

# *Thought Starter*

## *Combined Exposures to Multiple Chemicals*

### *Second International Conference on Risk Assessment*

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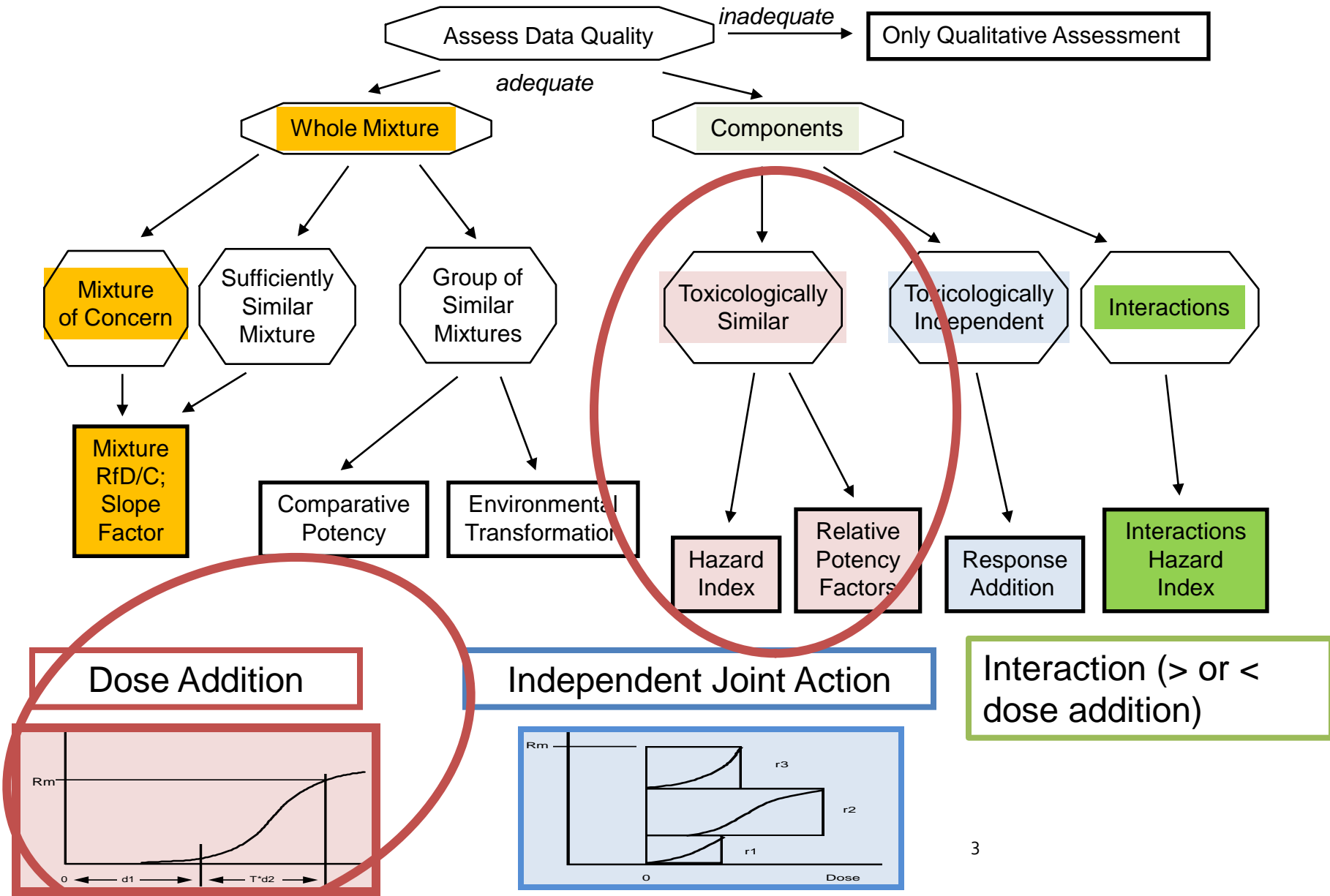


