Key Concepts, Theory and Approaches to Chemical Mixture and Cumulative Risk Assessments

Linda K. Teuschler

U.S. Environmental Protection Agency
Office of Research and Development (ORD)
National Center for Environmental Assessment - Cincinnati, Ohio

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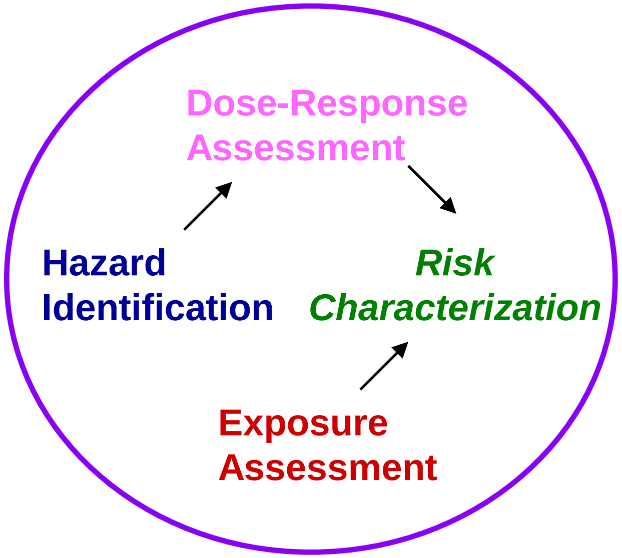
Overview

- Introduction to Chemical Mixtures Risk Assessment
  - Component vs. Whole Mixture Approaches
  - Key Concepts: Additive Joint Toxic Action, Similarity of Toxicological Action
- Methods
  - Dose Addition Approaches
  - Response Addition Method
  - Integrated Additivity Approach
  - Complex Mixture Fractions Approach
- Uncertainties in Chemical Mixture Risk Assessments
- Cumulative Risk Assessment – U.S. EPA Definitions

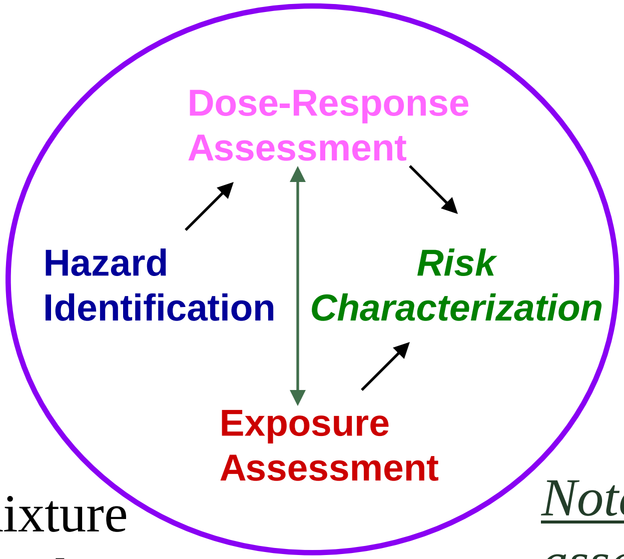
Risk Assessment Paradigm



Risk Assessment Paradigm for Chemical Mixtures: In Addition to Issues for Single Chemicals

Hazard Identification:

- identify effects from total mixture dose
- consider potential effects as a result of joint toxic action



Dose-Response Assessment:

- consider potential for effects below individual chemical thresholds
- incorporate toxicological judgment of similar toxicity within or between mixtures.

Exposure Assessment:

- consider changes in mixture composition from chemical interactions
-account for internal dose of several mixture components at the target tissue
-

Note: Dose-response & exposure assessment are interdependent

Risk Characterization:

- evaluate data support for assumptions about interactions, and similarity of toxicity
- consider uncertainty of changes in exposure

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The Big Divide: Component vs. Whole Mixture Approaches

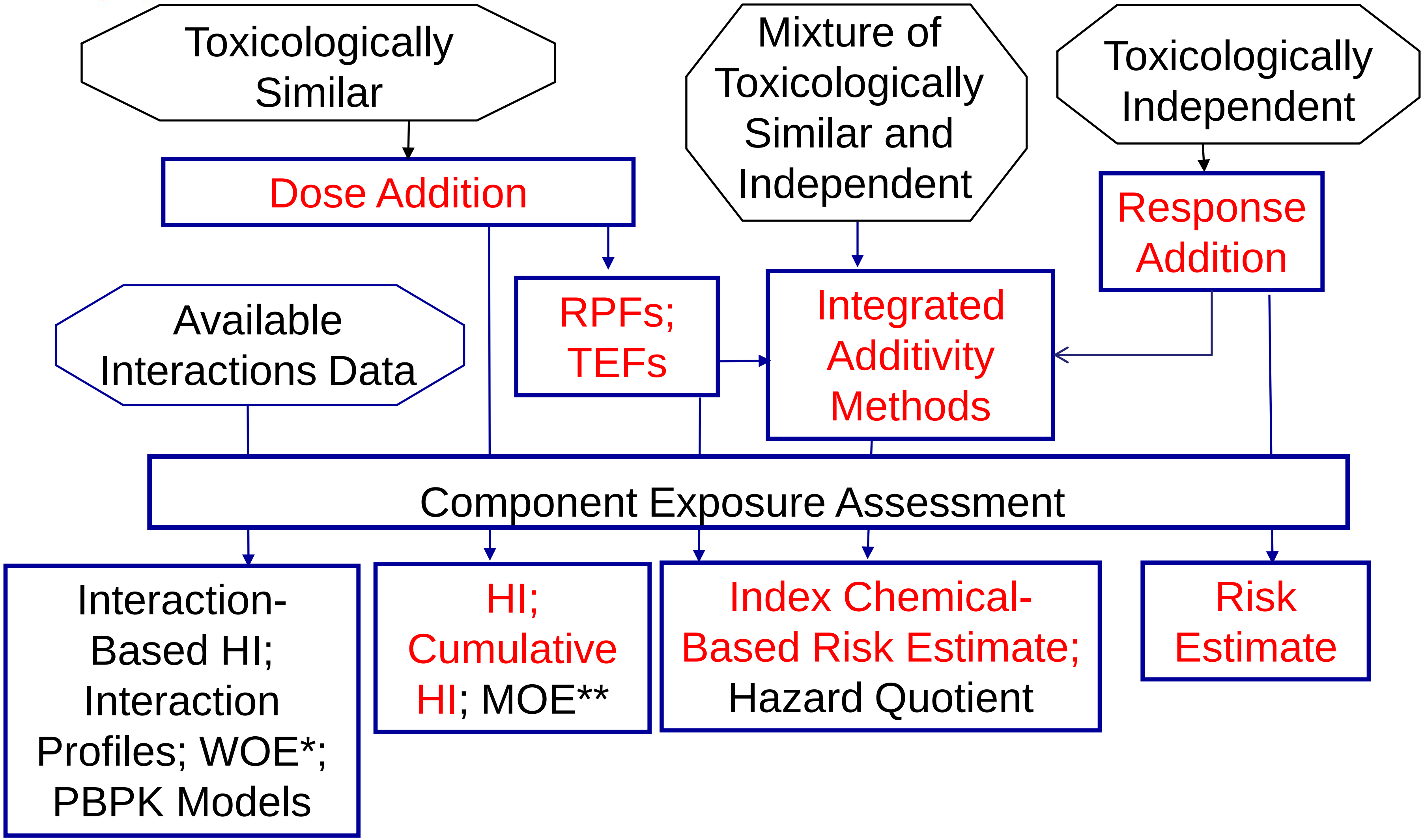
- Component-based methods (practical)
  - Simple models describe complex biological processes
  - Need good toxicity and exposure data on individual components
  - Assumptions regarding combinability of component data
- Whole mixture based assessments (preferred)
  - Need good toxicity and exposure data on the whole mixtures
  - Need to evaluate sufficient similarity
  - Can also assess fractions of the whole mixture

