Grouping Chemicals for Assessment and Conducting Assessments with the Hazard Index and Related Methods

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Conflict of Interest and Disclaimer Statement

The author declares that she has no actual or potential conflicts of interest.

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Talk Objectives/Outline

- Placing Component-Based Approaches in a Mixtures Risk Assessment Context
- Grouping Chemicals for Assessment
- Hazard Index (HI)
  - Target Organ HI
  - Multi-Route HI
- Margin of Exposure

Abbreviations

- AOP: Adverse outcome pathway
- BDCM: Bromodichloromethane
- CHCl3: Chloroform
- DR: Dose-response
- HAA: Haloacetic Acid
- HI: Hazard Index
- IKE: Intermediate Initiating Event
- IVIVE: *In vitro* to *in vivo* extrapolation
- MIE: Molecular Initiating Event
- MOA: Mode of Action
- MOE: Margin of Exposure
- POD: Point of Departure
- RA: Risk Assessment
- RfD: Reference Dose
- RfV: Reference Value
- SDH: Sorbitol Dehydrogenase
- TTD: Target Organ Toxicity Dose
- THM: Trihalomethane

Placing Component-Based Approaches in a Mixtures Risk Assessment Context

Mixture

Start with a mixture of concern

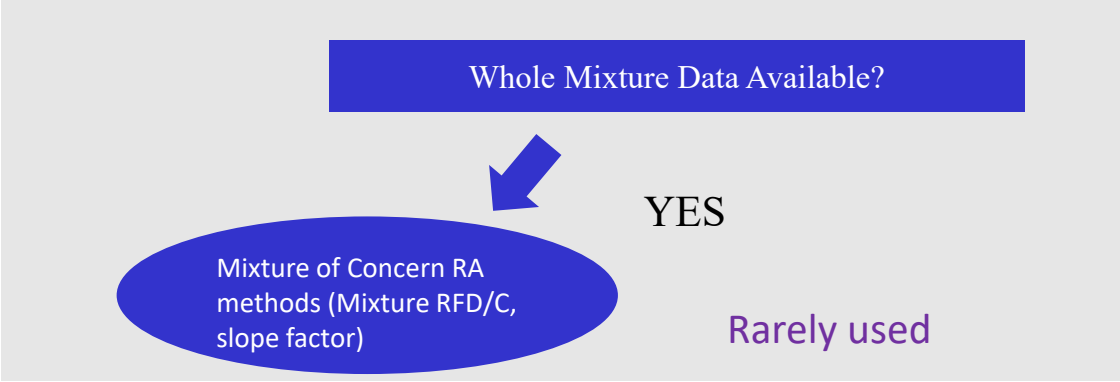
- Co-Occurring Chemicals (in environmental media or internally)
- Co-Exposure to Chemicals and Persistent Biological Effects

The assessment conducted depends on:

- the purpose of the evaluation
- the intended use of the results
- the quality and quantity of available data

Data Availability Drives Risk Approach

- Actual mixture data are preferred



Why??

Whole mixture data are almost never available.

Data Availability Drives Risk Approach

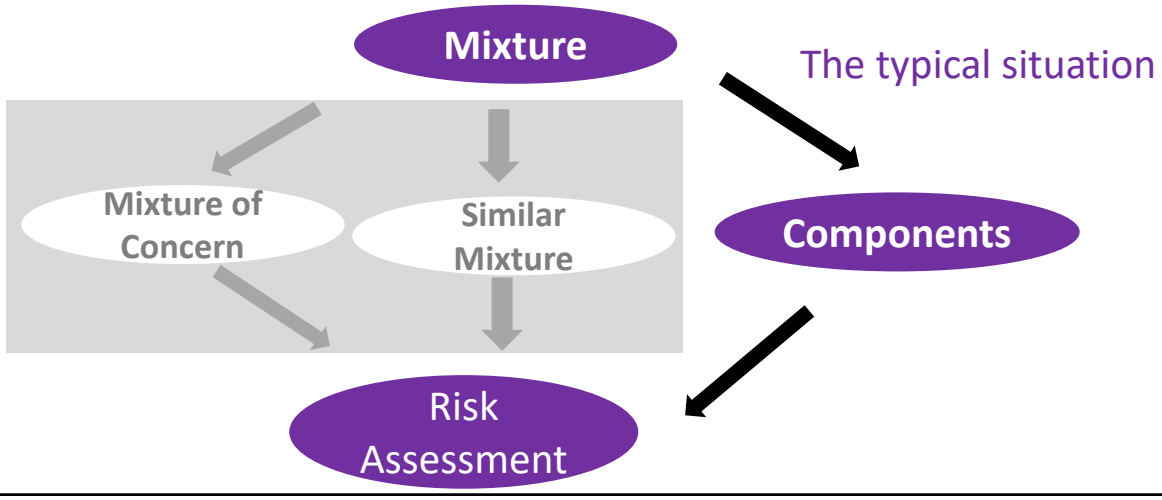
- When data on the actual mixture are not available, data on a 'sufficiently similar' mixture or group of similar mixtures are preferred.
- Very rarely used

