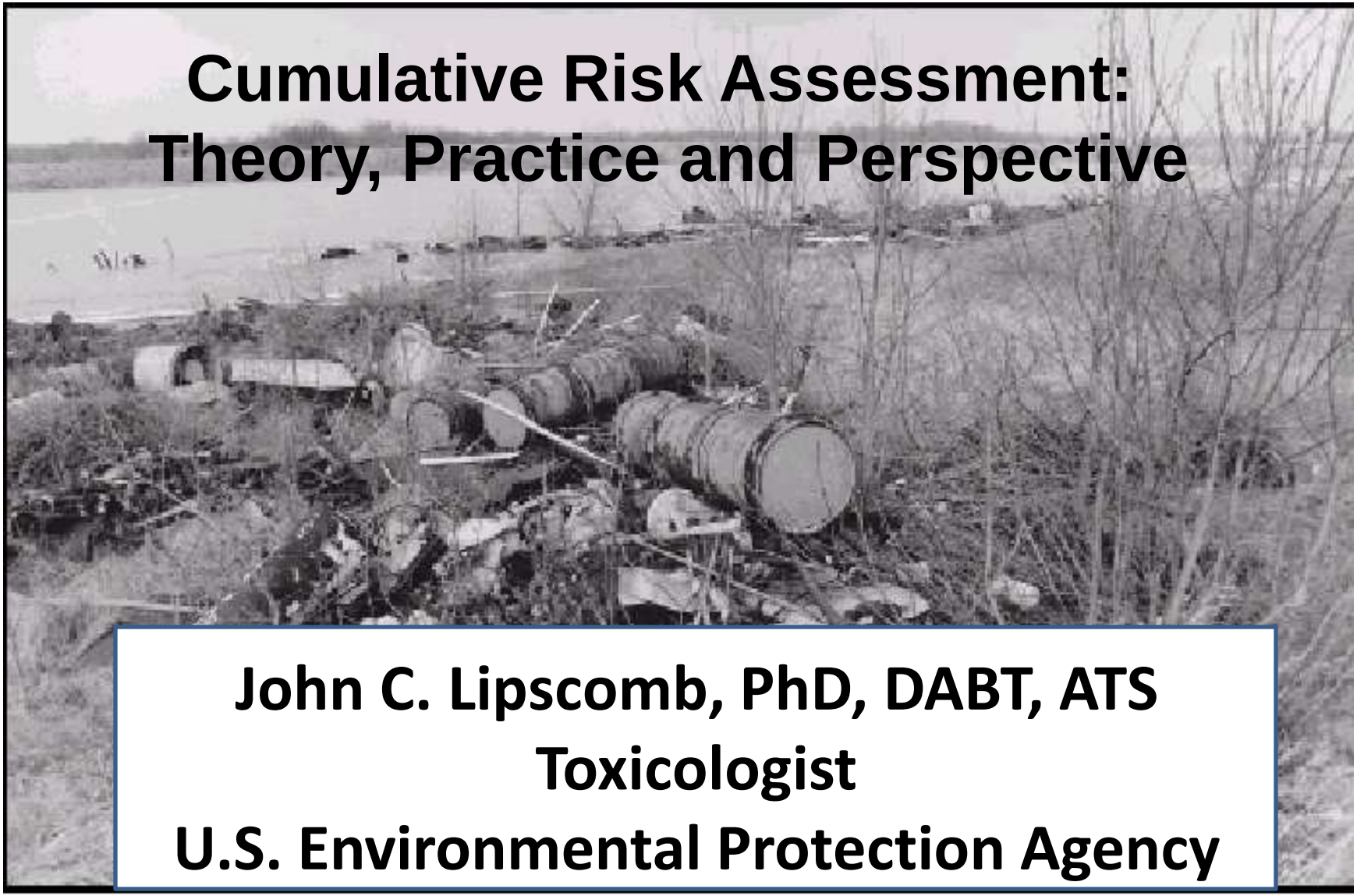
Cumulative Risk Assessment: Theory, Practice and Perspective



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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

Source: U.S. EPA. 2003. Framework for Cumulative Risk Assessment. U.S. EPA/ORD/NCEA, Washington, DC. EPA/600/P-02/001F. Available at: http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=54944.