Key Concept: Additive Joint Toxic Action of Mixture Components

- Simple Similar Action [Dose Addition – e.g., Hazard Index (HI), Cumulative HI, Relative Potency Factors (RPFs), Toxicity Equivalence Factors (TEFs)]
  - Addition of component doses, scaling factors for relative toxicity:
    - TEFs for Dioxins
    - RPFs for other chemical classes, e.g., organophosphates
    - 1/Reference Value for HI's
  - Assumes common toxic mechanism/mode of action or similar toxicity of components
- Simple Dissimilar Action [Response Addition – e.g., Cancer Risk Sums]
  - Addition of component risks
  - Assumes toxicological and statistical independence

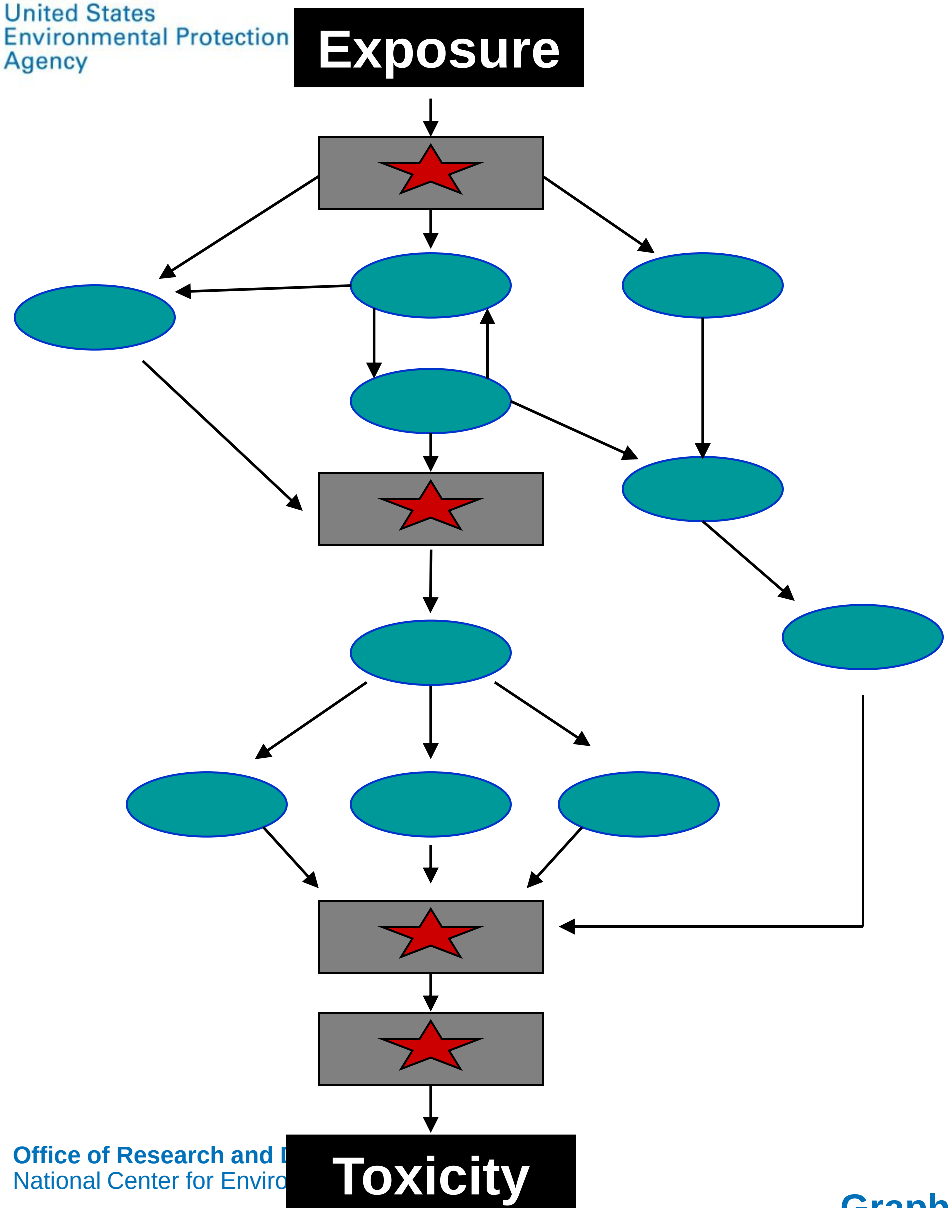
US EPA, 2000

Flow Chart for Evaluating Mixture Components – Today!



*Weight of Evidence for Toxicological Interactions
**Margin of Exposure

Schematic of Toxic Events



Event – Mechanism of Action
Detailed understanding at biochemical and molecular level

Key Event – Mode of Action
Identification of key and required steps

Toxicity Outcome – Observable adverse effect

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Key Concept: Similarity of Toxicological Action as a Continuum

