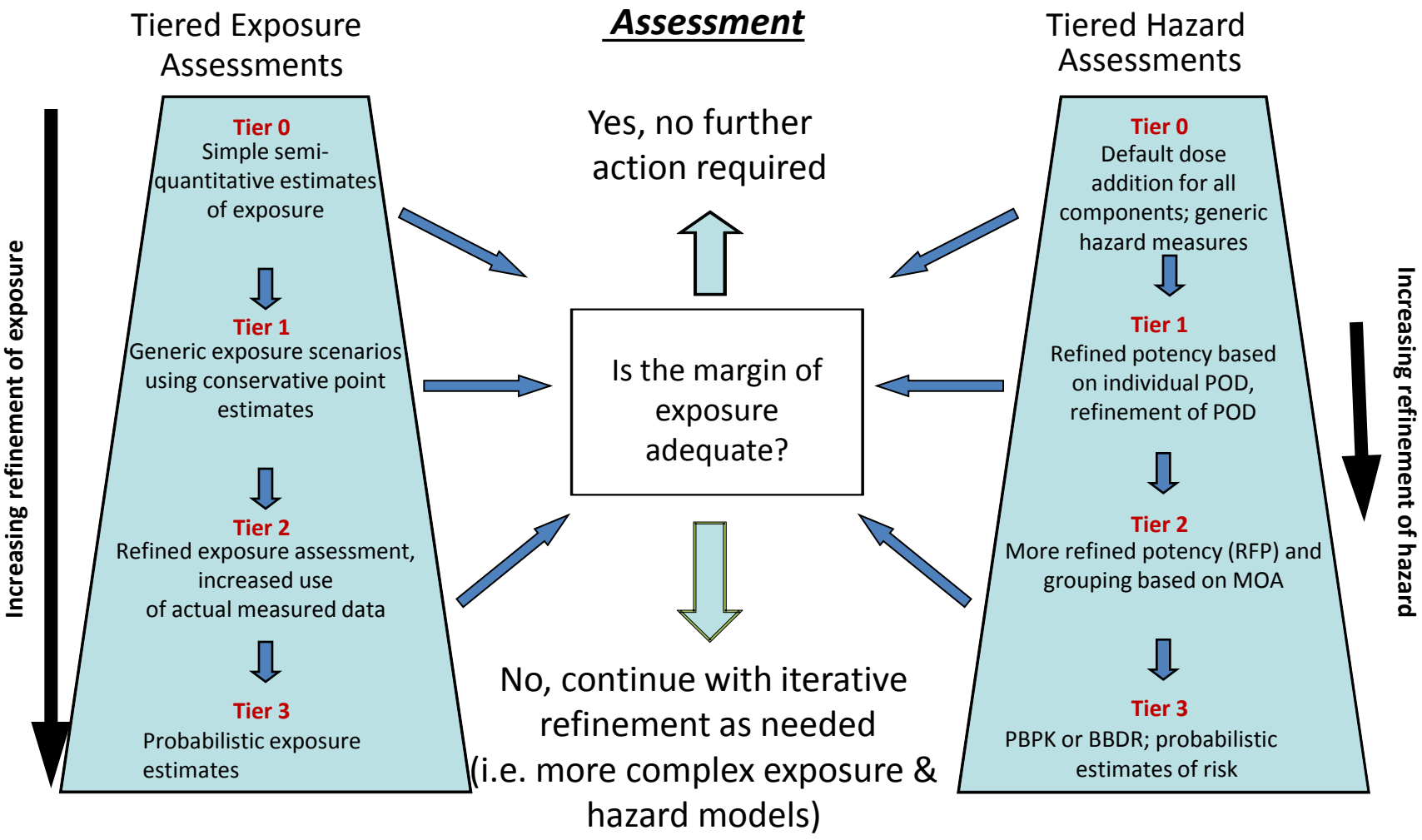
Uncertainty

Sensitivity

Modified from Meek et al., 2011

Problem Formulation for Grouping

Assessment



Limited use of predictive/screening methods Example Tier 0 Exposure

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

Intake = $300 \times 0.025 \times 0.25 + 200 \times 0.1 \times 0.25 = 7$ mg/kg bw/d

food drinks

Limited use of predictive/screening methods The Challenge to the Exposure Community

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

Screening of Hazard

- need for simpler, more predictive measures of potency
- Some progress

Review Article

Journal of Applied Toxicology

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New developments in the evolution and application of the WHO/IPCS framework on mode of action/species concordance analysis†

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

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

Introduction

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

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

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

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† *This publication contains the collective views of an international group of experts and does not necessarily represent the decisions or the stated policy of the World Health Organization or the authors' affiliated organizations.*

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Applied Toxicol.34: 1-18 (2014 a).