  Why??

  Lack of methods for determining similarity

Placing Component-Based Approaches in a Mixtures Risk Assessment Context

- When data on mixture of interest and data on similar mixtures are lacking, risk is assessed by component-based approaches



What Are Component-Based Approaches?

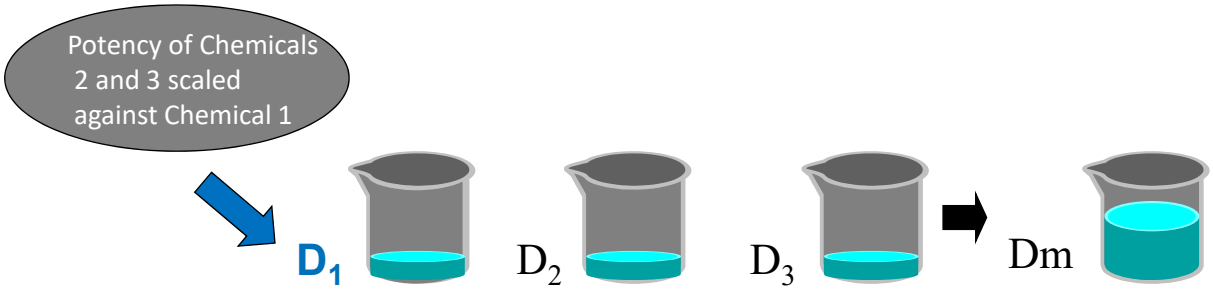
- Use toxicological data on component chemicals
- May incorporate information on interactions among component chemicals
- Do not require mixture data

Advantages
- Single-chemical data are abundant relative to mixture data
- A growing data base on interactions

What Are Component-Based Approaches?

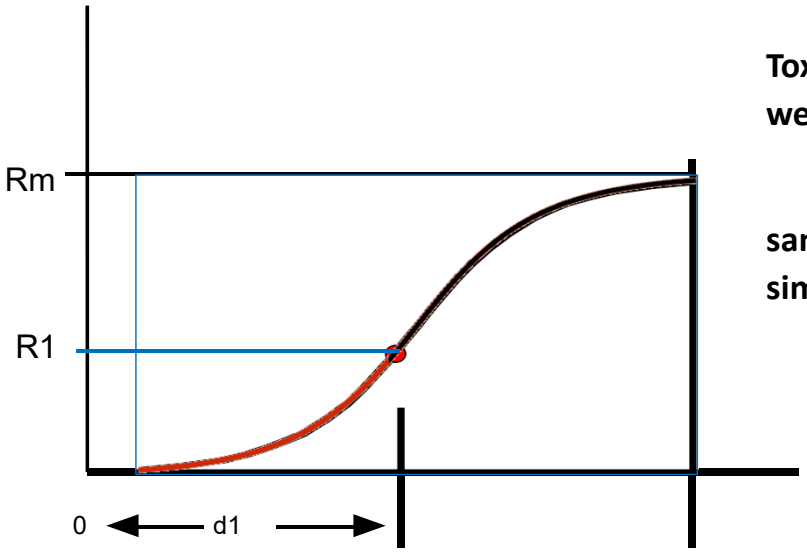
- Two major categories
  1) Those assuming toxicological similarity (i.e., dose/concentration addition), summing scaled doses
  2) Those assuming independent action, summing responses (covered by Borgert and Hertzberg)
- Current data indicates component dose addition methods are reasonable default approaches.
  - From experiments comparing experimentally observed toxicity to that predicted assuming dose addition or independent action
  - Database too limited to make sweeping conclusions (in my opinion)

Understanding Dose Addition: Dilution Concept



- Concern is for total dose (Dm)
- **Must scale doses for potency before adding doses**
- An important issue
  - Criteria for developing chemical groups