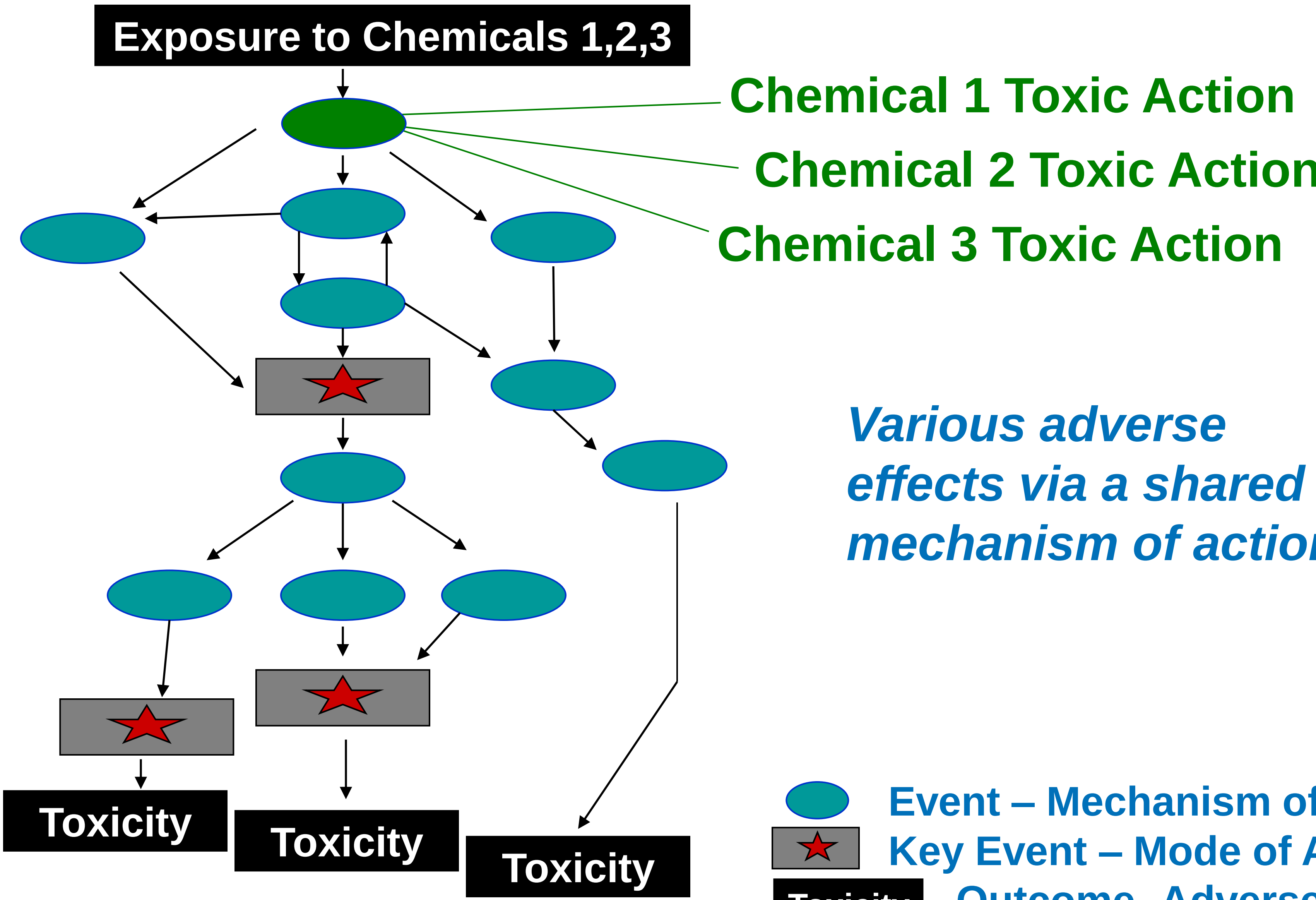
Factor	Information on Common Toxicological Action			
Term Applied	Mechanism-of-Action			
Data Need, Availability	High Low			
Knowledge of Toxic Action	Cellular/ Subcellular Level			
Choice of Risk Assess-ment Method: Example Effect and Mixture	Specific Methods: e.g., TEFs for Dioxin Ah receptor binding (van den Berg et al., 2006)			

Dioxin-Like Compounds Inclusion Criteria for the TEF Approach

- Structural similarity to polychlorinated dibenzo-*p*-dioxins or polychlorinated dibenzofurans
- Capacity to bind to the aryl hydrocarbon receptor (AhR)
- Capacity to elicit AhR-mediated biochemical and toxic responses, and
- Persistence and accumulation in the food chain

Van Den Berg et al., 2006

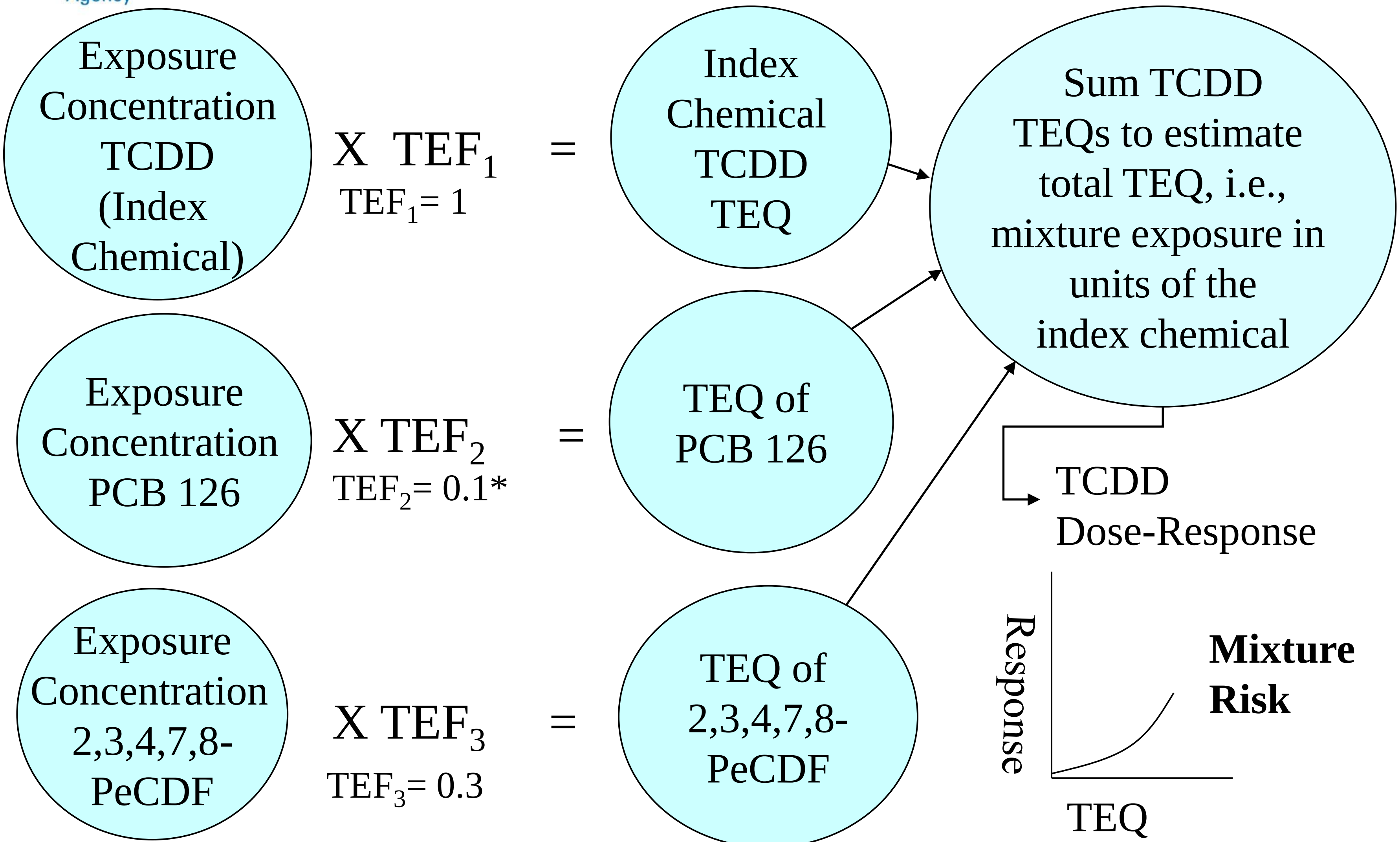
Dose Addition via Same Mechanism of Action



Various adverse effects via a shared mechanism of action

Event – Mechanism of Act
Key Event – Mode of Action
Toxicity Outcome -Adverse Effect

Toxicity Equivalence (TEQ) Analysis Schematic



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U.S. EPA. 2010. *TEF = 0.00003 for the 8 Dioxin-Like Mono-ortho–substituted PCBs