Features of Cumulative Risk Assessment

Multiple chemical, physical, biological stressors

Complex, multiple-route exposures

Stakeholder emphasis

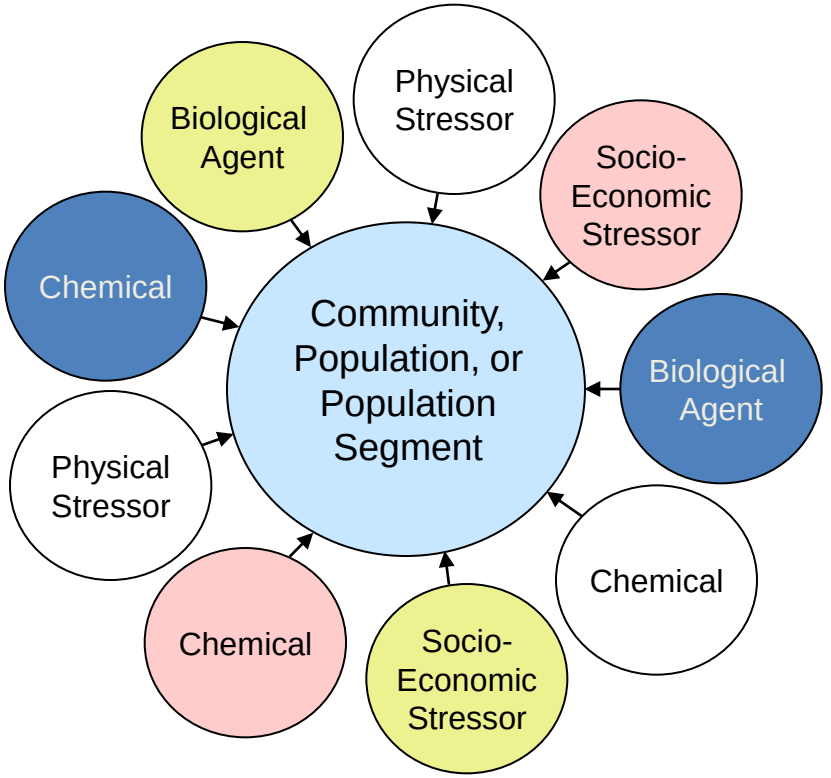
Human health and ecology

Population vulnerabilities

Benefits of healthy communities

Benefits of healthy ecosystems

Population focus



Cumulative Risk Assessment

Population-Based

- **General population**
- **Susceptible (?) groups**

Characterize Exposures

- **Sources & components**
- **Routes of exposure**

Group Components

- **Target tissues / outcomes**
- **Toxicokinetics**
- **Mode(s) of action**

Characterize & Communicate Risk

- **Health concerns**
- **Components**
- **Sources**

U.S. EPA CRA Theory and Practice

Risk Assessment Guidance for Superfund (1989)

Methodology for Multipathway Exposures to Combustor Emissions (1998)

Guidance for Assessing Health Risks of Chemical Mixtures (1986, 2000)

4 CRA's & Guidance on Cumulative Risk of Pesticides (2002b;2006a,b,c;2007a)

Concepts, Methods and Data Sources for Cumulative Health Risk Assessment of Multiple Chemicals, Exposures and Effects: A Resource Document (2007b)

Planning & Scoping for Cumulative Risk Assessment (1997)

Planning & Scoping Lessons Learned (2002a)