Understanding Dose Addition: Dilution Concept



Toxicological similarity:

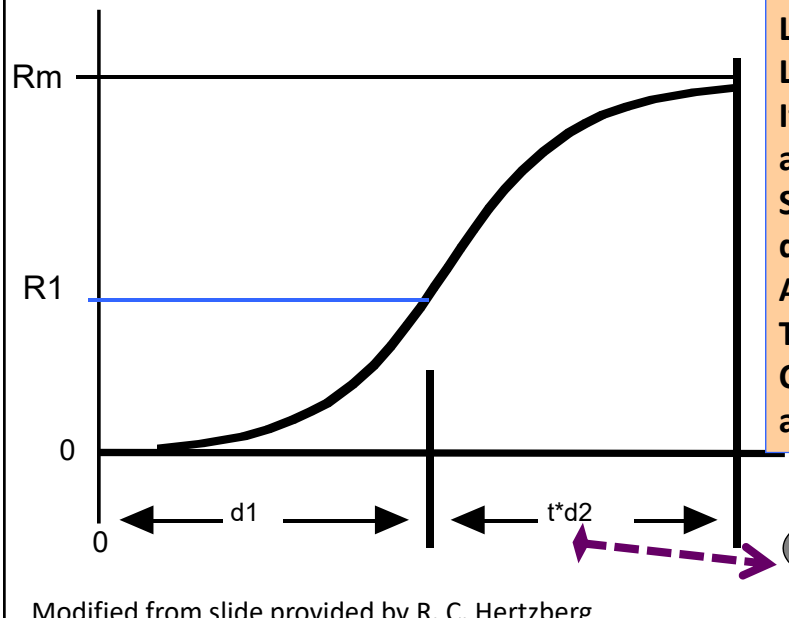
weaker chemical acts like a dilution of the other chemical

same DR model

similarly shaped DR curves

courtesy of R.C. Hertzberg

Understanding Dose Addition: Scaling for Toxic Potency



Let Chem 1, d1 = 4mg,
Let Chem 2, d2 = 3mg
If Chem 2 is twice as toxic as Chem 1, then t=2
So,
d2 = 3mg is as toxic as d1 = 6mg
AND
The combined doses (d1, d2) of Chem 1 and Chem 2 are as toxic as Chem 1 at a dose = 10mg

t*d2 is Chem 2 expressed as equivalent dose of Chem 1.

Modified from slide provided by R. C. Hertzberg

Dose Addition Assumptions

- ✓ Required: Same toxic effect (can default to same target organ)
- Frequent assumptions fall into two categories:
  - ❖ Toxicological similarity
    - ❖ Similarity of mode of action, adverse outcome pathway
    - ❖ Components have similar uptake, metabolites, PK
  - ❖ Empirical Similarity
    - ❖ Similarity of shape of dose response curves
    - ❖ The ratio of equitoxic doses is the same and independent of effect level
    - ❖ For equal effects, the dose of one component is a constant multiple of the dose of a second component

(It is noteworthy that Berenbaum's often accepted definition of dose addition does not require either toxicological or empirical similarity assumptions)

Example: Evaluation of Dose Addition Assumption

- Doses placed for threshold/slope estimation and assessment of greater than, and less than, additive effects
- Environmentally relevant mixtures and varied mixing ratios
- *In vivo* study (CD-1 female mice) to eliminate uncertain IVIVE

CHCl3:BDCM (mixing ratio)	Dose (mmol/kg/d)	Predicted SDH (IU/l)	95% Prediction Interval (IU/l)	Observed SDH (IU/l)
1:1	0.1	13	(6 20)	14
1:1	1.0	28	(13 41)	24
1:1	3.0	118	(18 220)	156
2.7:1	1.0	26	(12 41)	26
2.7:1	3.0	111	(42 180)	142

No deviations from dose additivity detected; all experimentally derived means fall within the 95% prediction interval constructed with component data