Key Concept: Similarity of Toxicological Action as a Continuum

Factor	Information on Common Toxicological Action			
Term Applied	Mechanism-of-Action	Mode-of-Action		
Data Need, Availability	High Low	Medium-High Low-Medium		
Knowledge of Toxic Action	Cellular/ Subcellular Level	Tissue Level		
Choice of Risk Assess-ment Method: Example Effect and Mixture	Specific Methods: e.g., TEFs for Dioxin Ah receptor binding (van den Berg et al., 2006)	General Methods, Limited by Route, Endpoint, Exposure Time: e.g., RPFs for Organophos-phorus Pesticides Cholinesterase Inhibition (U.S. EPA, 2002;2006)		

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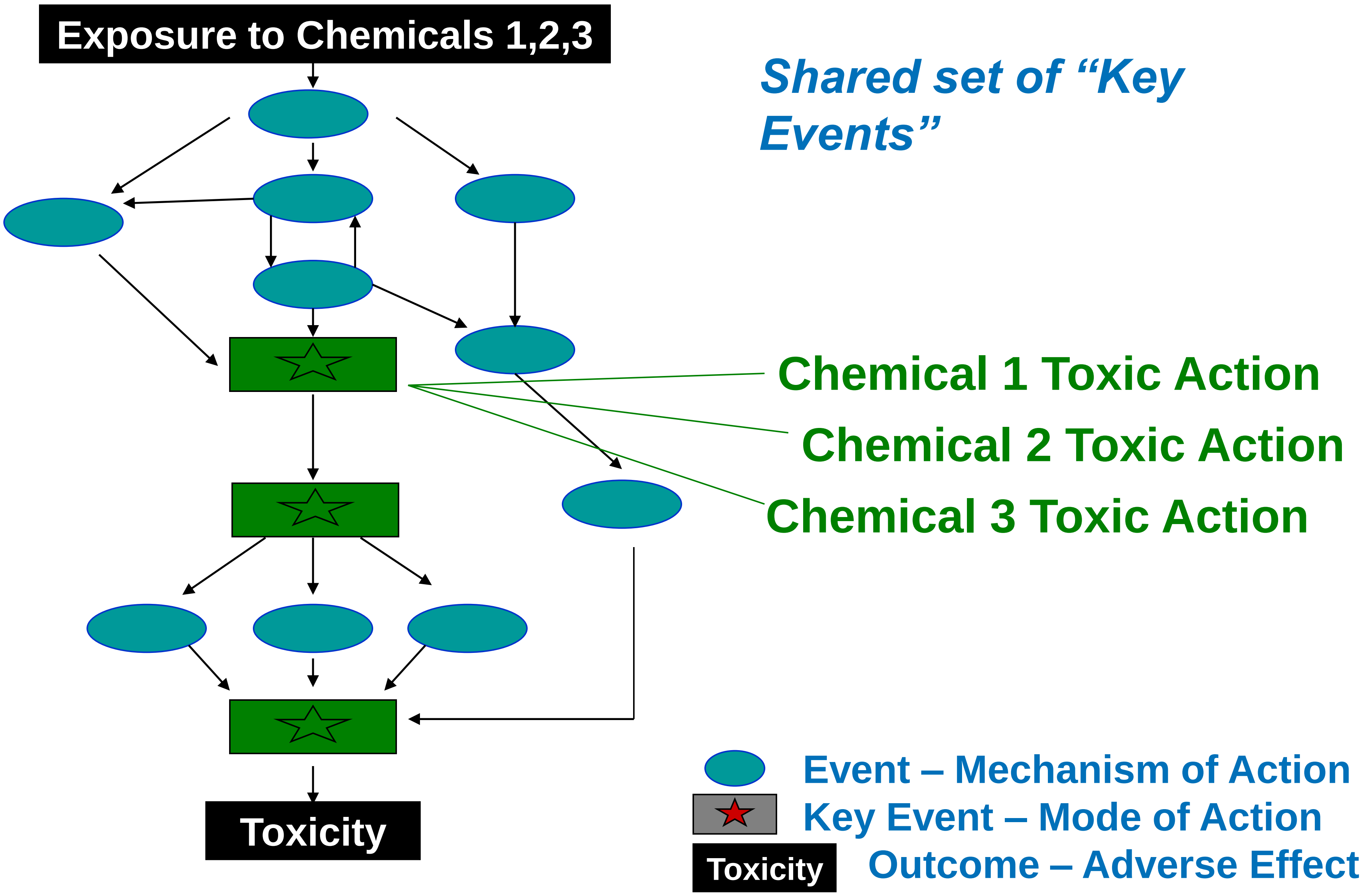
Inclusion Criteria for Organophosphorus Pesticides

- **Food Quality Protection Act of 1996**
  - –common mechanism of toxicity
- **ISLI Expert Panel (Mileson et al. 1998)**
  - –cause the same critical toxic effect
  - –act on the same molecular target at the same target tissue
  - –act by the same biochemical mechanism of action, or
  - –share a common toxic intermediate
- **U.S. EPA. 2002**
  - –same toxic effect occurs in or at the same organ or tissue by essentially the same sequence of major biochemical events

Dose Addition via Common Mode of Action



Comparison of TEFs and RPFs

Toxicity Equivalence Factor	Relative Potency Factor
Specific Type of RPF	Generalized Case
All health endpoints	May be limited
All routes	May be limited
All timeframes of exposure	May be limited
Implies more abundant data are available	May be based on lower quality/ fewer data
Implies greater certainty about mechanism of action	Assumes similar mode of action
	May be more accurate because application can be constrained given available data
Less emphasis on analytic uncertainty	Greater emphasis on characterization of uncertainty

Calculations are the same for both methods!

U.S. EPA, 2000

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Methods to Calculate RPFs

For mixture components, chemical i and index chemical 1, the Relative Potency Factor (RPF_i) may be estimated as:

