Assessing Health Impacts of Diverse Mixtures in the Environment

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Agenda

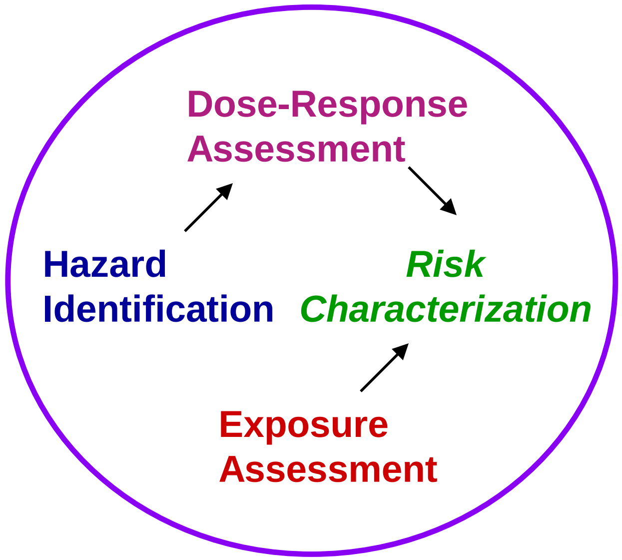
- **Comparison with Environmentally Allowable Levels**
  – MRLs, RfDs, EMEGs
- **Calculation of Hazard Quotient, Hazard Index**
  – Additivity principle for screening
- **Evaluation of multiple organ toxicity Dose**
  – Target organ toxicity doses (TTD)
- **Integrating the Influence of Interactions**
  – Binary Weight of Evidence (BINWOE) analysis
- **Interaction Profiles Program**
  – Resources Available
- **Proposed Draft ATSDR Guidance Manual**
  – Case studies

Risk Assessment Paradigm for Mixtures: **Issues Beyond Single Chemicals**

Hazard identification:

- consider potential interaction effects

- identify effects from total mixture dose.



Dose-response:

- consider potential for effects below individual chemical thresholds

- incorporate toxicologic judgment of similar toxicity within or between mixtures.

Exposure assessment:

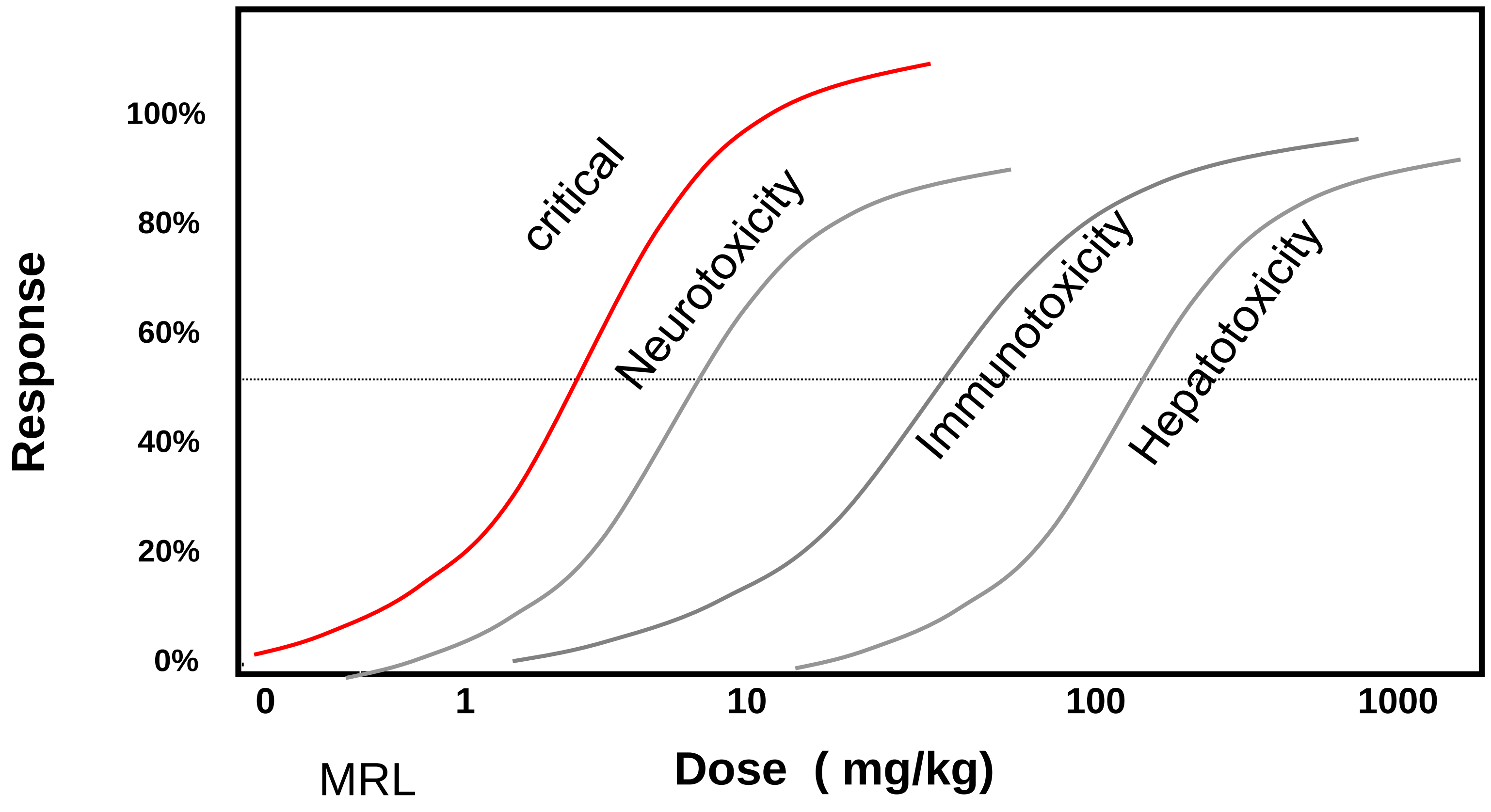
- account for chemical characterization of unidentified material

- evaluate degradation of the mixture in the environment.

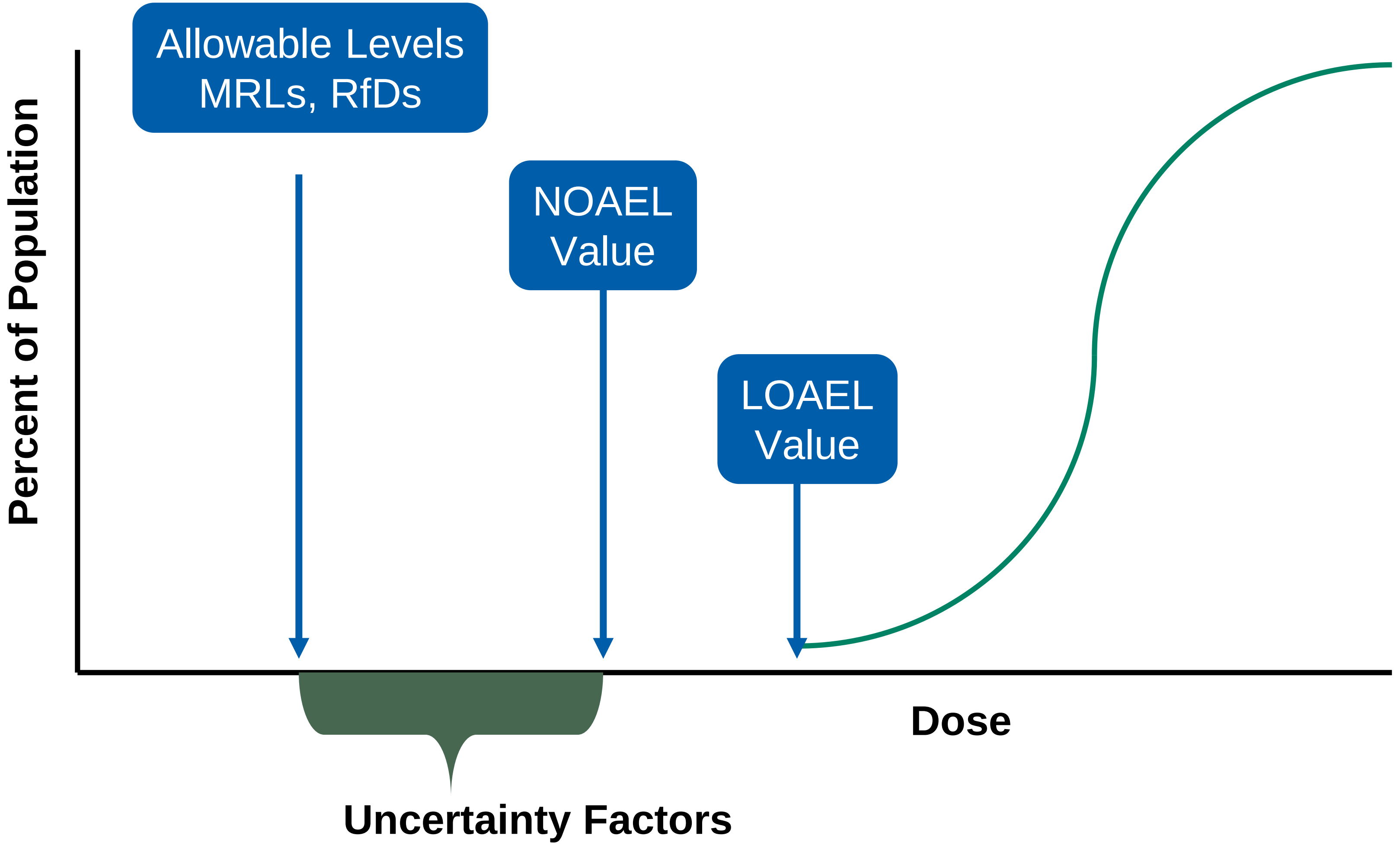
Risk characterization:

- evaluate support in the data base for assumptions made about interaction effects, toxicologic similarity of mixtures or their components, and exposure.

Dose-Response Curves
Multiple Target Toxicities from a Single Chemical



Derivation of Health Guidance Values



Elements of ATSDR Mixtures Program

- Identification of Priority Mixtures
- Academically-based Applied Research
- Development of Generalizable Rules

Environ Health Perspect 106: 1271-1280 (1998)

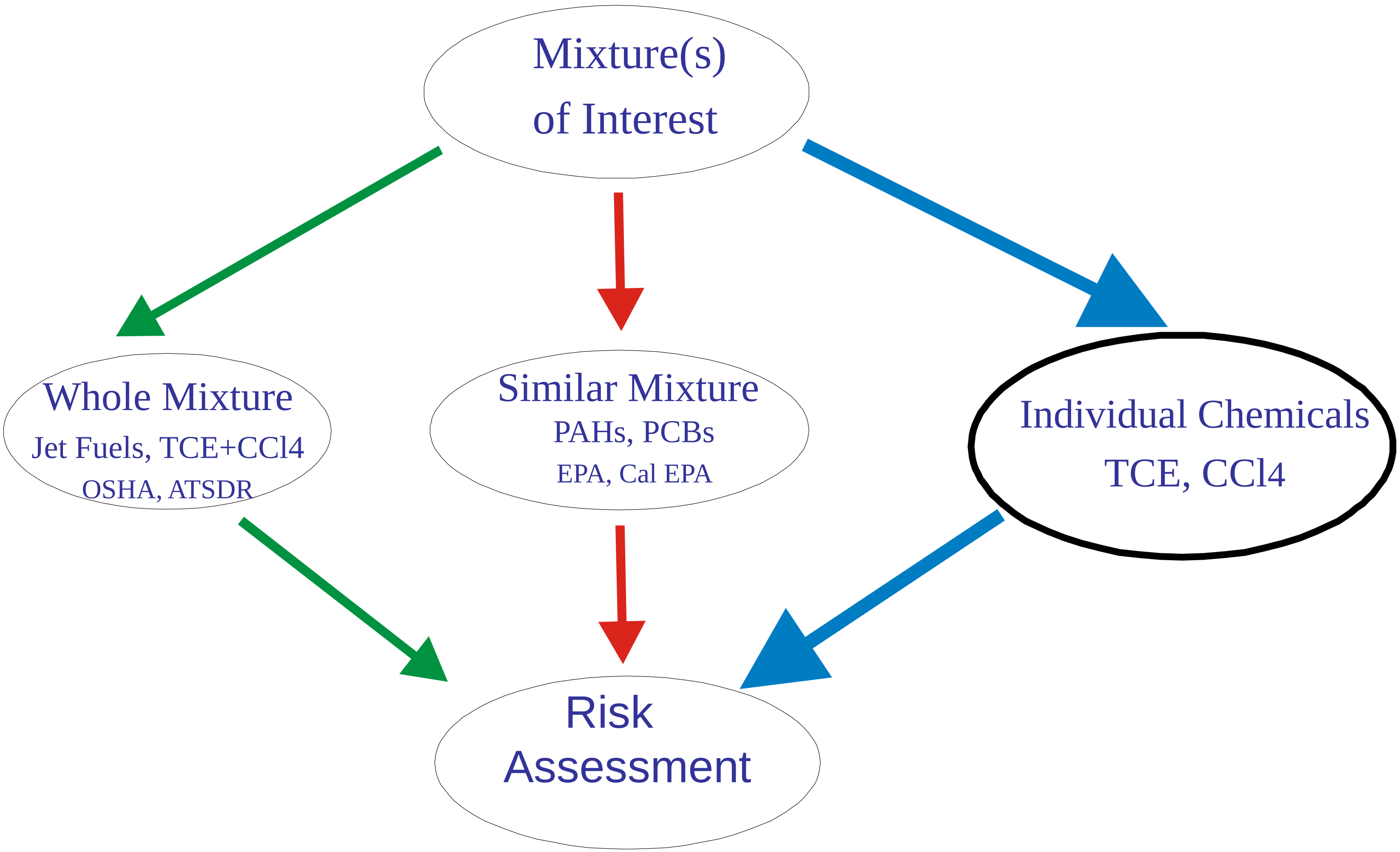
Implementation of ATSDR Mixtures Program