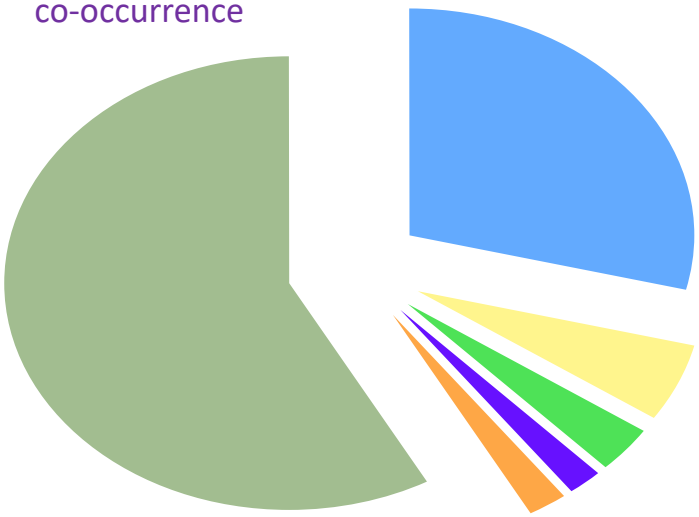
Data from J.E. Simmons lab

Grouping Chemicals for Assessment

- Essential: articulate the grouping criteria
- Groups typically defined through:
  - Common co-occurrence (exposure-based grouping)
  - Common adverse outcome (toxicity-based grouping)
- Groups may also be defined through:
  - Legislation. e.g.,
    - Superfund Amendments and Reauthorization Act, 1986
    - Food Quality and Protection Act (FQPA), 1996
  - Purpose and Intended Use, e.g.,
    - Reduce poly-pharmacy risk in the elderly
    - Enhance potency of cancer chemotherapies

Grouping Chemicals for Assessment

Group based on environmental co-occurrence

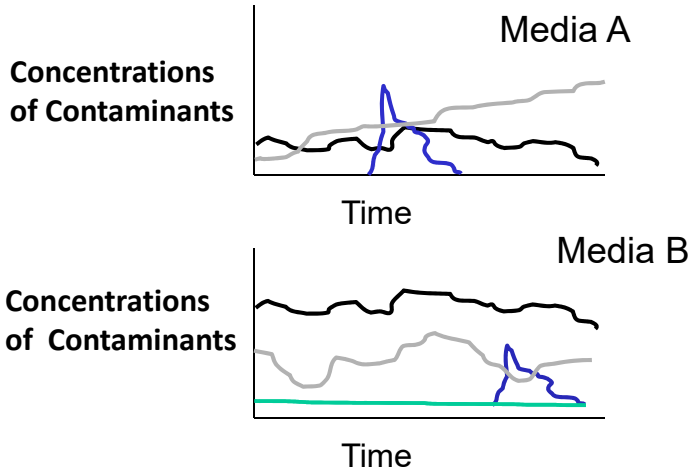


Chlorination DBPs

- Four Regulated THMs 29%
- Five Regulated HAAs 5.5%
- Other HAAs 3.5%
- Haloacetonitriles 1.8%
- Haloaldehydes 2.4%
- Unknown Organic Halogen 58%

Adapted from Richardson et al., 2008

Concentration Profiles of Contaminants Vary Over Time

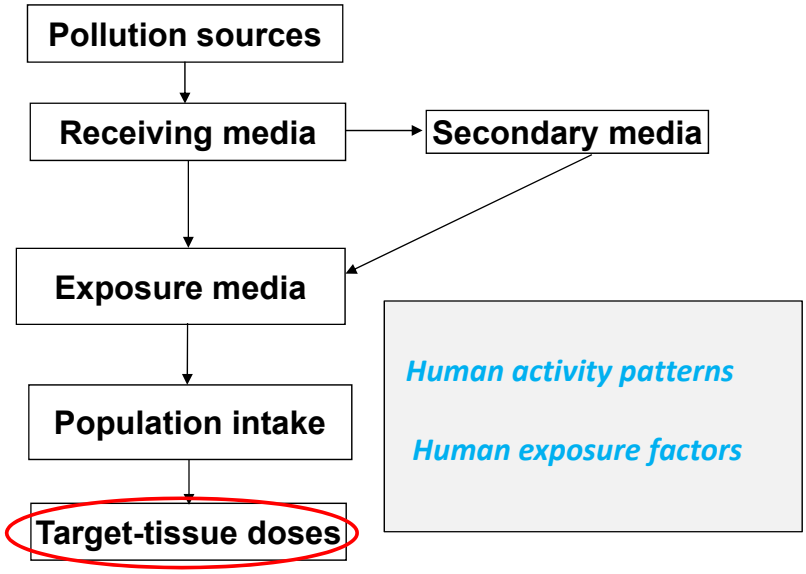


- **Processes distributing contaminants in the environment occur at different rates**
- **Exposure rates differ across media**