1) the ratio of equally toxic doses of the 2 chemicals, e.g.,

$$RPF_i = \frac{ED_X(\text{Index Chemical})}{ED_X(\text{Chemical}_i)}$$

ED_x = The "Effective Dose" at which **an x% response is observed.**

2) the ratio of potency factors of the 2 chemicals, e.g.,

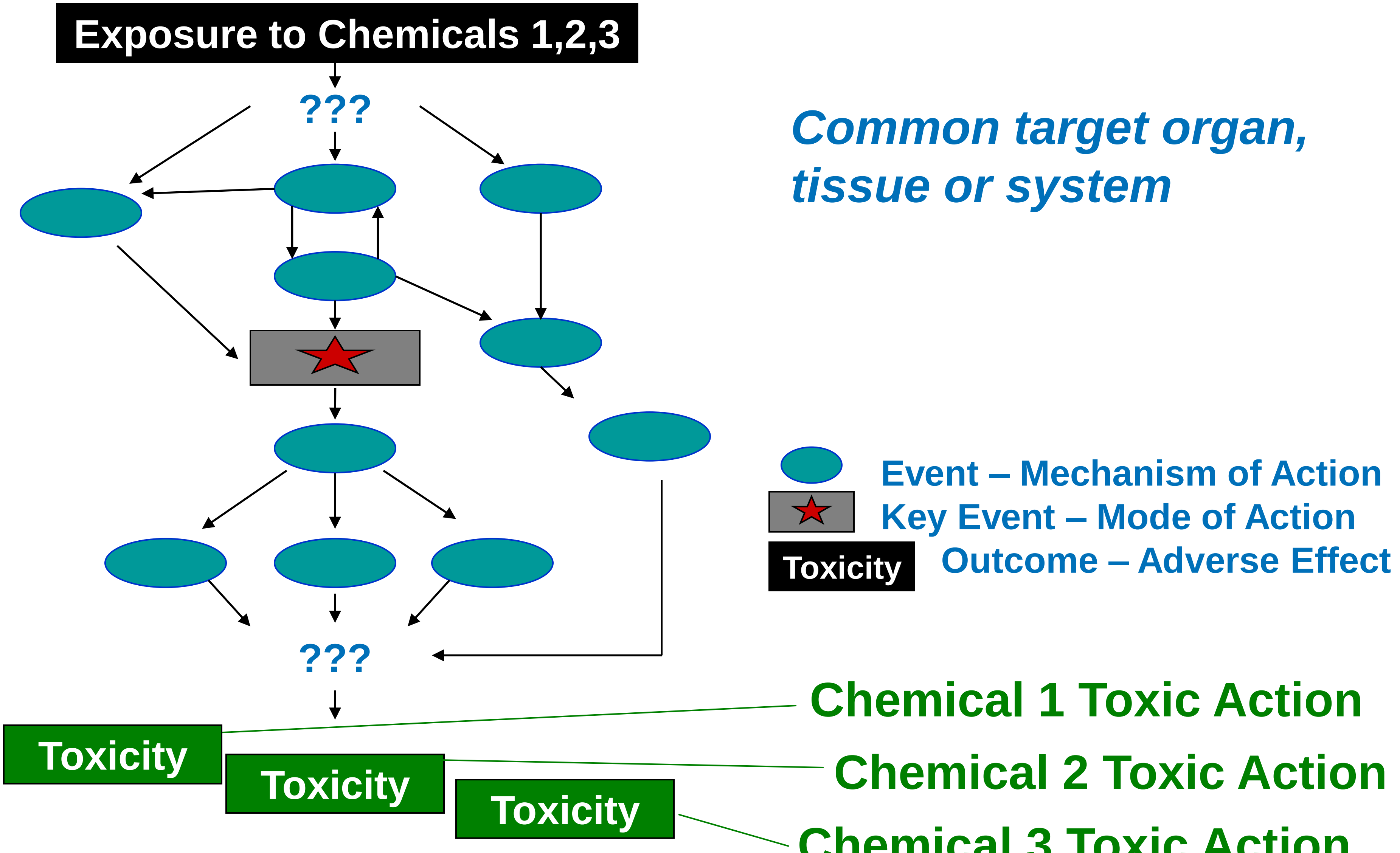
$$RPF_i = \frac{\text{slope factor}(\text{Chemical}_i)}{\text{slope factor}(\text{Index Chemical})}$$

US EPA, 2000

Key Concept: Similarity of Toxicological Action as a Continuum

Factor	Information on Common Toxicological Action			
Term Applied	Mechanism-of-Action	Mode-of-Action		Toxicological Similarity
Data Need, Availability	High Low	Medium-High Low-Medium		Low High
Knowledge of Toxic Action	Cellular/ Subcellular Level	Tissue Level		Target Organ Level
Choice of Risk Assess-ment Method: Example Effect and Mixture	Specific Methods: e.g., TEFs for Dioxin Ah receptor binding (van den Berg et al., 2006)	General Methods, Limited by Route, Endpoint, Exposure Time: e.g., RPFs for Organophos-phorus Pesticides Cholinesterase Inhibition (U.S. EPA, 2002;2006)		Simple Additive Methods, e.g., HI or Cumulative HI for Contaminated Sites - Various Effects in a Target Organ (U.S. EPA, 1989)

Dose Addition via Toxicological Similarity



Hazard Index Method (HI)

Chemical	Intake (mg/kg/d)	RfD* (mg/kg-d)	HQ Intake/ RfD	% Total Intake	Toxicity Target	UF*
Arsenic	3.00E-04	3.00E-04	1.0	4.4	Dermal	3
Chlordane	9.00E-05	5.00E-04	0.2	1.3	Liver	300
Dieldrin	1.00E-04	5.00E-05	2.0	1.5	Liver	100
Lindane	4.00E-04	3.00E-04	1.3	5.8	Liver	1000
Methoxychlor	6.00E-03	5.00E-03	1.2	87.1	Reproductive	1000
	6.89E-03			100		

	Dermal	Liver	Repro	Cumulative HI**
Hazard Index	1	3.5	1.2	5.7

*Reference Doses (RfD) and Uncertainty Factors (UF) from EPA's IRIS Database, Accessed July 2011

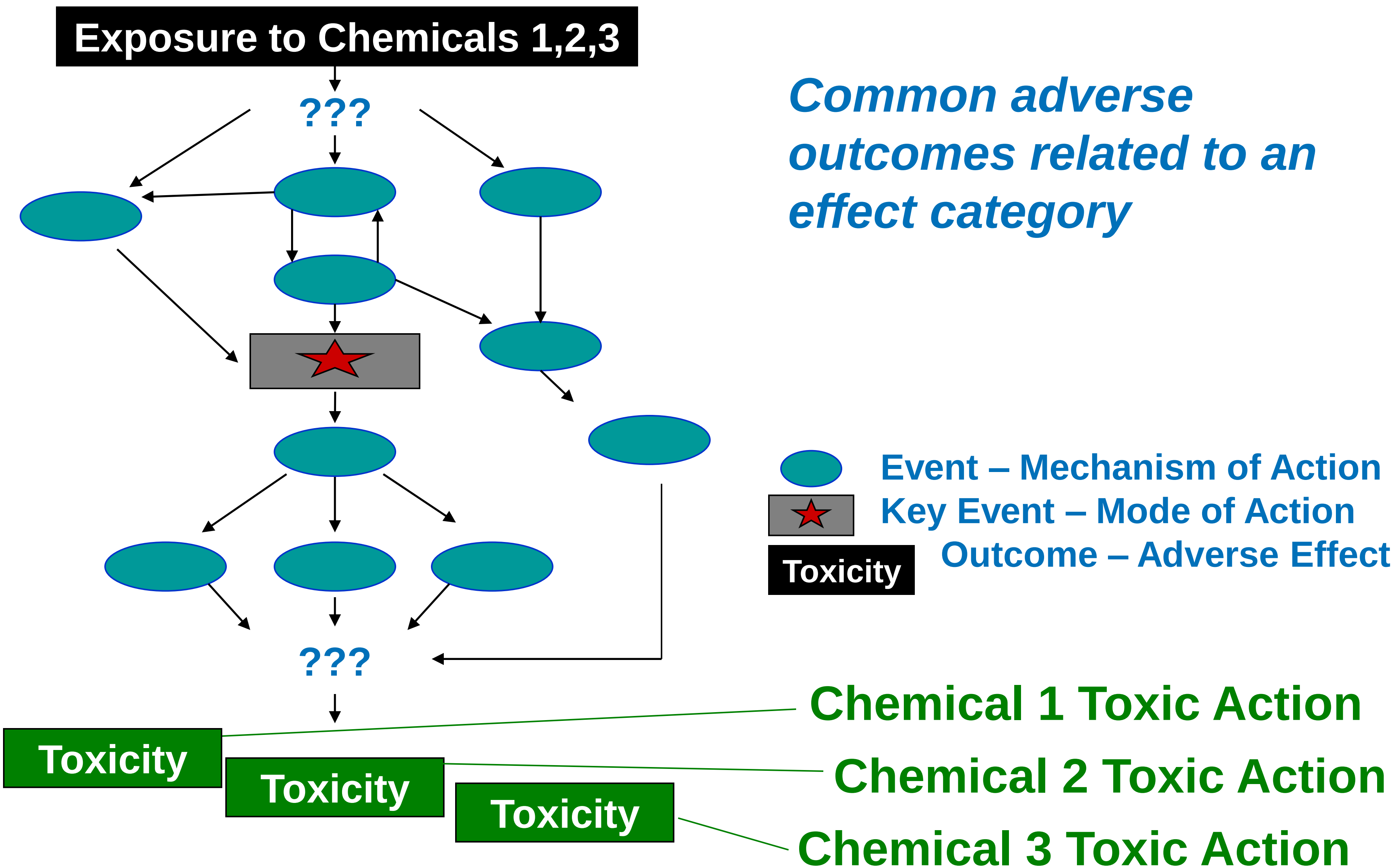
**CHI also may aggregate across exposure routes/pathways