Extra-Mural Resources And Mechanisms Used

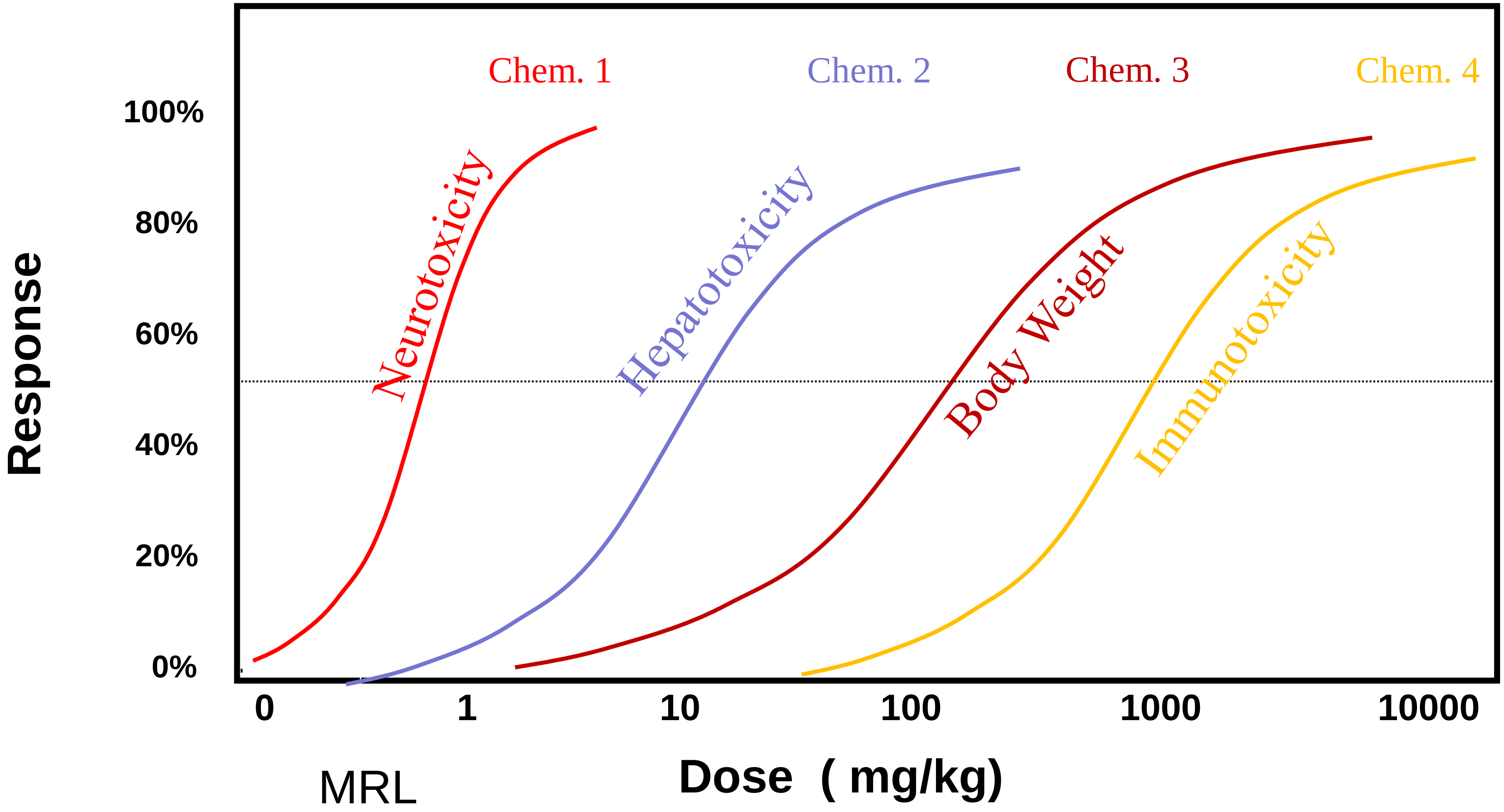
• Cooperative Agreements	- Announcement #02133
• Collaborative Research	- TNO, The Netherlands *TCE, Methyl Mercury, Benzene, and Lead*
• Interagency Agreements	- NIEHS/USEPA Great Lake *Chemical Mixtures*
• Purchase Orders	- Methyl Mercury and PCB Mixtures

Mumtaz , De Rosa, Groten, Feron, Hansen and Durkin, 1998. Estimation of toxicity of mixtures through modeling. Env. Health Persp. 106: 1353-1360.