Considerations when Grouping by Exposure Factors

Differential *fate* of mixture components

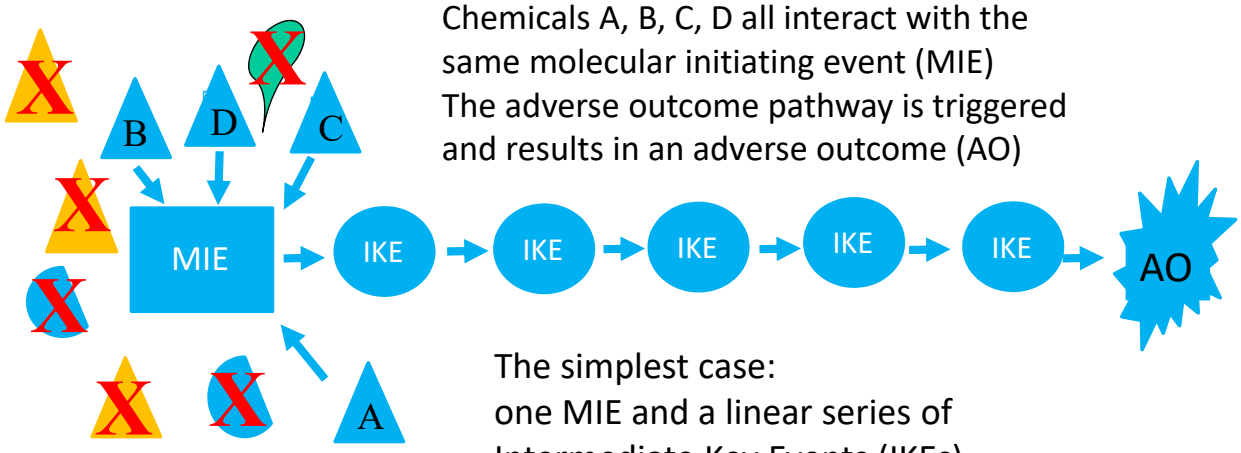
Differential *kinetics* of components



Grouping by Exposure Considerations

- ✓Consideration of internal dose refines chemical groupings
- ✓Consider
  - Bioavailability of contaminant
  - Persistence, or not, of contaminants inside the body
  - Tissue changes that may persist after exposure ends or occur after the contaminant(s) no longer present
    - Induction of metabolism
    - Altered tissue sensitivity
  - The timing of exposures relative to one another (the order in which the exposures occur)
  - The time between temporally separated exposures

Grouping Chemicals by Toxicity Using Adverse Outcome Pathways (AOPs)