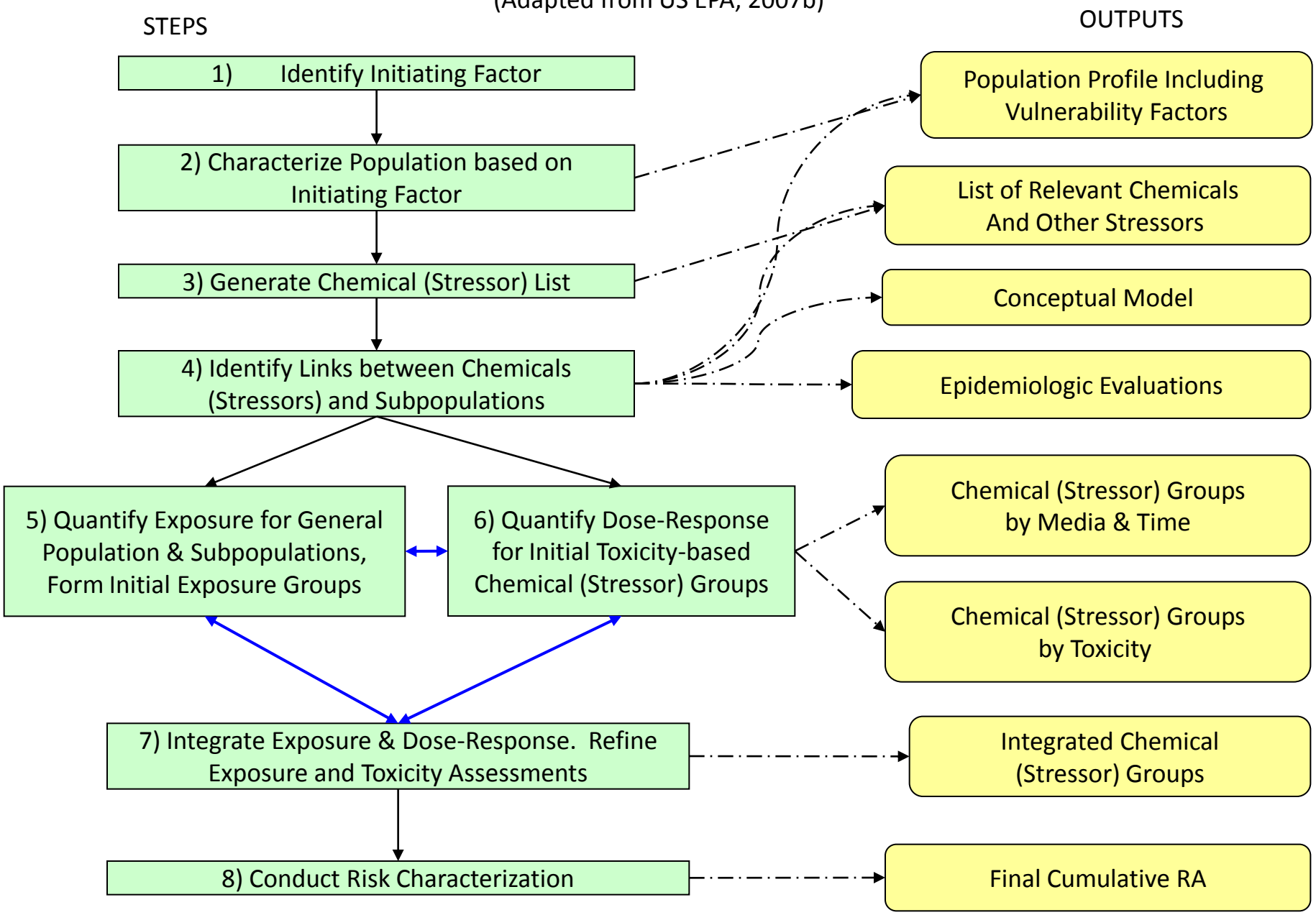
Framework for Cumulative Risk Assessment (2003)

5 White Papers on CRA: Directions for CRA, Vulnerability, Combined Effects from Multiple Stressors, Environmental Mixtures, Biomarkers (2007c)