Overview of Mixtures Guidelines



MRLs Available

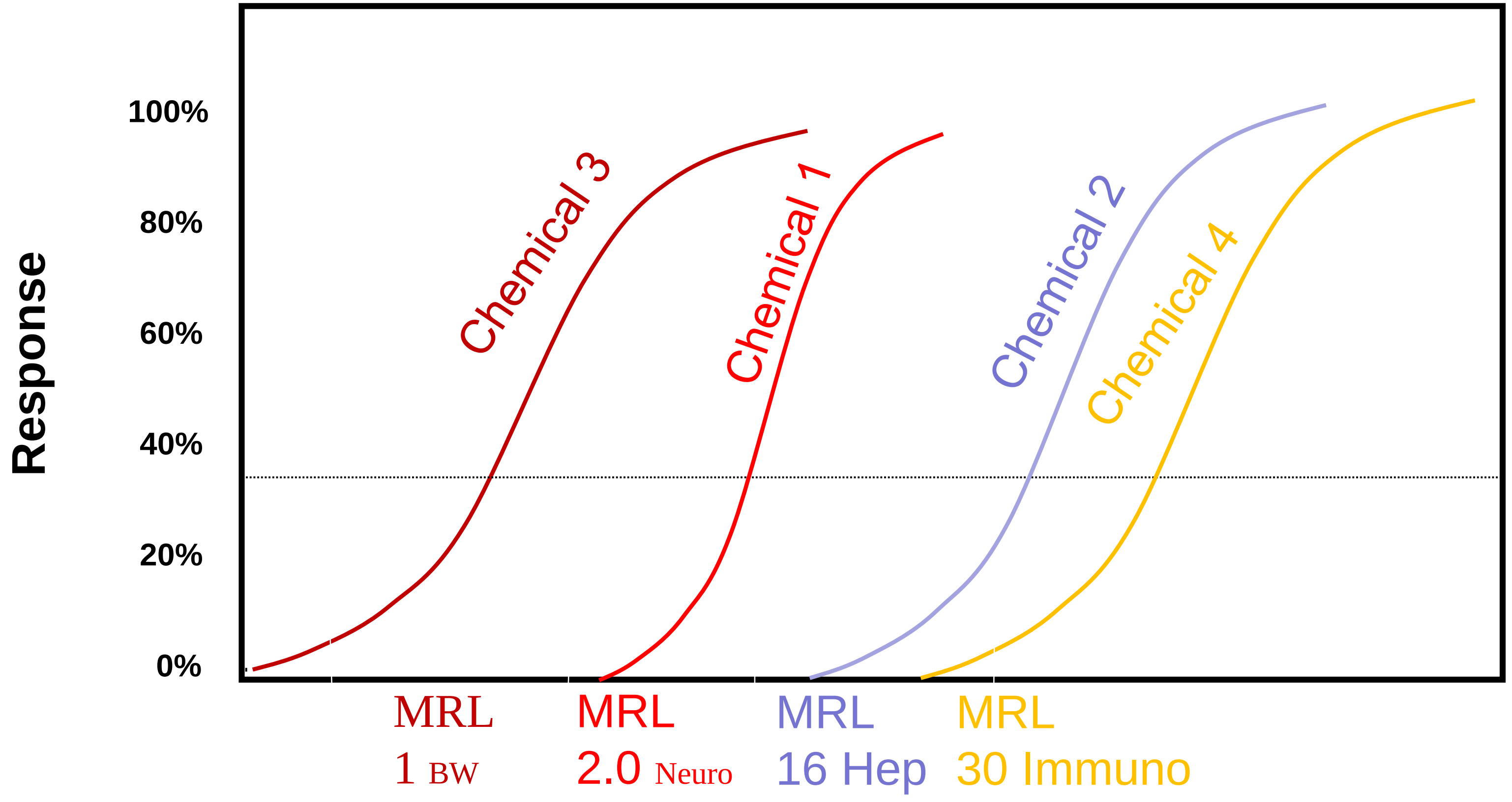


Component Based Assessment

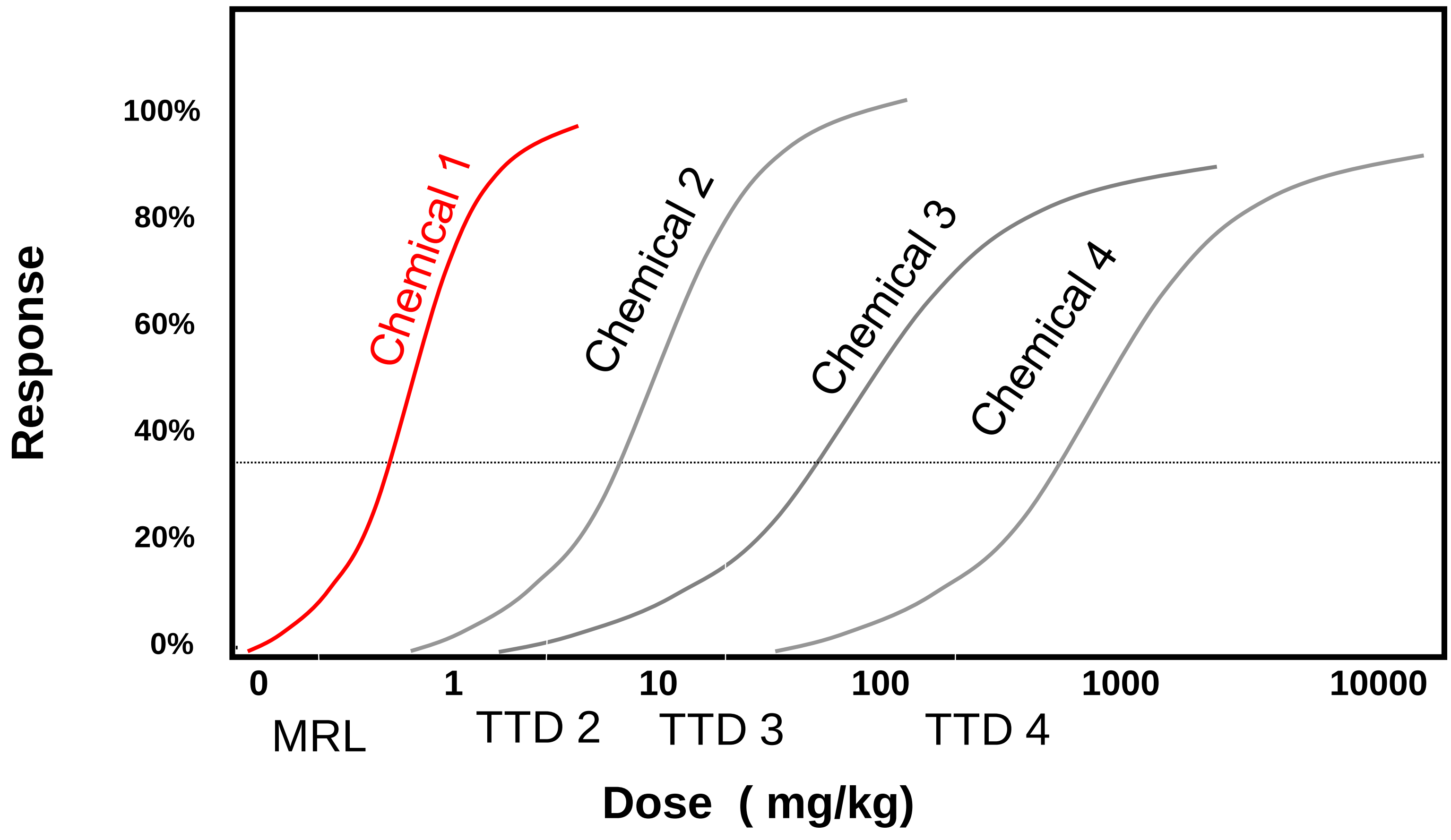
$$\text{Hazard Index(HI)} = E_A/MRL_A + E_B/MRL_B + \ldots E_n/MRL_n$$

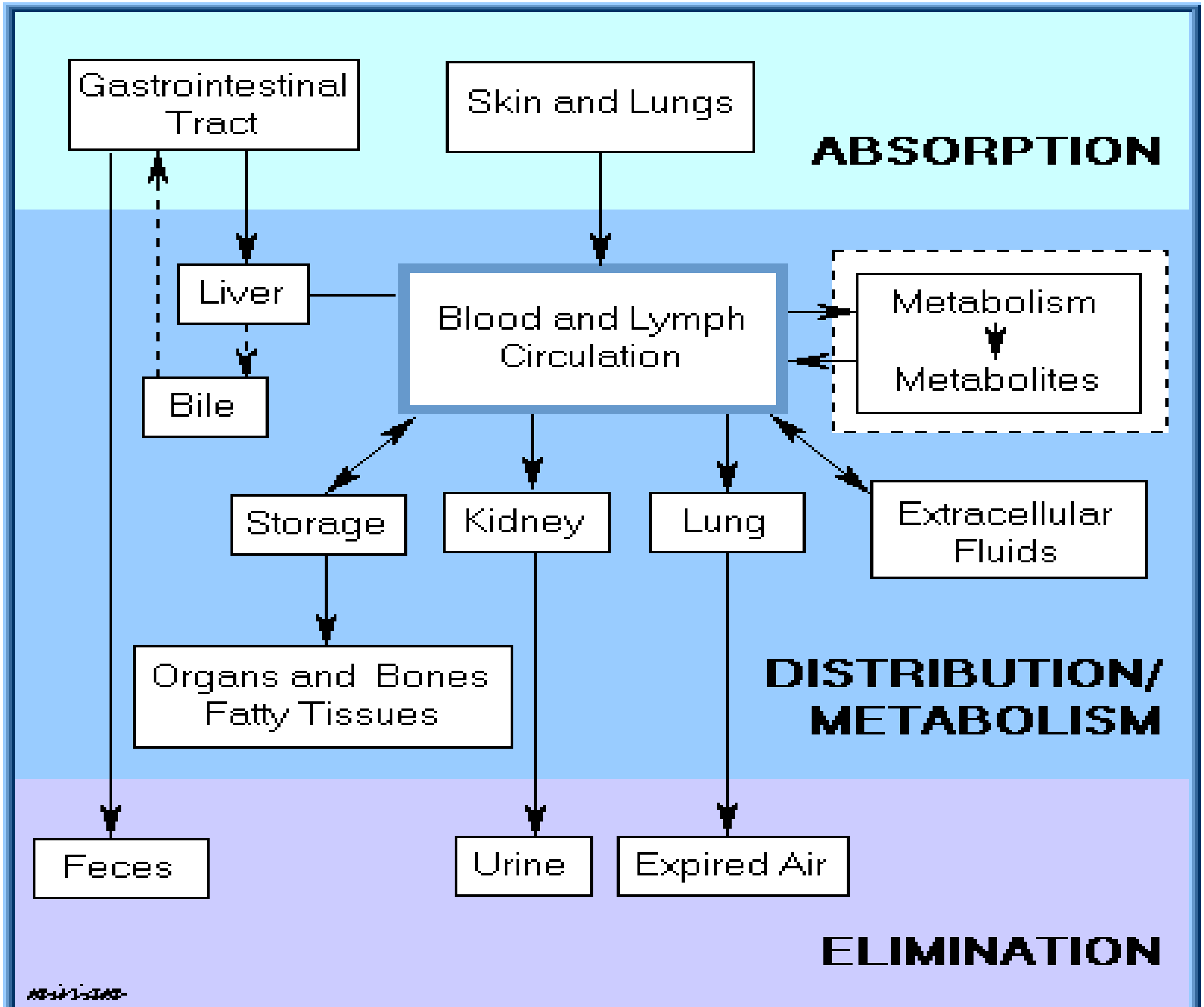
Mixture Component	MRL	Exposure	Hazard Quotient	Toxicity Endpoint
1	2	1	0.5	Neurotoxicity
2	16	8	0.5	Hepatotoxicity
3	1	1	1	Body Weight
4	30	10	0.3	Nephrotoxicity
	HI (MIXTURE)		~2	Mixed Toxicity