# *Outline*

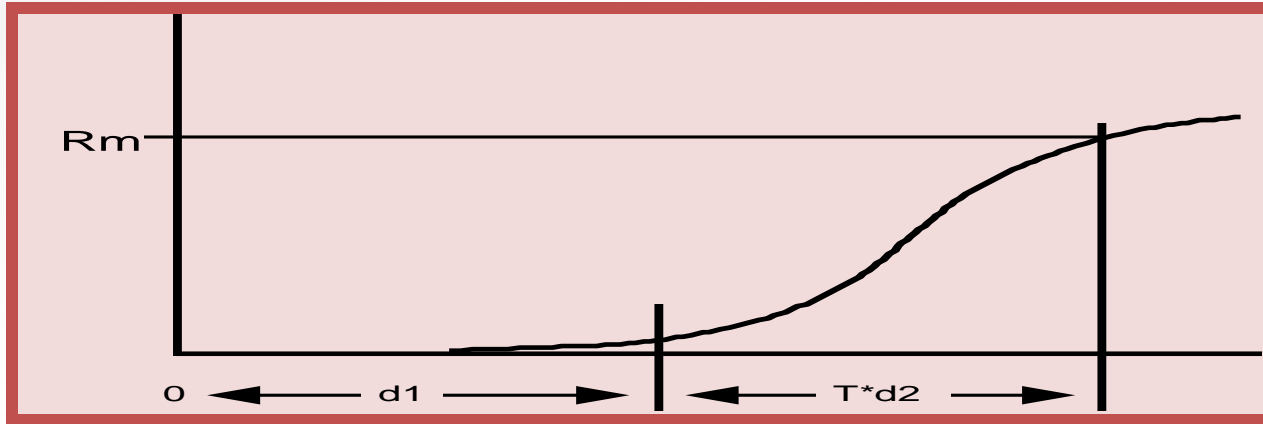
- State of the Art – Assessment of Mixtures (aka “Combined Exposures to Multiple Chemicals”)
- Recent International Developments
- Some Examples
- Questions for Discussion

# Assessment for Combined Exposures

## State of the Art



# Dose Addition



Hazard Index,  
Reference Dose

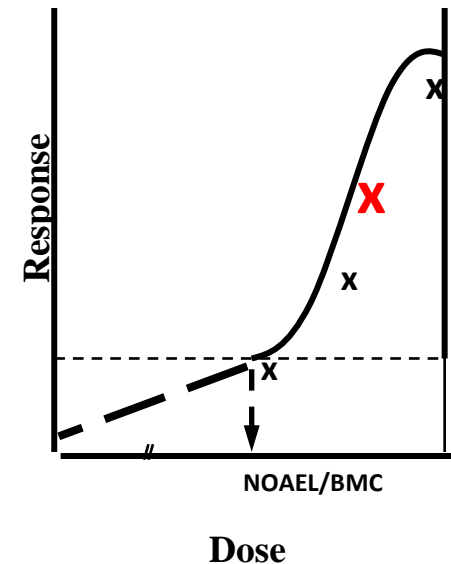
$$HI = \sum_{i=1}^n \frac{\text{estimated intake}_i}{RfDi}$$

Point of Departure  
Index

$$PODI = \sum_{i=1}^n \frac{\text{estimated intake}_i}{PODi}$$

Toxic Equivalency

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



# ***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
  - Maximized input/incorporation of developments from various mandates
- Post workshop development of framework/case studies
  - WHO IPCS
  - International Life Sciences Institute (ILSI)
  - European Centre for Ecotoxicology & Toxicology of Chemicals (ECETOC)
- Framework & case studies posted for public comment
  - Comment period closed October 31/09
- Framework revised based on public comment
  - Feb/2010 meeting - London

# *Recommendations from the '07 Workshop*

## Terminology:

- Avoid use of non-descriptive terms such as aggregate (e.g., multimedia), cumulative (exposure or effects)
- Avoid generic use of the term “mixtures”
  - Exposure can be at same (mixtures) or alternative times
- “Simple”, “complex” to relate to modes of action, rather than numbers of components

## Framework:

- Approach to be iterative involving stepwise consideration of both exposure & hazard
  - Essential to focus resources

# *Recommendations from the '07 Workshop (Cont'd)*

## Framework (Cont'd):

- Potential for exposure to be systematically taken into account early
- Appropriate tiering to be illustrated through case studies
- Approach to be hypothesis driven involving transparent and systematic analyses
  - “weight of evidence” approach consistent with the IPCS Mode of Action Human Relevance framework
  - to be based on all relevant information including predictive methodologies
    - (e.g., exposure modeling and quantitative structure activity analysis)

## *Recommendations from the '07 Workshop (Cont'd)*

Identifiable testable hypothesis for the research community:

- Potential for interaction at relevant exposures (i.e., Reference Doses or Concentrations)



# *Post Workshop Revised Terminology*

- “Single Chemical, All Routes”
- “Multiple Chemicals”, “Single” or “Multiple Routes”
- (Combined)“Assessment Group”
- “Dose additive” – same mode of action
- “Independent Joint Action” - independent modes of action or different target
- “Departing from Dose Additivity”
  - Interactive effects
    - Synergy/antagonism