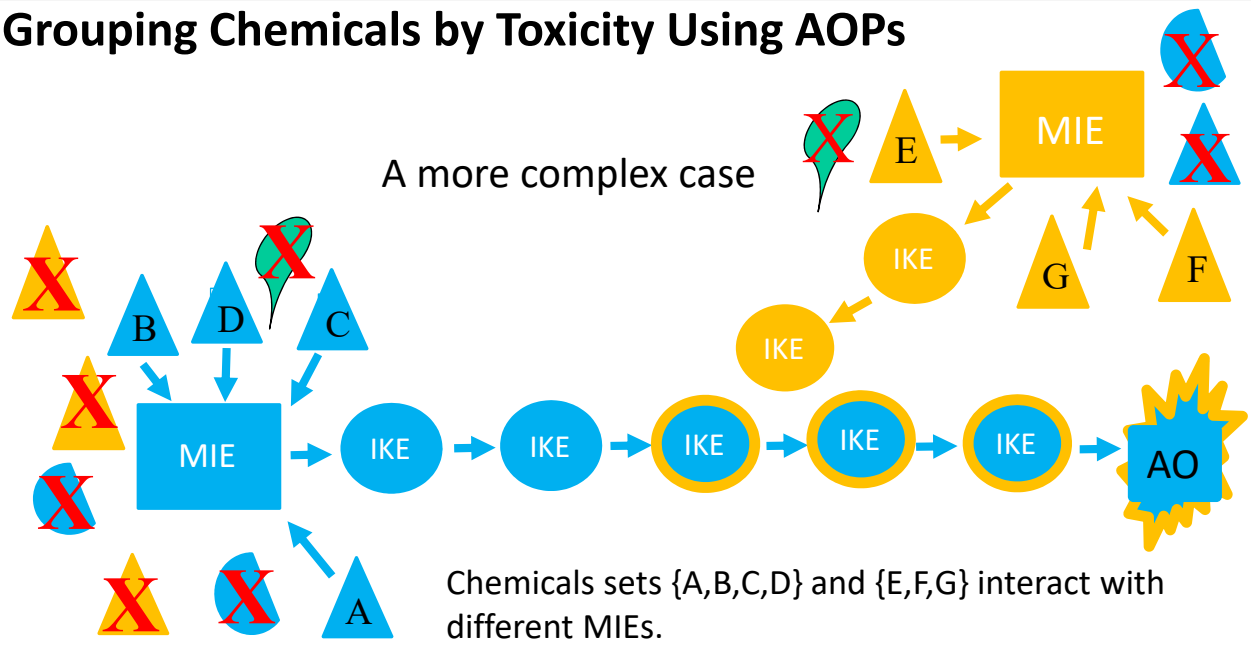


Chemicals A, B, C, D all interact with the same molecular initiating event (MIE)
The adverse outcome pathway is triggered and results in an adverse outcome (AO)

The simplest case:
one MIE and a linear series of Intermediate Key Events (IKEs)

Grouping Chemicals by Toxicity Using AOPs

A more complex case



Chemicals sets {A,B,C,D} and {E,F,G} interact with different MIEs.
The MIE pathways converge at a common IKE.

Hazard Index (HI)

- Most basic, most used component-based mixture RA approach
- Based on dose addition assumptions, but violates more of them than other approaches

$$HI = \sum_{i=1}^{n} \frac{Estimated\ Intake_i}{RfV_i}$$

Note that: Exposure/RfV = Hazard Quotient (HQ)
Thus: The Hazard Index is simply the sum of the HQs of the chemicals in the mixture

Hazard Index (HI) Example

Mixture Alpha

Chemical	Exposure (mg/kg/d)	RfD (mg/kg-d)	HQ (Exposure/RfD)
A	1.00E-06	1.00E-05	0.1
B	8.00E-05	4.00E-03	0.02
C	6.00E-06	3.00E-03	0.002
D	2.00E-05	2.00E-04	0.1

HI = 0.1 + 0.02 + 0.002 + 0.1 = 0.222

Hazard Index (HI)

- Decision Criterion:

HI ≤ 1 : minor / no concern, requiring no further analysis

HI > 1 : of potential concern, indicates further analysis is needed

(Using these criteria, we would not be concerned about increased health risk from exposure to Mixture Alpha)

- Notes of Caution:
  - HI has no units. Exposure and health reference value units must match
  - The underlying RfVs have differing degrees of uncertainty, so do not compare HIs across mixtures

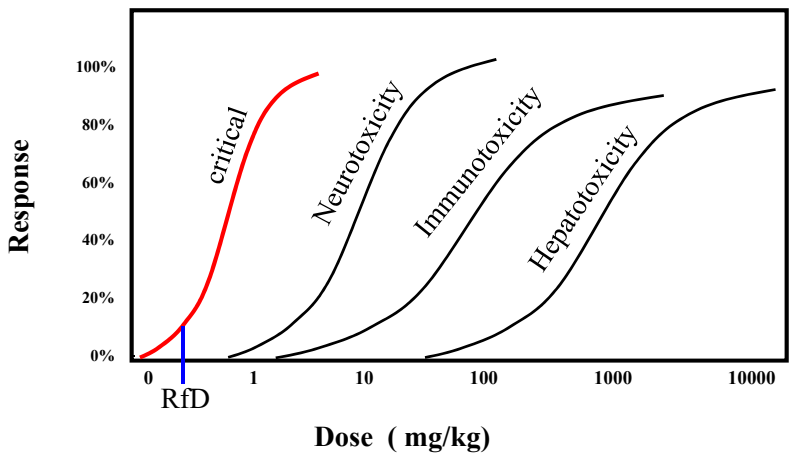
Hazard Index (HI): Dropping 'Low' HQ Chemicals

- Some applications of HI routinely 'drop' all chemicals for which the HQ is ≤ 0.1 from the HI calculation
  - What can happen when large numbers of chemicals are present?
    If 200 DBPs, each with HQ = 0.01, then HI = 2.
- Exert caution when dropping chemicals with an established RfD value. Why?
  - The chemicals often represent just a small portion of exposure.
  - Chemicals that are present may not have reference health values
  - Including as many chemicals as reasonable, given the intended purpose, is health protective
  - Calculations are easy, spreadsheet friendly, and don't require much additional effort