MRLs Available

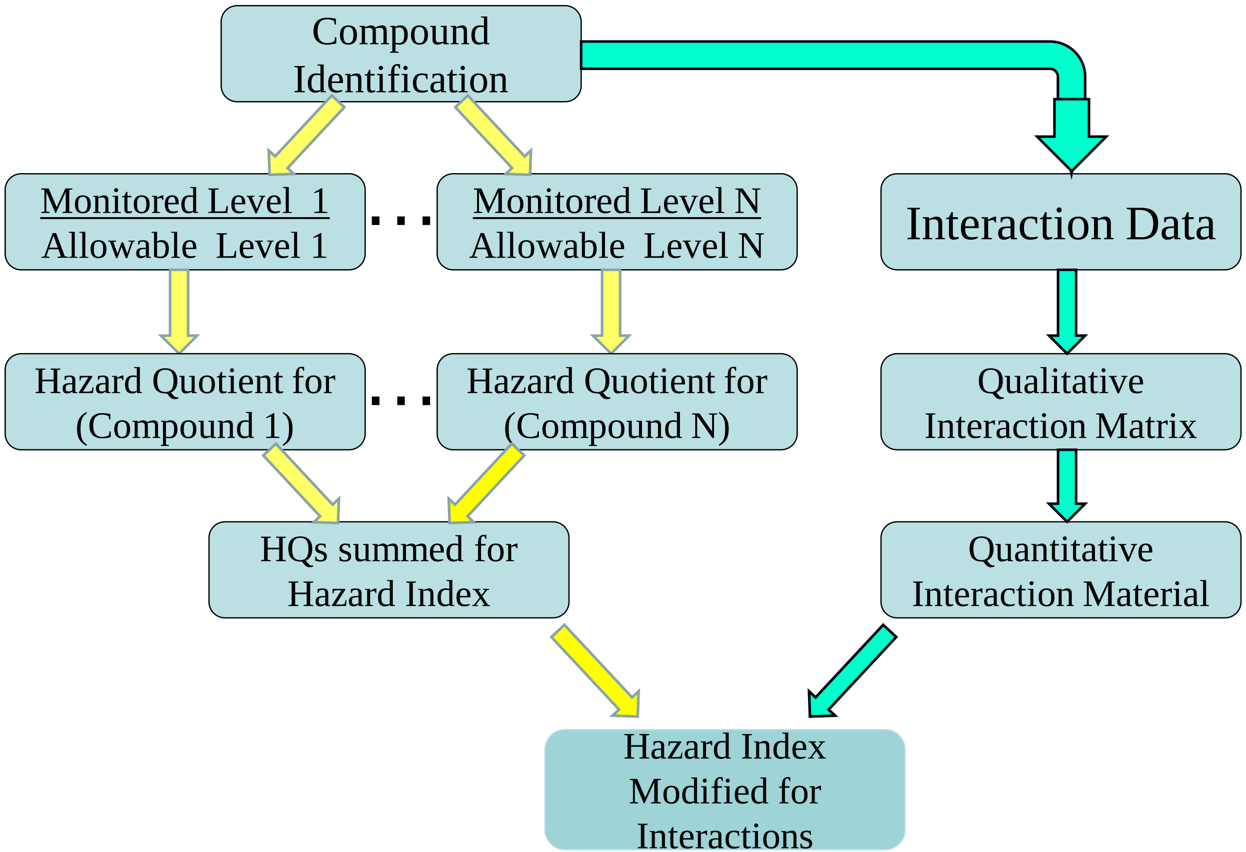


TTD Derivation for Neurotoxicity




Gastrointestinal Tract
Skin and Lungs
ABSORPTION
Liver
Blood and Lymph Circulation
Metabolism
Metabolites
Bile
Storage
Kidney
Lung
Extracellular Fluids
Organs and Bones Fatty Tissues
DISTRIBUTION/ METABOLISM
Feces
Urine
Expired Air
ELIMINATION

Hazard Index Modification



Interactions Evaluation

- A qualitative judgment, based on empirical observations and understanding of the mode of Action (MOA) or mechanistic data
- Characterize the plausibility that one agent influences the toxicity of another

Criteria for Methodology Development

- Use an IARC-type system for expressing the weight-of-evidence (WOE).
- Can be applied consistently.
- Can be used to quantitatively alter risk assessment.
- Subject to “validation” with experimental data

Mechanics of the Methodology

- Develop qualitative binary WOE determinations based on available information.
- Translate qualitative WOE's to quantitative interaction factors.
- Use data on estimated exposure levels, individual hazard quotients, and interaction factors to quantitatively modify risk assessment.

Protocol Weight of Evidence for Binary Interactions

- Direction of an interaction
- Mechanistic support
- Toxicological observations
- Modifying factors
- Limitations
- Uncertainties
- References

Mumtaz, M.M., De Rosa, C., and Durkin, P.R. (1994) "Approaches and Challenges in Risk Assessments of Chemical Mixtures", in Toxicology of Chemical Mixtures, Raymond S.H. Yang, ed., Academic Press, pp. 565-597

Components of the Binary WOEs

Mechanistic data on related compounds

Different duration or sequence of exposure

Different route

<IIA2aii

Less than additive

Direct toxicological significance

***In Vivo* data**

Nomenclature Used in ATSDR Interaction Profiles

Strength of Mechanistic Data

<IIA

Direction of Interaction

Strength of Data on Toxicological Significance

Mumtaz et al. 1994. ATSDR. 2004

Major Components of the Methodology

MOA or Mechanistic Understanding

- I. Direct MOA or mechanistic data
- II. MOA or mechanistic data on related compounds
- III. Inadequate MOA or mechanistic data

Toxicological Significance

- A. Directly demonstrated
- B. Inferred or based on related chemicals
- C. Inadequate

Mumtaz, MM; Durkin, PR. (1992) A weight-of-evidence scheme for assessing interactions in chemical mixtures. Toxicol Ind Health 8:377-406.

Interaction Matrix of Metals

		ON TOXICIY OF			
		Pb	Mn	Zn	Cu
EFFECT OF	Pb		=IIIC neuro	=IIB hema	=IIIC hepatic
	Mn	>IC neuro		?	?
	Zn	<IA hema	?		<IB hepatic
	Cu	<IB hema	?	<IIA hema	

Effect of Zinc on Lead (Pb)

<1A

- <: less than additive action
- I: *in vivo* and *in vitro*
  - lead (Pb) inhibits ALAD, a zinc-containing enzyme in the heme synthesis pathway. Zinc protect against the inactivation.
  - zinc induces metallothionein
  - zinc protects against lead absorption in GI tract
- A: oral zinc supplement protective of lead-induced hematopoietic effects in children

Interaction Profiles Program

- Implementation of the Methodology
- Interaction profiles are used as public health tool
- Interaction profiles are not designed for regulatory activities

Interaction Profiles Provide

- Information about a specific mixture of concern
- Evaluation whether, and at what levels of exposure, interactions may occur among the chemicals in the mixture
- Evaluation on what types of interactions occur
- Conclusions and relevance to public health

First Interaction Profiles

- Interaction profile for persistent organic pollutants (POPs)
  - Found in breast milk
  - Found in fish

- Combinations of
  - chlorinated dibenzo-*p*-dioxins (**TCDD**s),
  - Hexachlorobenzene (**HCB**)
  - dichlorodiphenyl dichloroethane (*p,p'*-**DDE**),
  - methyl mercury ($\boldsymbol{CH_3}$**Hg**)
  - polychlorinated biphenyls (**PCB**s).

Health Effects of POPs in Humans or Animals

Effects	**TCDD**	**HCB**	**DDE**	CH_3**Hg**	**PCB**
Liver damage	X	X	x		
Immunosuppression	x	x	x	x	x
Thyroid hormones	X	X			x
Female repro-function	x	X			
Male repro-function	X		x	x	x
Neurological	X	X	X	X	x
Neurodevelopmental	x	X		X	X
Reprodevelopmental	x		x		x
Other developmental	x	X	x	x	x
Cancer	X	x	x	x	x

Interaction Matrix of POPs

EFFECT OF	ON TOXICIY OF: TCDD	HCB	DDE	CH_3Hg	PCBs
TCDD		?	=IIIC repro	=IIIB immuno	=IIIC weight
HCB	>IIIA weight		?	?	?
DDE	=IIIC repro	?		?	?
CH_3Hg	?	=IIIC liver	?		>IIC neuro
PCBs	<IIIB immuno	?	?	>IIC neuro	

Recommendations Based on Interaction Matrix

- WOE analyses indicate that the evidence for interactions among the components of this mixture is limited and inadequate to characterize most of the pertinent targets of toxicity
- Additivity is either supported by data (for some components) or recommended as public health preventive measure
- TTD modification of the HI is recommended

Initial Chemical	Chemical that Influences Toxicity (Added Chemical)			
	Atrazine	Simazine	Diazinon	Nitrate
Atrazine		Additive Reproductive Effects High confidence	Greater than additive Neurological effects Medium confidence	Greater than Additive Cancer effects Low confidence
Simazine	Additive Reproductive Effects High confidence		Data Gap	Greater than Additive Cancer effects Low confidence
Diazinon	Greater than additive Neurological effects Medium confidence	Greater than Additive Neurological Effects Medium confidence		Data Gap
Nitrate	Greater than additive Cancer effects Low confidence	Greater than Additive Cancer effects Low confidence	Data Gap	