Key Concept: Similarity of Toxicological Action as a Continuum

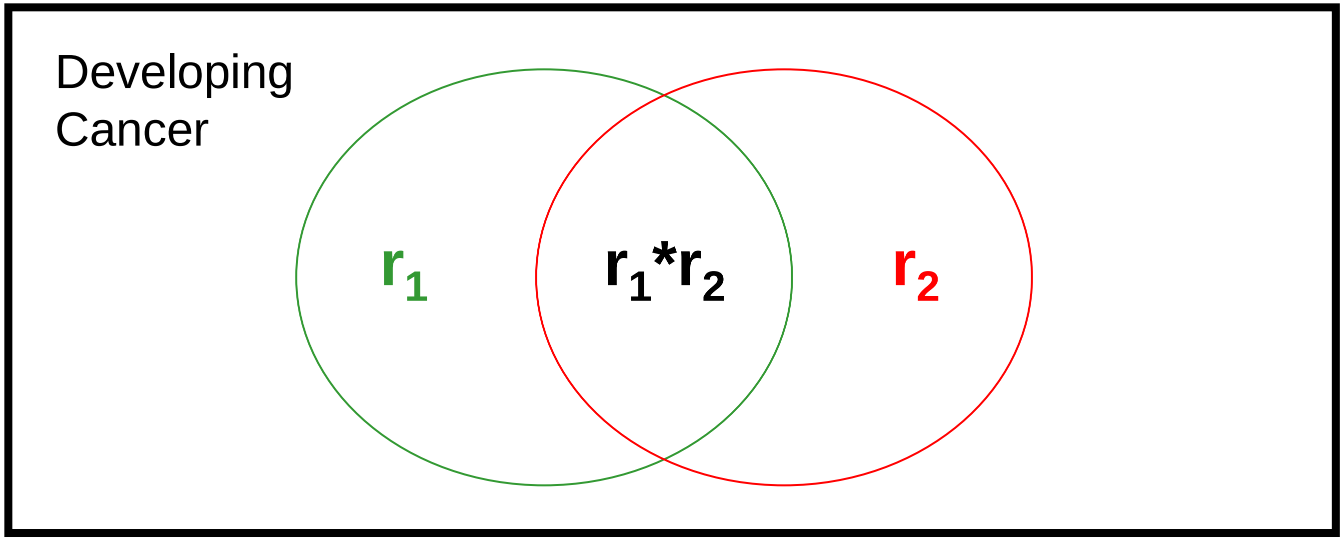
Factor	Information on Common Toxicological Action			
Term Applied	Mechanism-of-Action	Mode-of-Action	Common Adverse Outcome	Toxicological Similarity
Data Need, Availability	High Low	Medium-High Low-Medium	Medium-High Low-Medium	Low High
Knowledge of Toxic Action	Cellular/ Subcellular Level	Tissue Level	Ranges from Tissue to Biological Systems Level	Target Organ Level
Choice of Risk Assess-ment Method: Example Effect and Mixture	Specific Methods: e.g., TEFs for Dioxin Ah receptor binding (van den Berg et al., 2006)	General Methods, Limited by Route, Endpoint, Exposure Time: e.g., RPFs for Organophos-phorus Pesticides Cholinesterase Inhibition (U.S. EPA, 2002;2006)	General Methods: e.g., Integrated Additivity Methods or Cumulative HI for Phthalates Altered Male Reproductive Outcomes (NRC, 2008)	Simple Additive Methods, e.g., HI or Cumulative HI for Contaminated Sites - Various Effects in a Target Organ (U.S. EPA, 1989)

Dose Addition via Common Adverse Outcome

Common adverse outcomes related to an effect category



Key Concept: Response Addition Statistical Law of Independent Events



r_1 = 0.01, lung cancer risk for chemical 1

r_2 = 0.02, skin cancer risk for chemical 2

then $r_1 * r_2$ = 0.0002, and we get,

$$Rm = 0.01 + 0.02 – 0.0002 = 0.0298 \text{ or } \sim 0.03$$

For small risks, the risk intersection has virtually no impact.

U.S. EPA 2000

Response Addition via Independent Toxic Action

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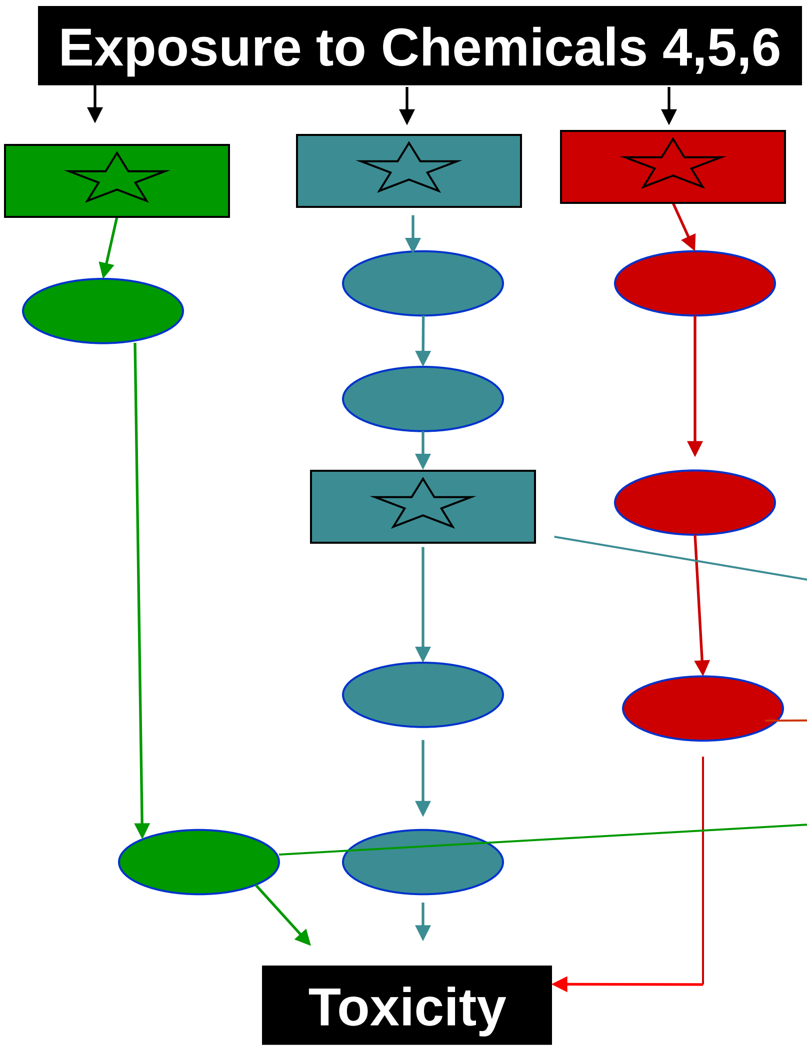