Target Organ HI

- The critical target organs on which RfV's are based vary among chemicals.
- Target Organ HI includes only those chemicals known or suspected to affect a particular target organ.
- Target Organ HI will never be higher than the HI.
- Requires Target Organ Toxicity Dose (TTD) values (i.e., RfV's for target organs other than the critical endpoint).
- TTD values are rarely available**.**

Same Chemical, Different Target Organs



RfD is an overestimate of hepatotoxic risk

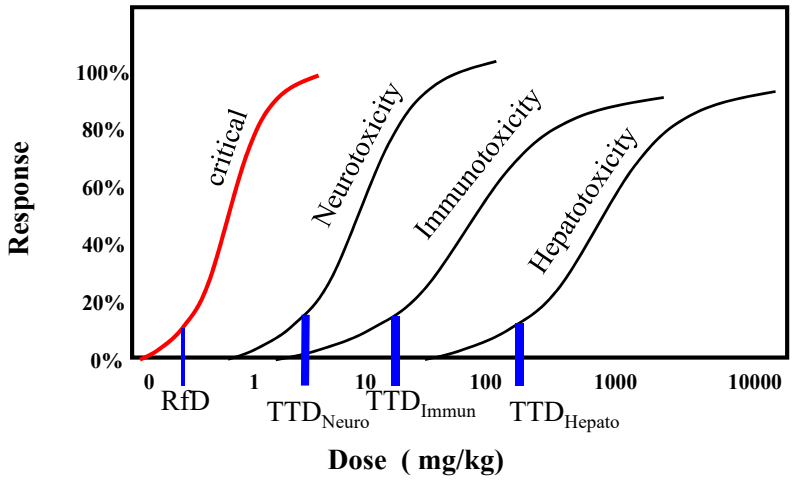
Courtesy of Moiz Mumtaz

Target Organ Toxicity Dose (TTD)

- TTD is derived in same way as RfD
- TTD is based ONLY on data for the effect of concern (other information is ignored)
  - TTD-based HI is not over-protective (per critical effect bias), but closer to the EDx for that effect
  - No official program for developing TTDs

Mumtaz, M.M., et al., 1997

TTDs



Target Organ HI Example

	Exposure (mg/kg/d)	RfD (mg/kg-d)	HQ (Exposure /RfD)	POD Target organ	Liver TTD (mg/kg-d)	Liver Specific HQ
A	1.00E-06	1.00E-05	0.1	Liver	1.00E-05	0.1
B	8.00E-05	4.00E-03	0.02	Kidney	8.00E-03	0.01
C	6.00E-06	3.00E-03	0.002	Liver	3.00E-03	0.002
D	2.00E-05	2.00E-04	0.1	Kidney	4.00E-04	0.05
E	1.00E-05	2.00E-05	0.5	Liver	2.00E-05	0.5
F	6.00E-03	8.00E-03	0.75	Skin	8.00E-02	0.075
		HI	**1.472**		**Target Organ HI**	**0.737**

Multi-Route HI (MHI)

- Adds consideration of multiple routes (pathways) of exposure
- Multi-Route HI can be larger than the HI
- Two options for calculation:
  - Option 1:
    - Develop Route-specific HQs for each chemical
    - Sum those HQs across all chemicals to create a Route-specific HI
    - Sum those HIs across all routes to develop the Multi-Route HI for the mixture

Multi-Route HI (MHI)

Option 1 continued

$$HQ_{jk} = \frac{E_{jk}}{RfV_{jk}} \Rightarrow HI_k = \sum_{j=1}^{n} HQ_{jk} \Rightarrow MHI = \sum_{k=1}^{m} HI_k$$

where

HQ_{jk} = hazard quotient for the j^{th} chemical, k^{th} exposure pathway/route
E_{jk} = exposure for j^{th} chemical, k^{th} exposure pathway/route
RfV_j = the health risk value for j^{th} chemical, k^{th} exposure route

Multi-Route HI Example

Chemical	Exposure O mg/kg/d I mg/m3	RfD O mg/kg/d I mg/m3	HQ Oral	HQ Inh	
A	O 1.00E-06 I 8.00E-03	O 1.00E-05 I 2.00E-02	0.1	0.4	
B	O 8.00E-05	O 4.00E-03	0.02	-----	
C	O 6.00E-06 I 1.50E-06	O 3.00E-03 I 3.00E-03	0.002	0.0005	
D	O 2.00E-05	O 2.00E-04	0.1	-----	
E	O 1.00E-05 I 2.00E-04	O 2.00E-05 I 1.00E-03	0.5	0.2	
F	O 6.00E-03	O 8.00E-03	0.75	-----	
		Pathway Specific HI	1.472	0.6005	2.0725