Qualitative Application of WOE

- If the component-based analyses indicate that several binary combinations will have more than additive joint toxic action, the HI may underestimate the final toxicity of the mixture

- If the component-based analyses indicate that several binary combinations will have less than additive joint toxic action, the HI may overestimate the actual hazard presented by the exposure scenario

ATSDR Interaction Profiles for some Pollutant Mixtures

- http://www.atsdr.cdc.gov/interactionprofiles/index.asp

- **Final Interaction Profiles**
- Arsenic, Cadmium, Chromium, Lead
- Benzene, Toluene, Ethylbenzene, Xylenes
- Lead, Manganese, Zinc, Copper
- Persistent chemicals found in breast milk
- Persistent chemicals found in fish
- 1,1,1-TCE, 1,1-DCE, TCE, PERC
- Cesium, Cobalt, Polychlorinated Biphenyls, Strontium, and Trichloroethylene
- Arsenic, Hydrazines, Jet Fuels, Strontium-90, and Trichloroethylene
- Cyanide, Fluoride, Nitrate, and Uranium
- Atrazine, Deethylatrazine, Diazinon, Nitrate, and Simazine
- Chlorpyrifos, Lead, Mercury, and Methylmercury

ATSDR Interaction Profiles for some Pollutant Mixtures

- http://www.atsdr.cdc.gov/interactionprofiles/index.asp

- **Draft Interaction Profiles**
- Carbon Monoxide, Formaldehyde, Methylene Chloride, Nitrogen Dioxide, Tetrachloroethylene
- Chloroform, 1,1-Dichloroethylene, Trichloroethylene, and Vinyl Chloride
- Chlorinated Dibenzo-*p*-dioxins, Polybrominated Diphenyl Ethers, and Phthalates

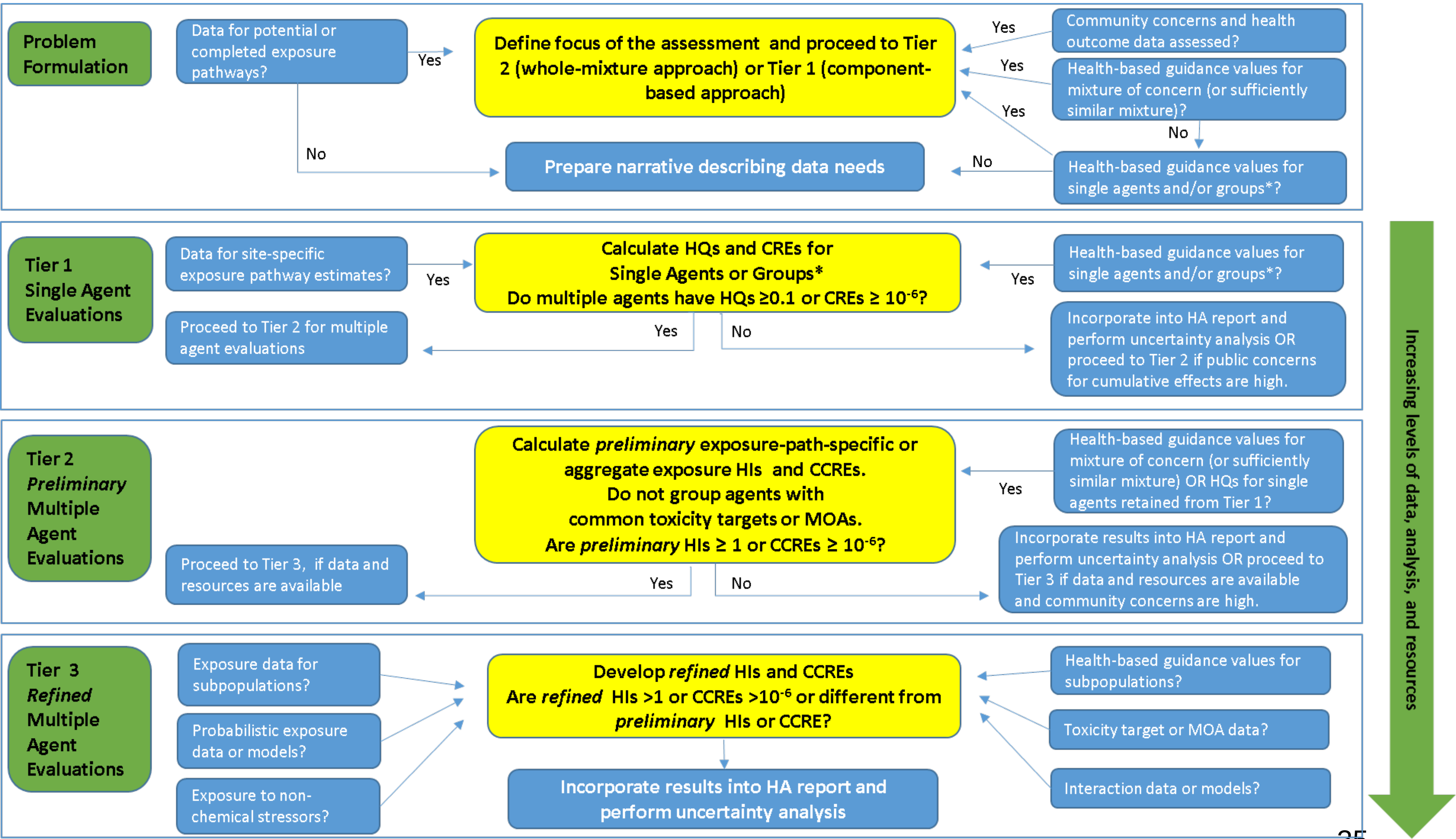
Proposed Draft ATSDR Tiered Framework

Assessing health impacts from combined exposure to multiple chemical or physical agents

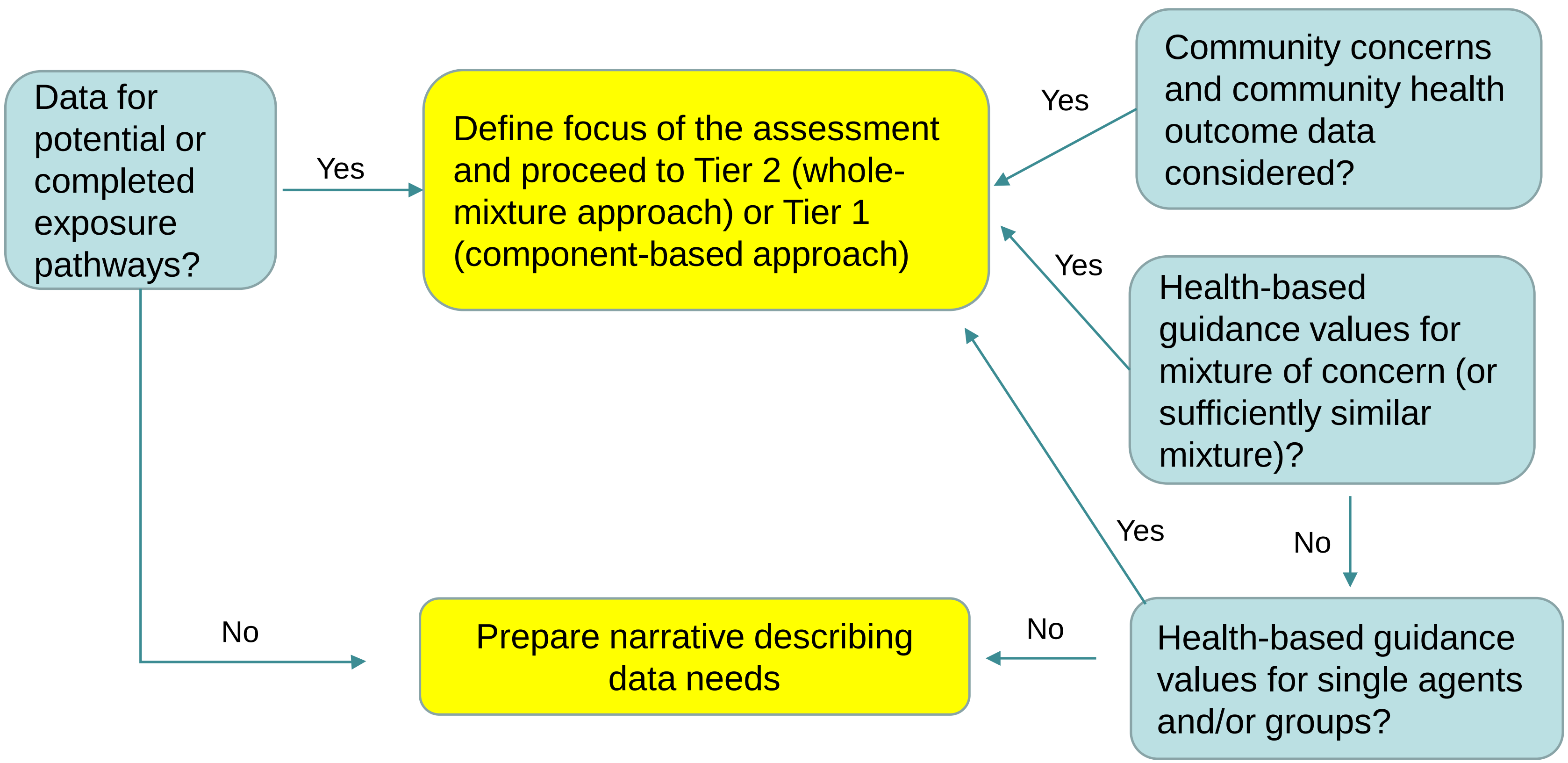
- **Similar tools and approaches as 2004 ATSDR Mixture Guidance**
  - Use whole-mixture exposure estimates and noncancer and cancer guidance values if feasible
  - Use component-based approaches when necessary
    - HQs and Hazard Index for noncancer assessment (dose additivity)
    - Cancer Risk Estimates (CRE) and Combined Cancer Risk Estimates (CCRE) (response additivity)