Same type of adverse effect via independent toxic mechanisms of action

Chemical 4 Toxic Action

Chemical 5 Toxic Action

Chemical 6 Toxic Action

Event – Mechanism of Action

Key Event – Mode of Action

Toxicity **Outcome – Adverse Effect**

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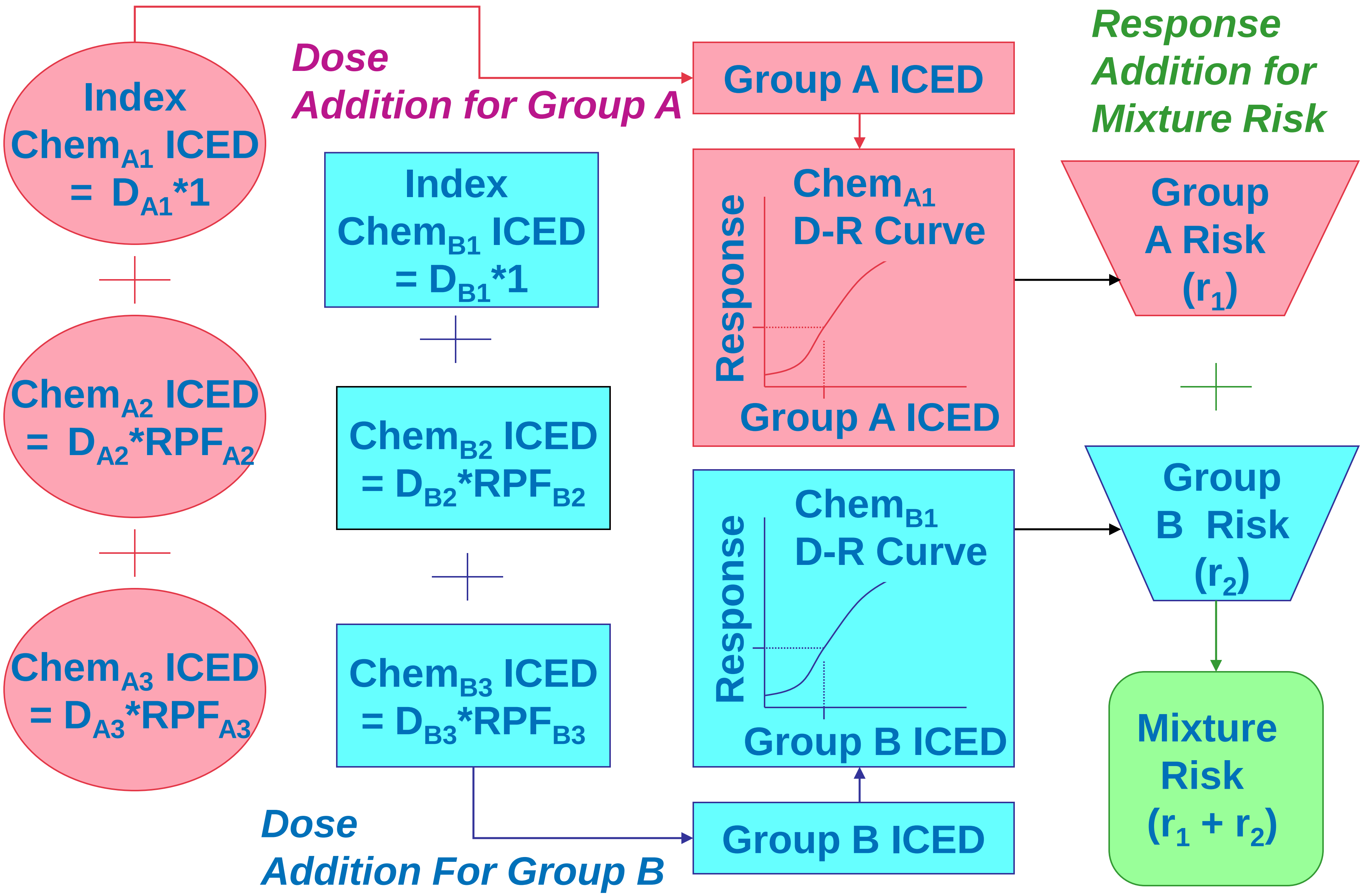
Key Concept: Integrated Additivity Approaches

- Mixed Toxic Modes of Action (MOA) for an Effect Category
    - Integrated Dose Addition and Response Addition
        - Addition of risks calculated for common MOA chemical groups
        - Assumes toxicological similarity within groups
        - Assumes toxicological independence between groups
- Cumulative Relative Potency Factors (CRPFs)
    - Divide mixture components into MOA groups
    - Calculate Index Chemical Equivalent Doses (ICEDs) for groups
        - Note these are called TEQ in the TEF approach for Dioxins
    - Use RPFs to calculate risks within groups under dose addition
    - Sum group risks under response addition

US EPA, 2003a

Cumulative RPFs for MOA Groups A and B



U.S. EPA, 2003a

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Evaluating Complex Mixtures

- **Which mixture to test?**
  - Actual environmental mixture
  - A sufficiently similar mixture
  - Lab concoction by similar process
  - Defined mixture of key chemicals
  - Complex fractions of whole mixture
- **Assessments based on**
  - Whole mixture data
  - Sufficiently similar mixtures
  - Complex mixture fractions
  - Surrogate chemicals (single chemical, defined mixture)
- **Evaluate sufficient similarity**
  - toxicity of one complex mixture used to evaluate another
  - surrogate chemical(s) used to evaluate a complex mixture