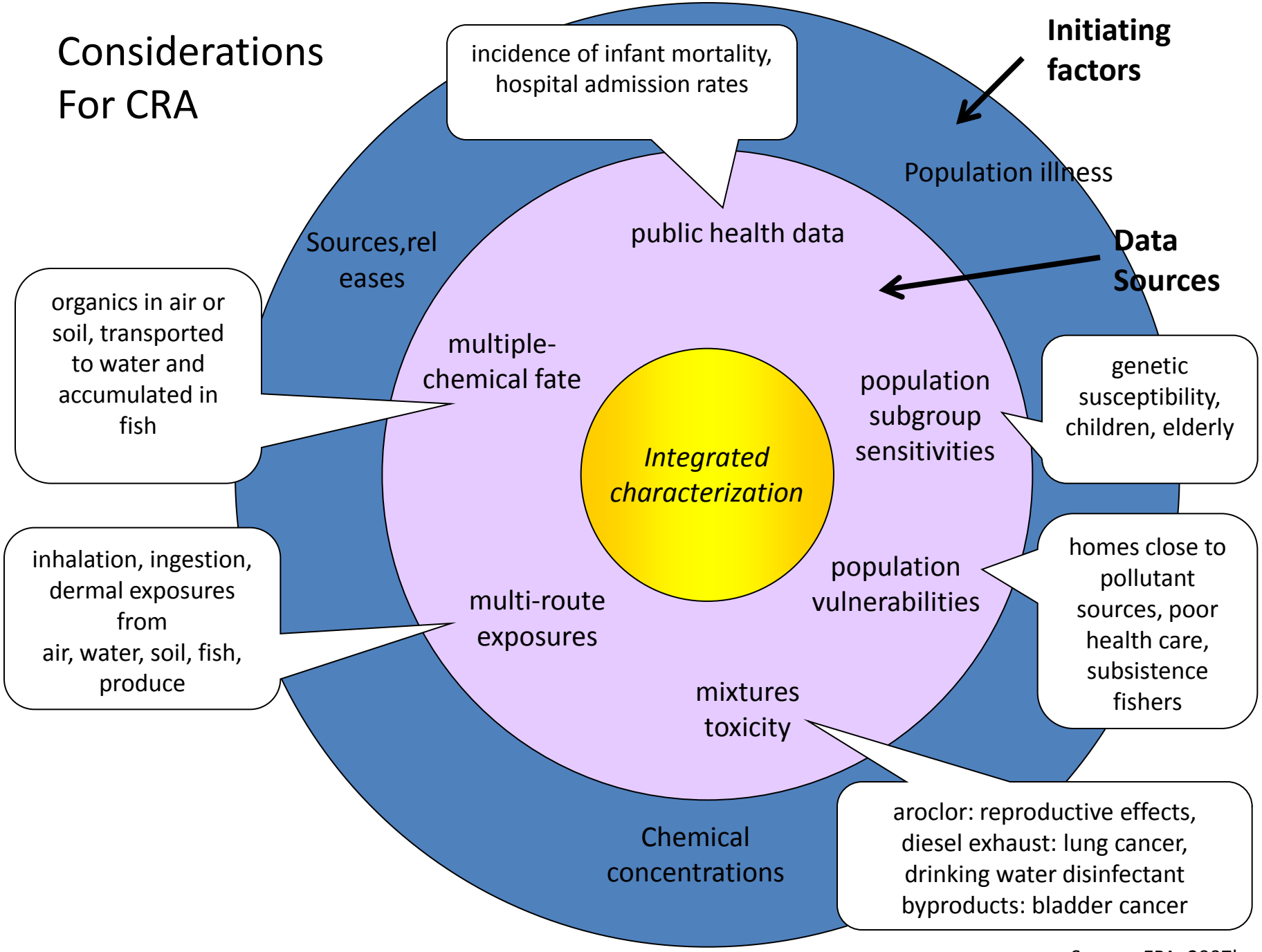
Continuing Risk Assessment Forum CRA Efforts

Steps for Conducting a Cumulative Risk Assessment

(Adapted from US EPA, 2007b)



Considerations For CRA



Source: EPA, 2007b

What are Vulnerability Factors?