- **New tiered approach**
  - Efficient use of analytical resources
  - How much analysis is enough?

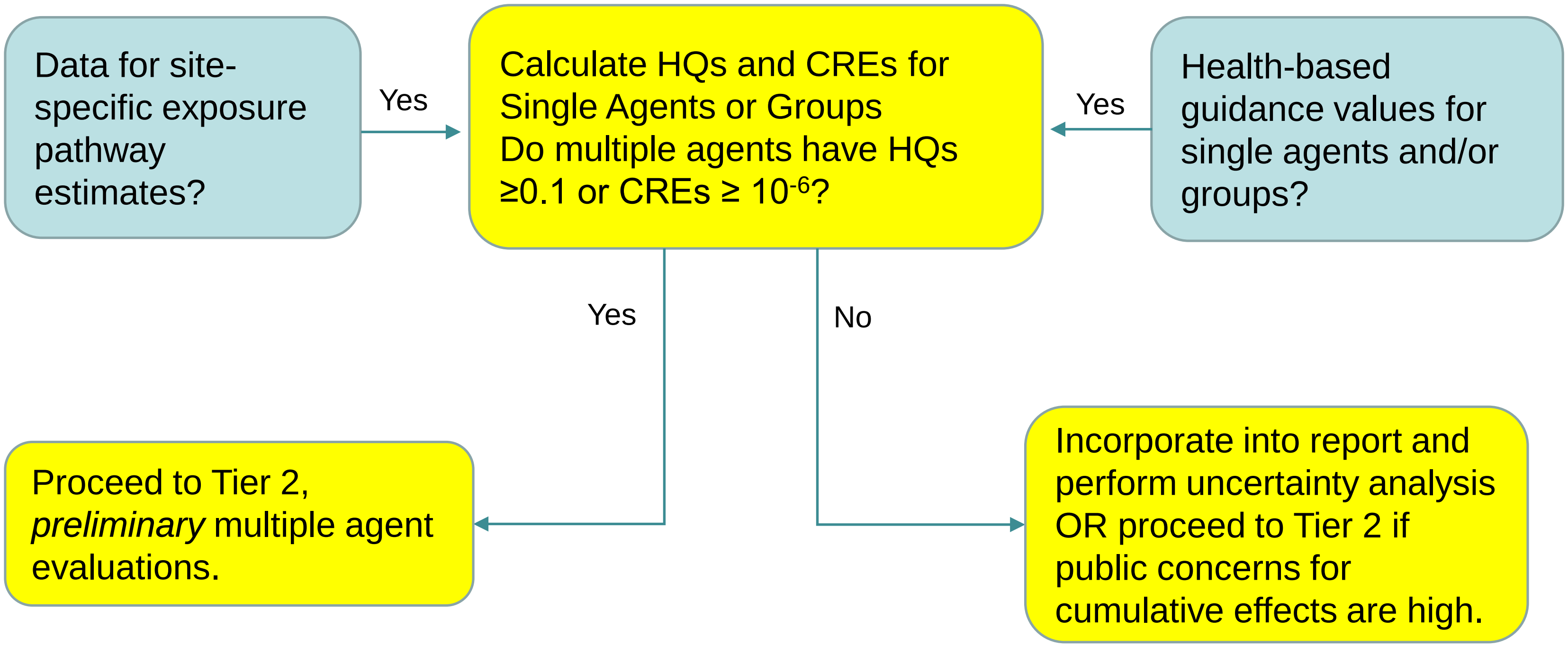
Proposed Draft Tiered Assessment Framework