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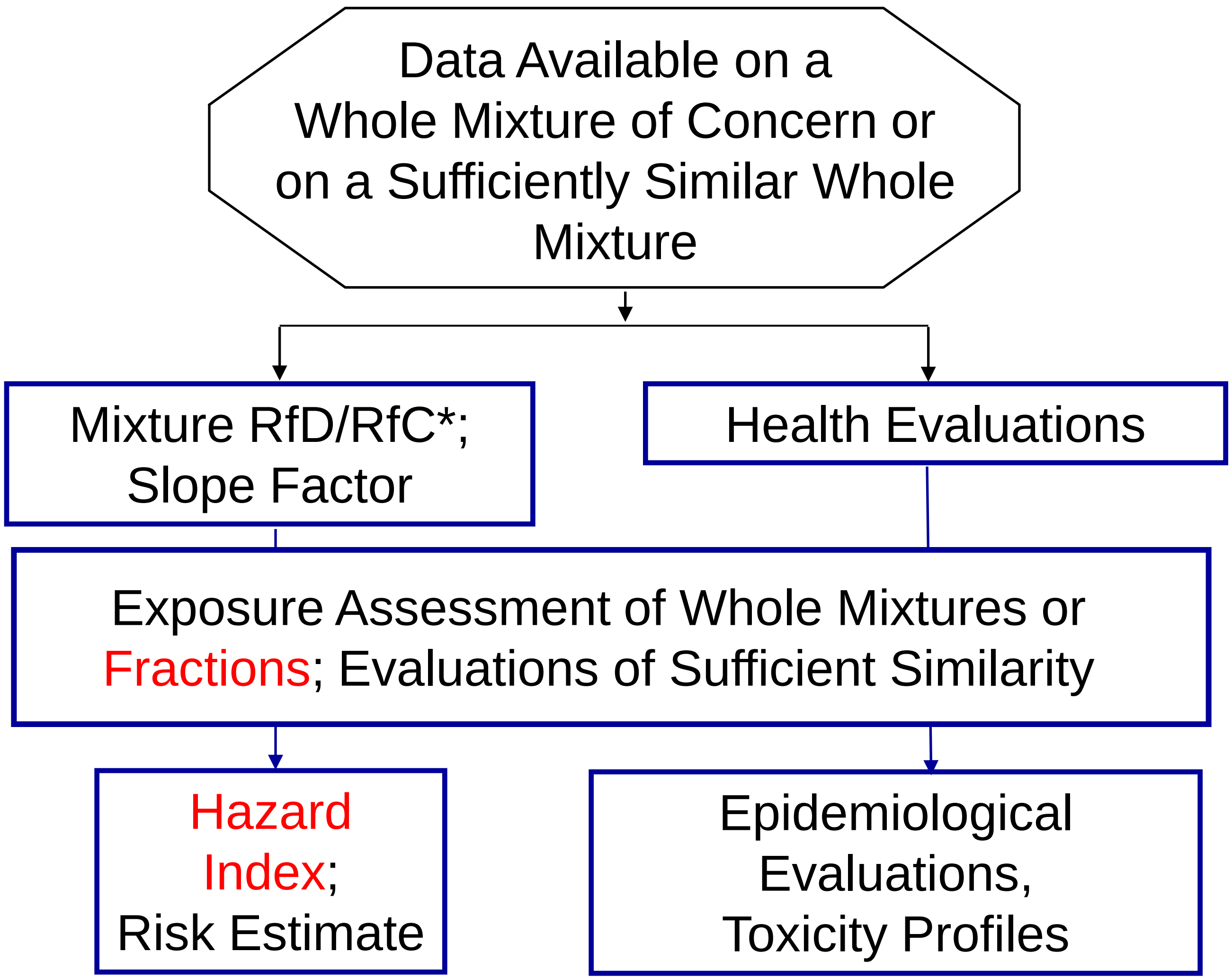
Flow Chart for Evaluating Whole Mixtures - Today



*Oral Reference Dose/Inhalation Reference Concentration

Procedure for Evaluating Complex Mixture Using Fractions

- Problem: Total Petroleum Hydrocarbon (TPH) mixture is prevalent, complex, highly variable contaminant mixture.

- Traditional approaches to risk assessment evaluate:

  1) Indicator compounds (e.g., benzene) – inadequate coverage

  2) Quantify the whole TPH mixture – not relevant to many sites, as composition is highly variable

- Massachusetts Dept of Environmental Protection (2002, 2003) VPH/EPH* approach fractionates the mixture

  1) VPH & EPH analytical methods differentiate & quantify collective aliphatic & aromatic TPH fractions at a site

  2) Toxicity values assigned to each fraction, based on surrogate chemicals

  3) Assesses mixture risk, accounts for variations in mixture composition

- Approach used by EPA (2009) for cancer and noncancer assessments

*Volatile Petroleum Hydrocarbon/Extractable Petroleum Hydrocarbon

Toxicity Values for TPH Fractions

Hydrocarbon Fraction	Oral RfD (mg/kg/d)	Inhalation RfC (mg/m3)
Aliphatic		
C5-C8	-	0.7
n-hexane ≤53%	-	0.6
C9-C18	0.01	0.1
C19-C32	3.0	NV*
Aromatic		
C6-C8	SC**	SC**
C9-C18	0.03	0.1
naphthalene	0.02	0.003
2-methylnaphthalene	0.004	-
C19-C32	0.04	NV*

*NV = not volatile

**SC = use single chemical IRIS values, fraction includes benzene, toluene, xylene, ethyl benzene

US EPA, 2009

HI For 6 TPH Fractions

$$HI_m = \sum_{i=1}^{6} HI_i$$

Aliphatic Fractions
HI_i =

$$\frac{E_{Aliph1}}{RfV_{n-hexane^*}}$$

**value dependent on % n-hexane*

$$\frac{E_{Aliph2}}{RfV_{MidRangeAHS}}$$

$$\frac{E_{Aliph3}}{RfV_{WhiteMineralOils}}$$

Aromatic Fractions
HI_i =

$$\sum_{i=1}^{4} \frac{E_i}{RfV_i}$$

i = Benzene, Toluene, Ethylbenzene, Xylene

$$\sum_{i=1}^{3} \frac{E_i}{RfV_i}$$

i = High Flash Aromatic Naphtha, Naphthalene, 2-MethylNaphthalene

$$\frac{E_{Arom3}}{RfV_{Fluoranthene}}$$

Hazard Index Aliph1 Fraction	Hazard Index Arom1 Fraction
Hazard Index Aliph2 Fraction	Hazard Index Arom2 Fraction
Hazard Index Aliph3 Fraction	Hazard Index Arom3 Fraction

Sum fraction specific hazard indices assuming dose addition

US EPA, 2009

Uncertainties in Chemical Mixtures Risk Assessment

- Professional judgment is an important element
  - Results biologically defensible, presented transparently
  - Assumptions confirmed whenever possible
- Uncertainty/sensitivity analyses are important
  - Discuss data gaps, data quality differences among chemicals
  - Describe exposure range for which assessment is valid
- Data needs from mixture researchers
  - Test environmentally-relevant doses and component proportions
  - Ensure sufficient statistical power to detect effects
  - Publish raw data if possible, otherwise include variance estimates/standard errors/confidence intervals
  - Chemically characterize complex mixtures

What is Cumulative Risk?

- Cumulative risk is the combined risks from aggregate exposures to multiple agents or stressors, which may include chemicals, biological or physical agents
- Cumulative risk assessment (CRA) is an analysis, characterization, and possible quantification of the combined risks to human health or the environment from multiple agents or stressors

U.S. EPA, 2003b

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What is Cumulative Risk?

- Population-based with stakeholder emphasis and consideration of different *Vulnerability Factors*:
  - Susceptibility/Sensitivity (e.g., genetics, age, race)
  - Differential exposure (e.g., cultural practices, subsistence fishing, homes close to pollutant sources)
  - Differential preparedness (e.g., inadequate access to prenatal care, lack of immunizations)
  - Differential ability to recover (e.g., poor nutrition, existing health conditions such as asthmatic or immuno-compromised)

U.S. EPA, 2003b

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