Cumulative risk assessment is population-based with stakeholder emphasis and consideration of *Vulnerability Factors*:

-Susceptibility/Sensitivity (e.g., genetics, age, race)

-Differential exposure (e.g., cultural practices)

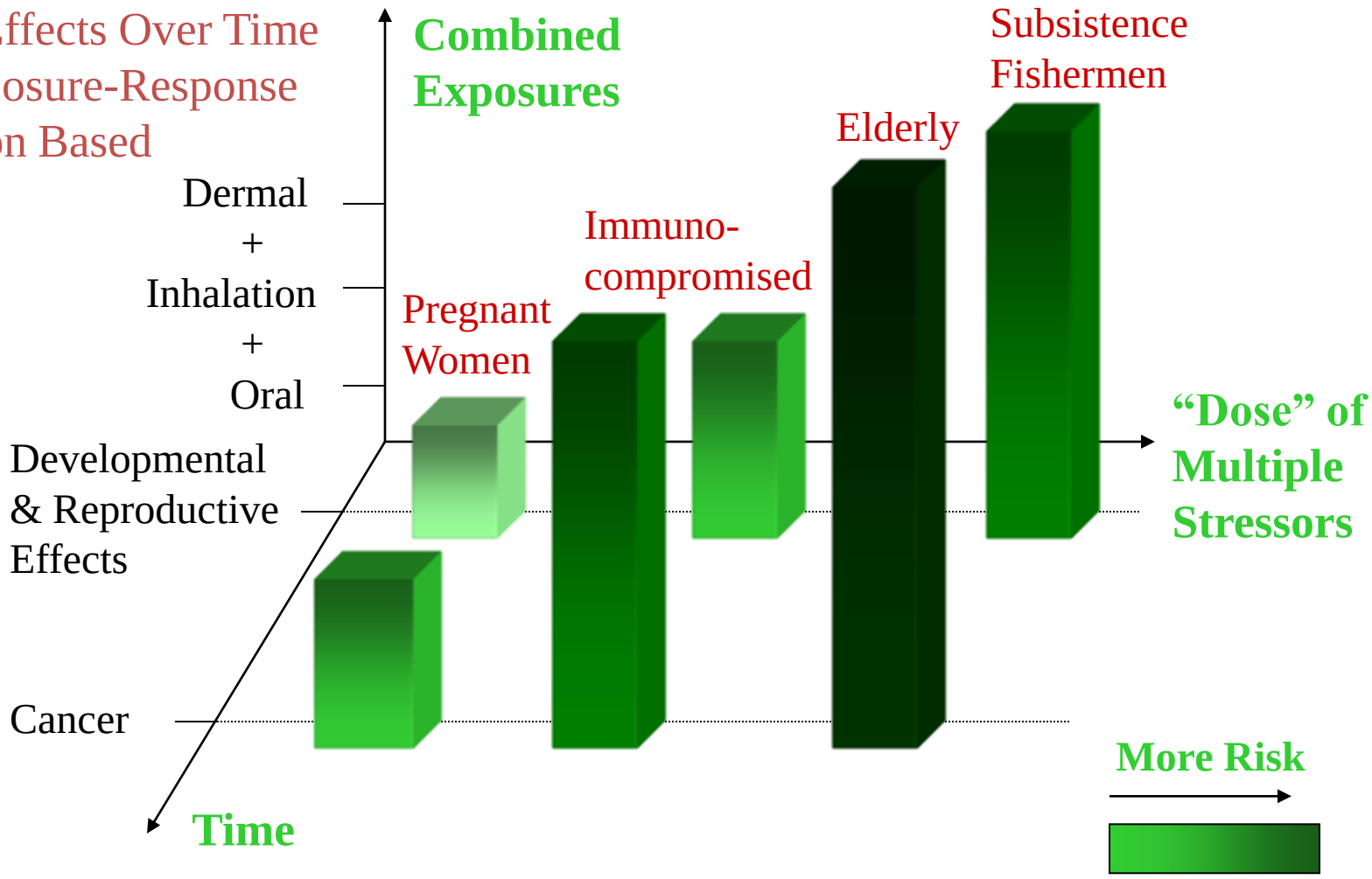
-Differential preparedness (e.g., lack of access to health care)

-Differential ability to recover (e.g., poor nutrition)