# *Objectives of the WHO IPCS "Combined Exposures" Framework*

- Provides overview harmonizing construct
  - Builds upon other related initiatives and methodologies
- Consideration of an assessment group based on:
  - purpose
  - focus (e.g., local, national)
- Designed to maximize efficiency in the consideration and generation of information, depending on:
  - the potential risk and
  - objective of the assessment (e.g., priority setting, screening for additional focus or risk management)

# *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
- Three case studies (examples, only)
  - Priority setting for drinking water contaminants
  - Screening assessment on PBDEs
  - Full assessment on conazoles

# Problem Formulation

*Nature of exposure?*

*Is exposure likely?*

*Co-exposure within a relevant timeframe?*

*Rationale for considering compounds in an assessment group?*

## Assessment

Yes, no further action required

Is the margin of exposure adequate?

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

### Tiered Exposure Assessments

#### Tier 0

Simple semi-quantitative estimates of exposure



#### Tier 1

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

### Tiered Hazard Assessments

#### Tier 0

Default dose addition for all components



#### Tier 1

Refined potency based on individual POD, refinement of POD



#### Tier 2

More refined potency (RFP) and grouping based on MOA



#### Tier 3

PBPK or BBDR; probabilistic estimates of risk

Increasing refinement of hazard

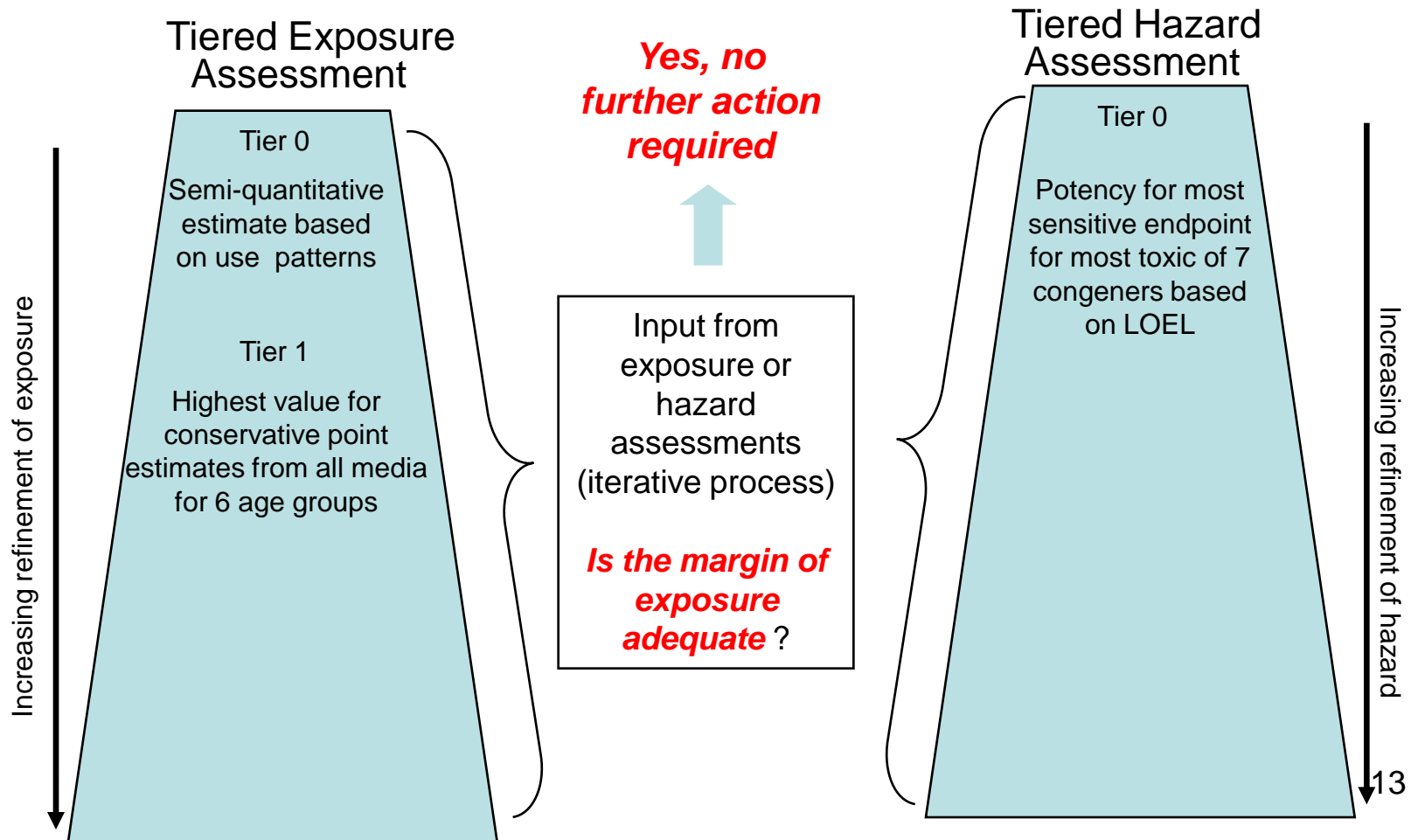
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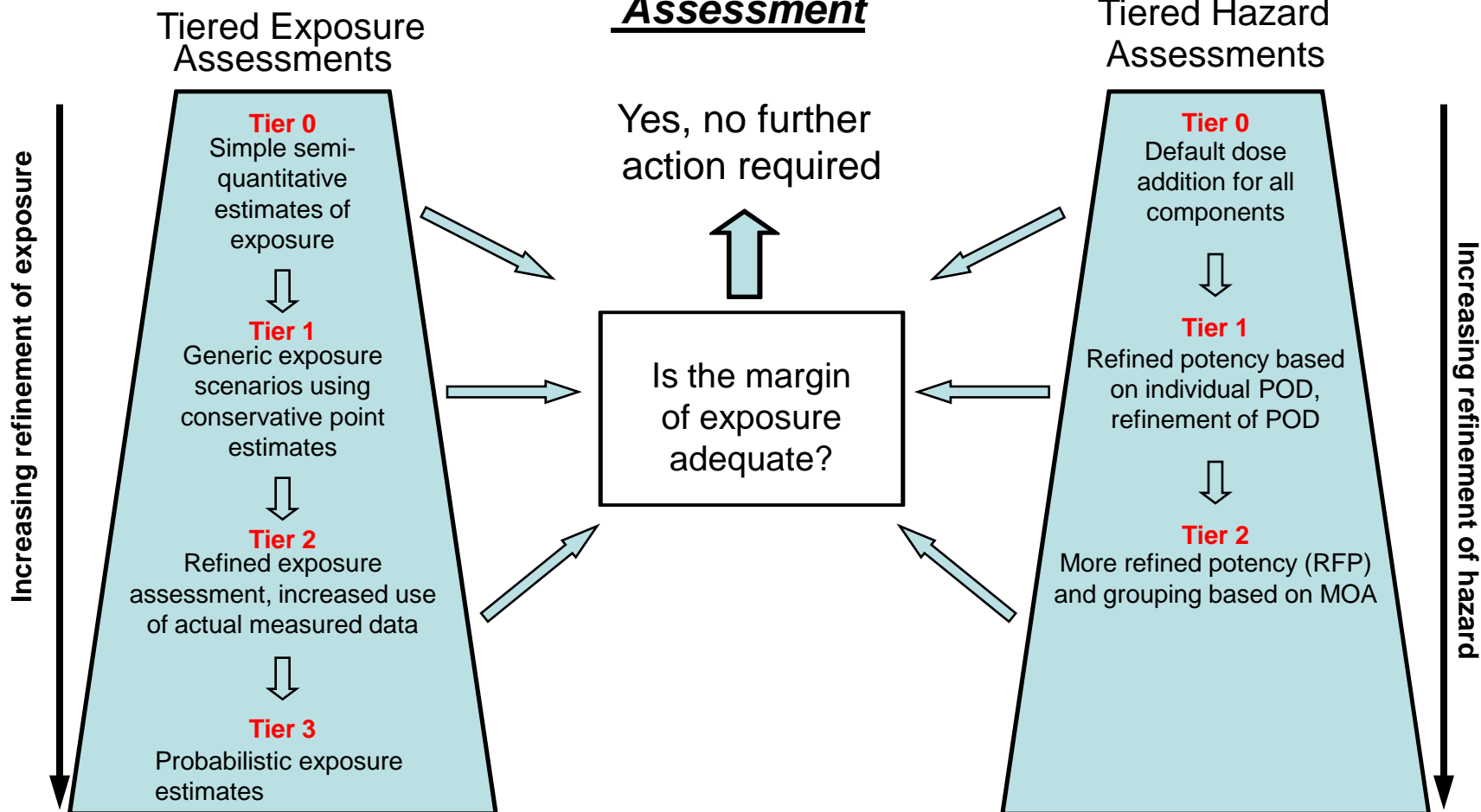
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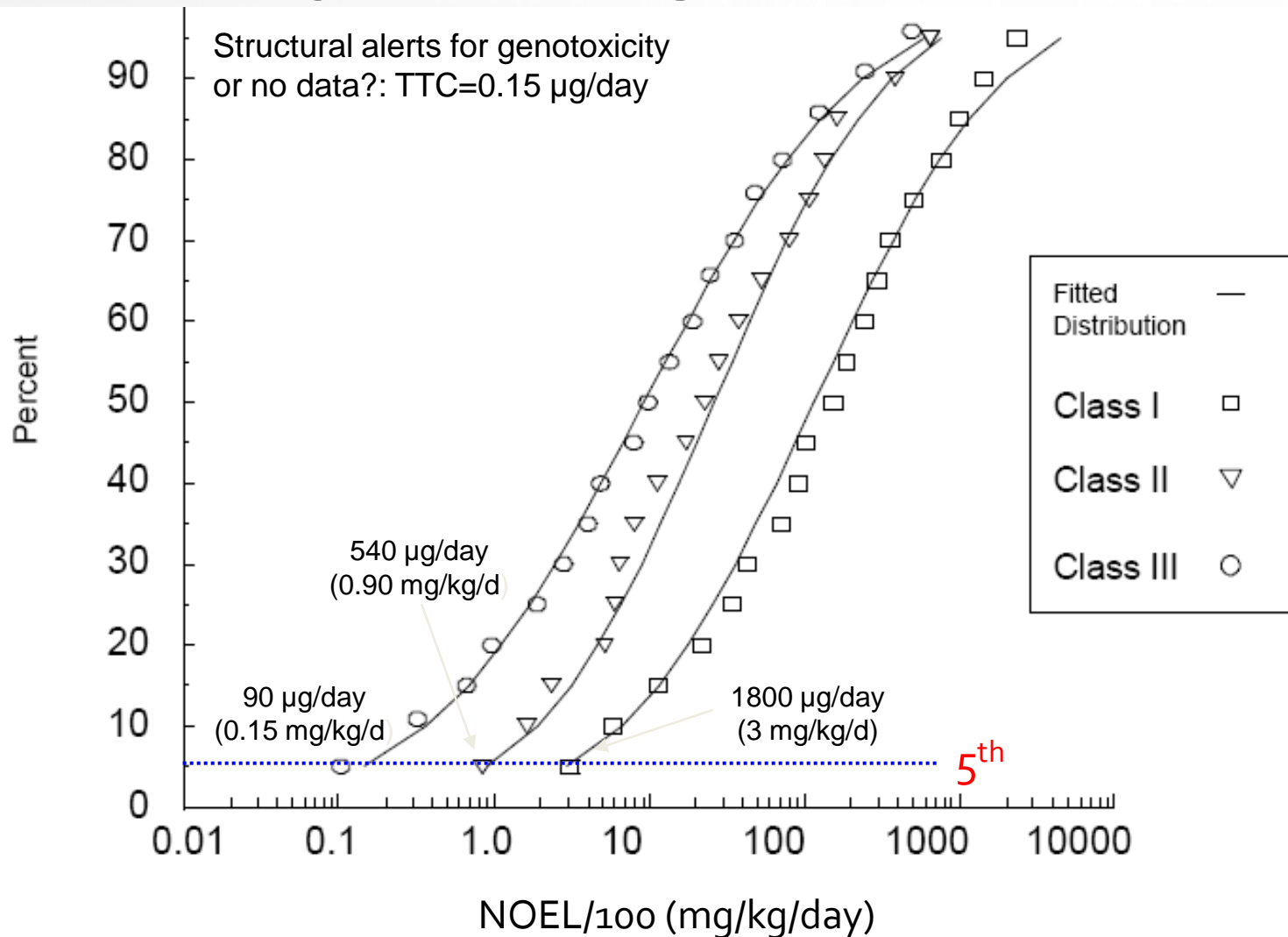
Is the margin of exposure adequate?



# ***Illustrative Case Study for Tier 0 – 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)





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

## *Illustrative 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

## *Illustrative case study (3)*

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

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

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

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

# *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

# *Questions for Consideration*

- 1. Barriers/challenges to assessments of combined exposures?
- 2. Appropriate criteria for consideration of combined exposures?
- 3. Applicability of tiered approaches. (E.g., WHO/IPCS framework). Other possibilities?
- 4. Suggestions for further elaboration of approaches for combined exposures assessment?
- 5. Additional aspects of harmonized terminology that would be helpful in facilitating combined exposures assessments?

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