- Roadmap for fit-for-purpose testing strategies and risk assessment
- MOA analysis in more predictive context
- Case examples

Case example 6: Mode of Action in Grouping and Potency Estimates for Combined Exposures

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

- Class of pesticides, same well established mode of action and insecticidal effects
  - reversible neurotoxicity through interaction with neuronal sodium channels
- Members of the class expected to share key events
  - Interaction with sodium channels
- Consider grouping and rank for potency for broader group of compounds in suitable *in vitro* system for this key event

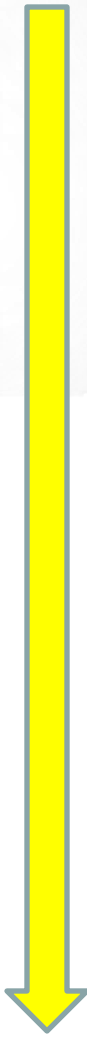
Importance of "Framing" of the Tiers Considering Uncertainty, Variability and Sensitivity in Hazard Values

- Tiered assessment requires explicit consideration of uncertainty/variability
  - exposure ***and*** effect (***not*** "uncertainty" factors)
- Need to specify which aspects are most important for refinement of assessment and data generation
  - Sensitivity analysis
- Consideration of MOEs has identified important sources of uncertainty and variability and their weighting for hazard
  - Beyond "uncertainty factors" for reference doses

RfD Components - "Sensitivity" Analysis

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

Relative Importance



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

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

More Recent International Developments

- ***OECD Task Force on Hazard Assessment (June, 2014)***
  - More guidance based on the WHO framework/2011 workshop (Canada co-lead with OECD)
    - Substances with limited hazard data; Estimated daily intake from biomonitoring; risk based criteria for moving to higher tiers
- ***WHO Drinking Water Guidelines***
  - Toolbox of methodologies framed in the context of tiers of the WHO framework
  - Several case studies in development
    - Pharmaceuticals (Statins, Non-Steroidal Anti-Inflammatories), Pesticides, Microcystins and Estrogens

Draft Pharmaceuticals Case Study

- Based on Hazard Index

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

- and the Minimum Therapeutic Dose (MTD)
  - lowest clinically effective dose for the most active of the compounds

Draft Pharmaceuticals Case Study

- Groups of 19 non steroidal anti-inflammatories & 4 statins
- Lower tiered assessment based on concentrations in surface water predicted by EMEA (2005) model:

$$PECdw = \frac{A \times (100-R) \times (100-M) \times (100-W)}{365 \times P \times V \times D \times 100 \times 100 \times 100}$$

Where:

PEC_{dw}	is the predicted concentration in drinking water ($mg.l^{-1}$);
M	is the percentage metabolised in humans
A	is the amount of active ingredient used per year in the catchment ($mg\ yr^{-1}$);
R	is the removal rate in sewage treatment (set as a percentage, see below);
P	is the population under consideration (i.e. for the UK; 59600000 or the population equivalent [PE] for each catchment scenario);
V	is the volume of waste water produced per capita per day (assumed to be 200L)
W	is the removal rate in the appropriate DWTW scenario and
D	is the dilution factor in the environment (derived from the 5%ile flow rate)

Pharmaceuticals – Lower & Higher Tier Exposure

- total usage per year [A] > than that data-based estimates
- no metabolism [M = 0%] i.e. all drug excreted unchanged
- no loss of the drug during water treatment (STW)
- no further dilution or loss of drug during transport between STW discharge point and drinking water intake point
- Removal rate in sewage treatment (W) is zero

Implications for Combined Exposure Assessment

- Consider exposure at outset in problem formulation
  - Do use profiles indicate likely co-exposure?
- The value of hierarchically addressing combined exposures
  - efficiency in assessment and management
- Maximizing understanding and availability of context specific tools for both exposure and hazard

More Information

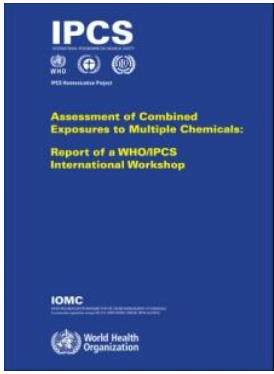
Meek, M.E. (2012) Toxicology: http://dx.doi.org/10.1016/j.tox.2012.09.015

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)

http://www.sciencedirect.com/science/article/pii/S0273230011000638

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