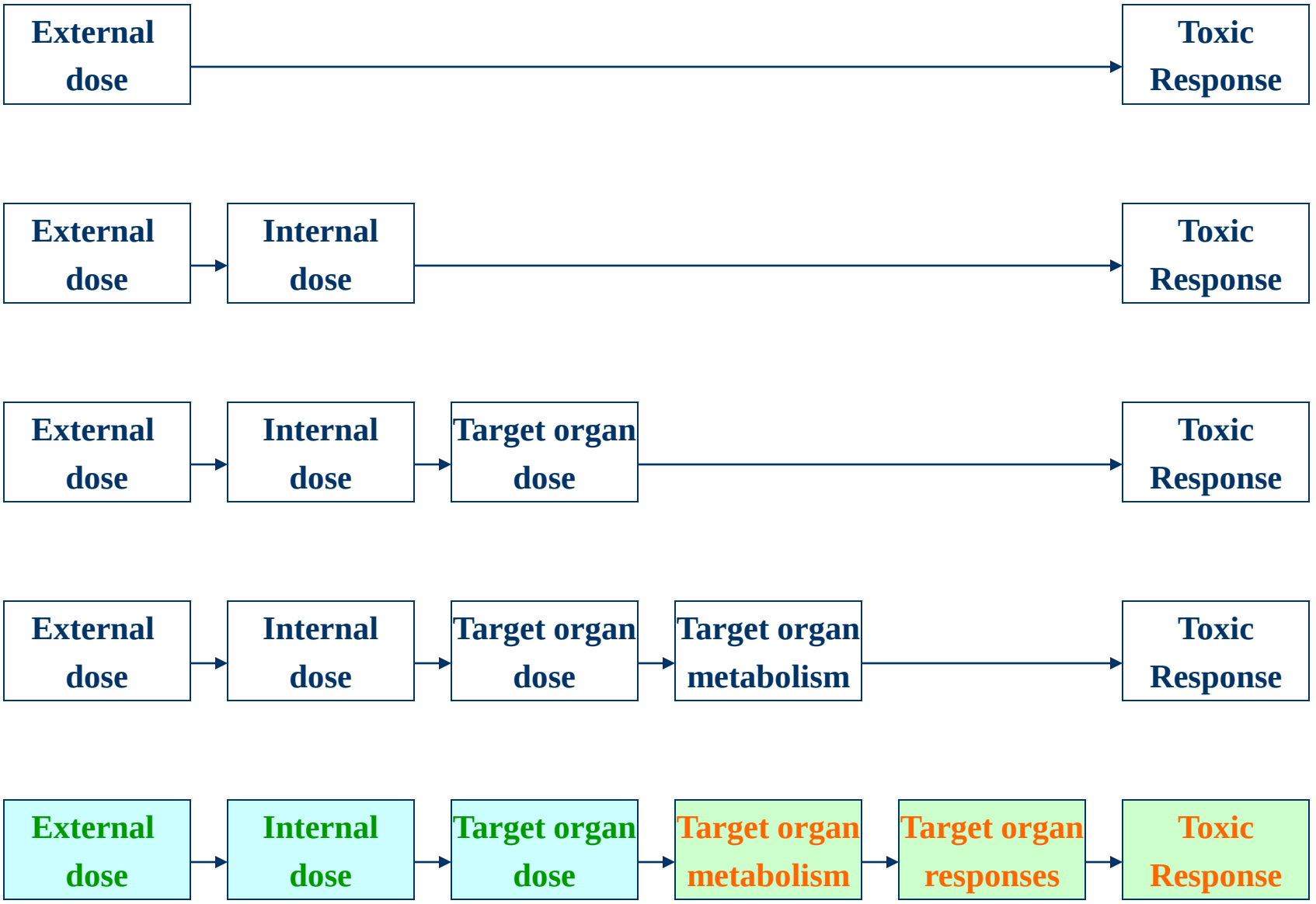
Source: U.S. EPA. 2003. Framework for Cumulative Risk Assessment. U.S. EPA/ORD/NCEA, Washington, DC. EPA/600/P-02/001F. Available at: http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=54944.

Cumulative *Risk Characterization*

- Several Stressors
- Multiple Exposure Routes
- Several Effects Over Time
- Joint Exposure-Response
- Population Based



Exposure → Dose → Response



Co-Exposures and Responses

Consideration of internal dose refines chemical groupings:

Persistence, or not, of chemicals inside the body.