Multi-Route HI

Multi-Route (MHI)

Option 2:

- Sum the Route-specific HQs across all routes to get a Multi-Route HQ for each chemical (in parens)
- Sum those Multi-Route HQs across all chemicals to get the Multi-Route HI

$$MHI = \sum_{j=1}^{n}\left(\sum_{k=1}^{m} HQ_{jk}\right)$$

Multi-Route HI Example

Chemical	Exposure O mg/kg/d I mg/m3	RfD O mg/kg/d I mg/m3	HQ Oral	HQ Inh	Aggregate Chemical HQ
A	O 1.00E-06 I 8.00E-03	O 1.00E-05 I 2.00E-02	0.1	0.4	0.5
B	O 8.00E-05	O 4.00E-03	0.02	-----	0.02
C	O 6.00E-06 I 1.50E-06	O 3.00E-03 I 3.00E-03	0.002	0.0005	0.0025
D	O 2.00E-05	O 2.00E-04	0.1	-----	0.1
E	O 1.00E-05 I 2.00E-04	O 2.00E-05 I 1.00E-03	0.5	0.2	0.7
F	O 6.00E-03	O 8.00E-03	0.75	-----	0.75
					2.0725

Multi-Route HI

Multi-Route HI Example

Chemical	Exposure O mg/kg/d I mg/m3	RfD O mg/kg/d I mg/m3	HQ Oral	HQ Inh	Aggregate Chemical HQ
A	O 1.00E-06 I 8.00E-03	O 1.00E-05 I 2.00E-02	0.1	0.4	0.5
B	O 8.00E-05	O 4.00E-03	0.02	-----	0.02
C	O 6.00E-06 I 1.50E-06	O 3.00E-03 I 3.00E-03	0.002	0.0005	0.0025
D	O 2.00E-05	O 2.00E-04	0.1	-----	0.1
E	O 1.00E-05 I 2.00E-04	O 2.00E-05 I 1.00E-03	0.5	0.2	0.7
F	O 6.00E-03	O 8.00E-03	0.75	-----	0.75
		Pathway Specific HI	1.472	0.6005	2.0725 Multi-Route HI

Margin of Exposure (MOE)

The margin of exposure (MOE) for an individual chemical is the RfV divided by exposure

The MOE is the inverse of the HQ and MOE_{mix} the inverse of the HI

$$MOE = \frac{POD\ (mg/kg/d)}{Exposure\ \ Concentration\ (mg/kg/d)}$$

- The MOE of a mixture (MOE_{mix}) is calculated as

$$MOE_{mix} = (1 / MOE_1 + 1 / MOE_2 \ldots + \ldots 1 / MOE_n)^{-1}$$

MOE has no units. Exposure and health reference value units must match

MOE_{mix} Example

Mixture Alpha

Chemical	Exposure (mg/kg/d)	POD (mg/kg-d)	MOE (POD/Exposure)
A	1.00E-06	1.00E-05	10
B	8.00E-05	4.00E-03	50
C	6.00E-06	3.00E-03	500
D	2.00E-05	2.0E-04	10

$MOE_{mix} = (1/10 + 1/50 + 1/500 + 1/10)^{-1} = 4.5$

How to interpret??

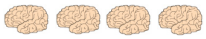
MOE_{mix}

- No set decision criterion
- The criterion for each individual chemical MOE is based on the uncertainty factors used in derivation of its RfV—chemical specific
- For each mixture, a group uncertainty factor needs to be developed, MixUF —mixture specific

Decision Criterion:
MOE_{mix} > MixUF : minor / no concern, requiring no further analysis
$MOE_{mix} \leq$ MixUF : of potential concern, indicates further analysis is needed

If MixUF = 3, we would not be concerned about increased health risk from exposure to Mixture Alpha, but
If MixUF = 10, we would be concerned about increased health risk from exposure to Mixture Alpha and would recommend further analysis

Methods Ratings*

Method	Difficulty	Data Availability	Ease of Interpretation	Ease of Communication
HI			★★★	★★★
Target Organ HI			★★	★★
Multi-Route HI			★★	★★
^MOE_{mix}			★	★

*Views are my own based on my understanding of the state of the science and experiences with these methods
^ Based on MOEmix as described here and not on the relative potency factor variation

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Any