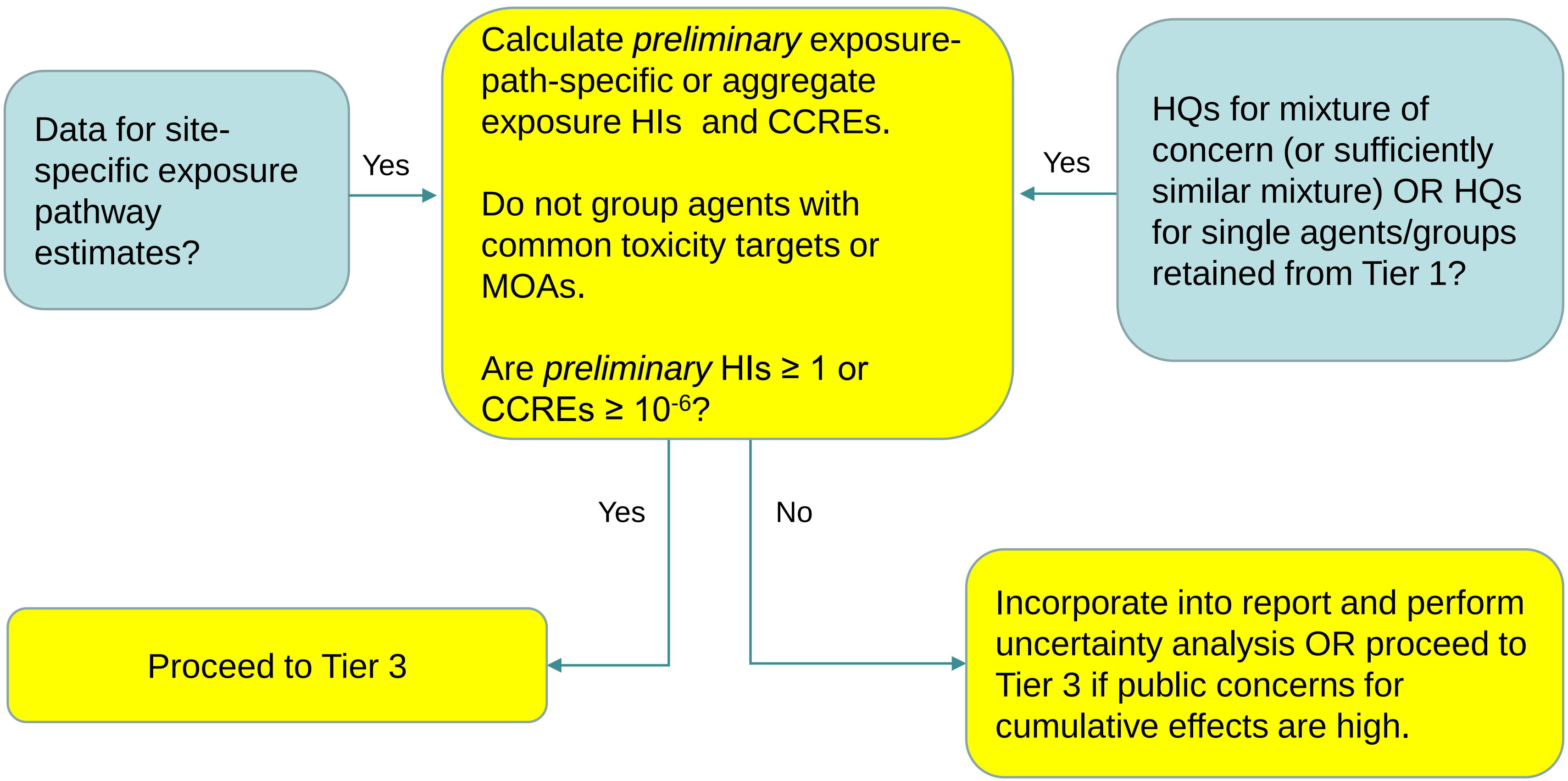
Problem Formulation



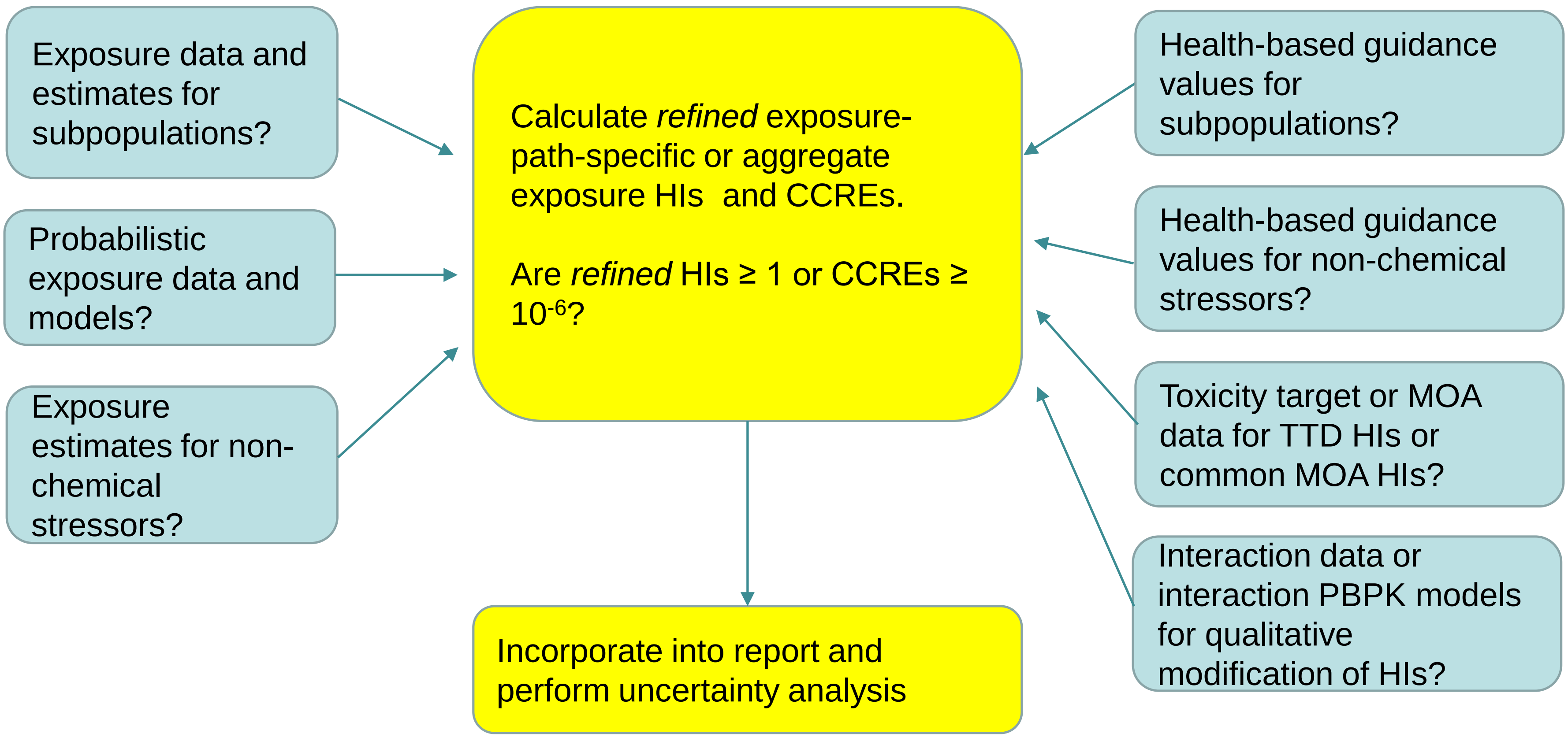
Tier 1 Single Agent Evaluations



Tier 2 *Preliminary* Multiple Agent Evaluations



Tier 3 *Refined* Multiple Agent Evaluations



4 Chemicals in School Drinking Water Fountains

Problem Formulation

- 4 chemicals at levels > EPA MCLs in routine and follow-up samples
- High community concern for health impacts to children
- Exposure Pathway Focus: Intermediate-duration DW at school
- Toxicity Focus: Only noncancer guidance values available

Assessment Focus: Potential for noncancer effects in school children from intermediate-duration oral drinking water exposure

4 Chemicals in School Drinking Water Fountains

Tier 1 Single Agent and Tier 2 Multiple Agent Evaluations

Chemical	Max Conc (mg/L)	Worst Case Intake Estimate (mg/kg/day)	Intermediate Oral MRL (mg/kg/day)	HQ
1	2.14	0.015	0.15 (liver)	0.1
2	1.71	0.012	0.03 (liver)	0.4
3	5.71	0.04	0.4 (kidney)	0.1
4	0.86	0.006	0.01 (developmental)	0.6
			Preliminary Hazard Index	*1.2*

4 Chemicals in School Drinking Water Fountains

Tier 3 Evaluation: Common Toxicity Target Hazard Index

Endpoint Affected	Chemical				Toxicity Target Hazard Index
	1	**2**	**3**	**4**	
Liver	Yes MRL=0.15 **HQ=0.1**	Yes MRL=0.03 **HQ =0.4**	No	Yes TTD=0.9 **HQ=0.01**	0.51
Kidney	Yes TTD=0.3 **HQ=0.05**	No	Yes MRL=0.4 **HQ=0.1**	Yes TTD=0.9 **HQ=0.01**	0.16
Neurological	Yes TTD=0.3 **HQ=0.05**	Yes TTD=0.9 **HQ=0.01**	Yes TTD=4 **HQ=0.01**	No	0.07
Developmental	Yes TTD=0.3 **HQ=0.05**	Yes TTD=1.2 **HQ=0.01**	Yes TTD=1 **HQ=0.04**	Yes MRL=0.01 **HQ=0.6**	0.7

4 Chemicals in School Drinking Water Fountains

Summary and Conclusions

- All toxicity target hazard indices < 1.
- The hepatic (0.51) and developmental (0.7) hazard indices approached 1, but the TTD hazard quotients were all calculated with worst-case intake estimates.
- A literature review found no evidence for >additive or <additive joint actions among the 4 chemicals
- Conclusion: Health impacts unlikely
- Recommended Public Health Action: To be protective, use bottled water at school until tap water could be mitigated.

Acknowledgments

Chris De Rosa	Pat Durkin
Bill Farland	John Lipscomb
Hana Pohl	Cynthia Rider
Jane Ellen Simmons	Kim Zaccaria

Cooperative Agreements PI
TNO Scientists

Recap of Agenda for Discussion

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