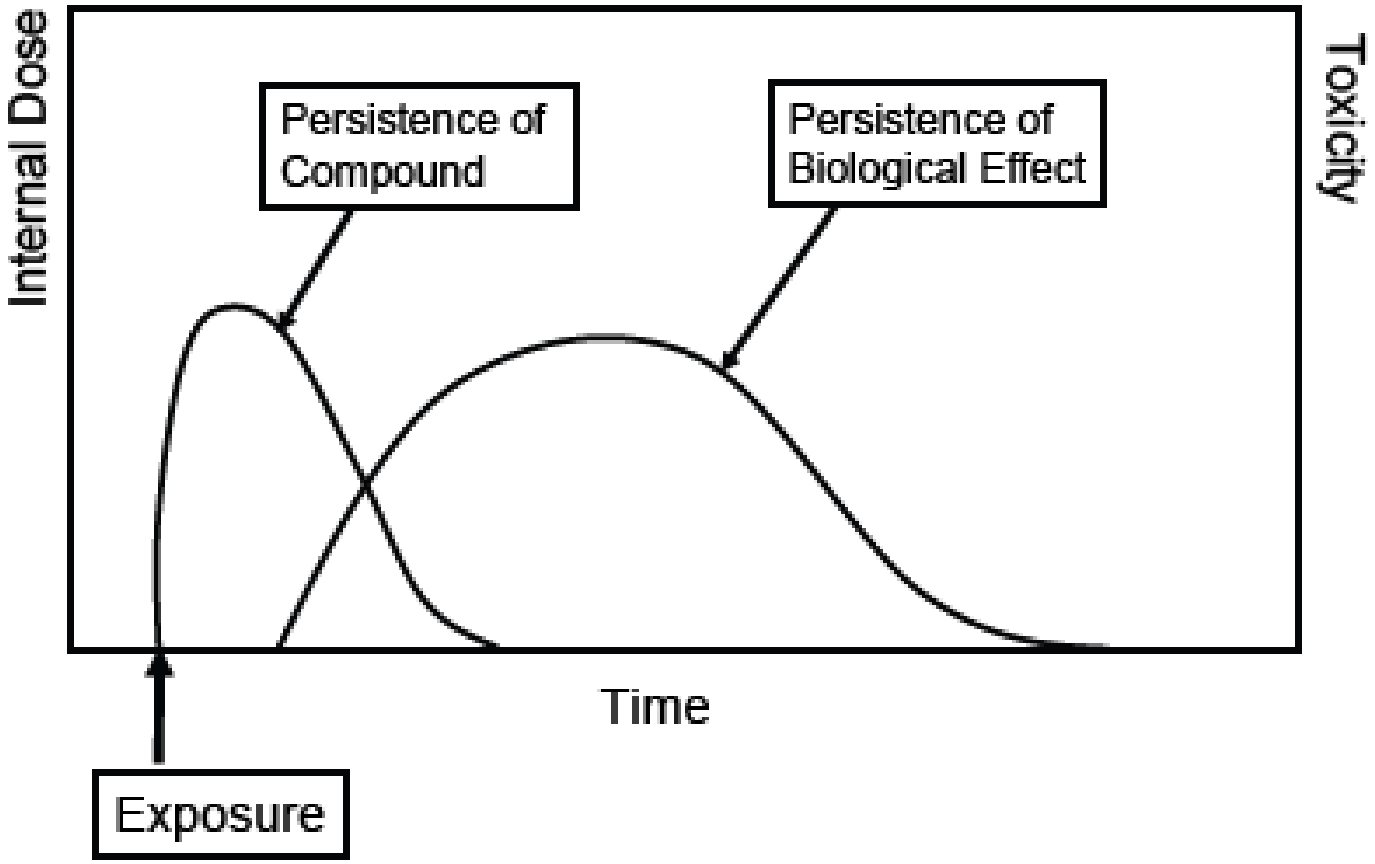
Persistence of effects beyond termination of chemical exposure:

- 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

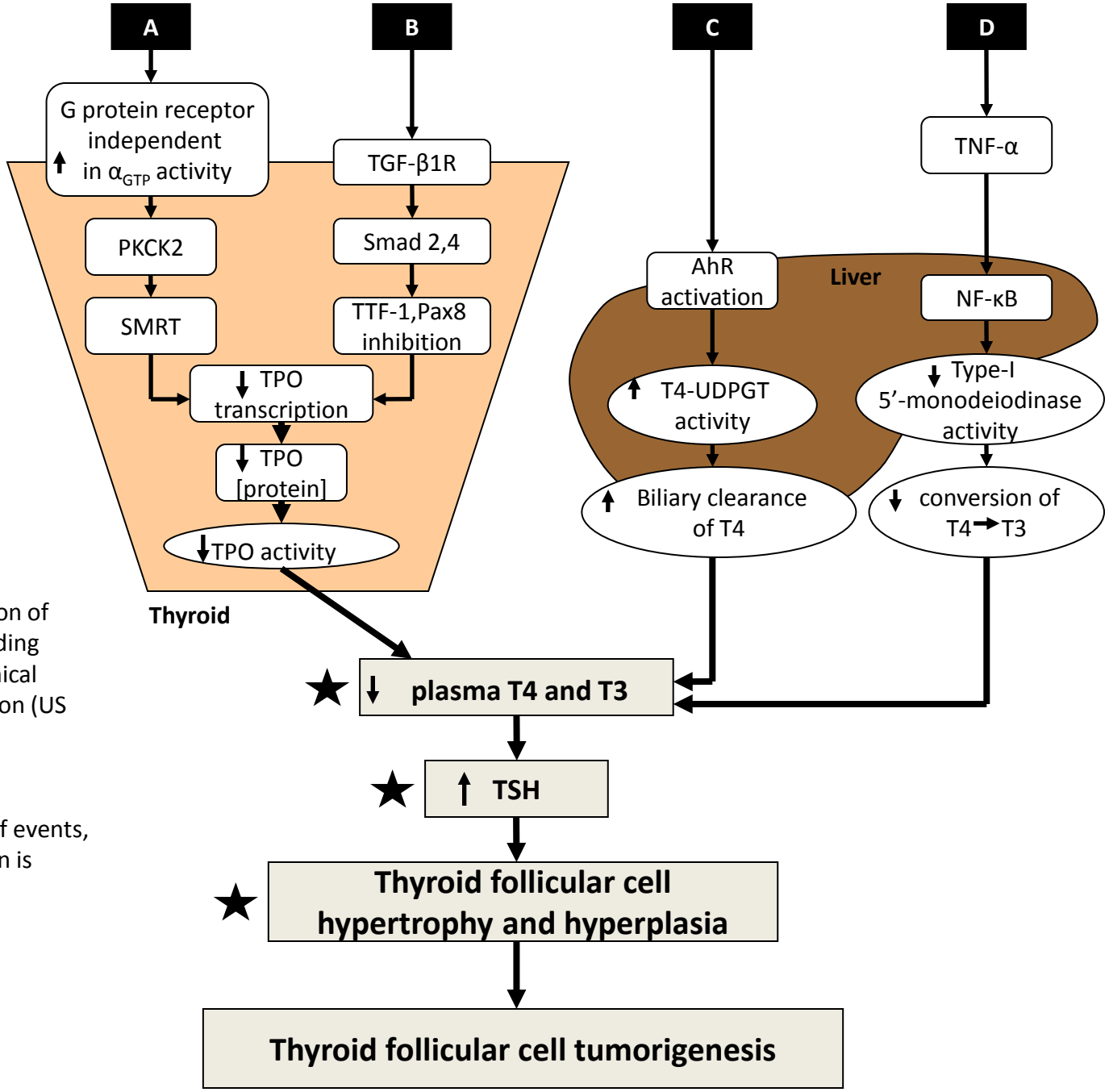
Persistence



2000 (ORD)

Mode-A series of key events and processes starting with interaction of an agent with a cell, and proceeding through operational and anatomical changes causing disease formation (US EPA Suppl. Mixtures Guidance).

Mechanism -A more detailed understanding and description of events, often at the molecular level, than is meant by mode of action.

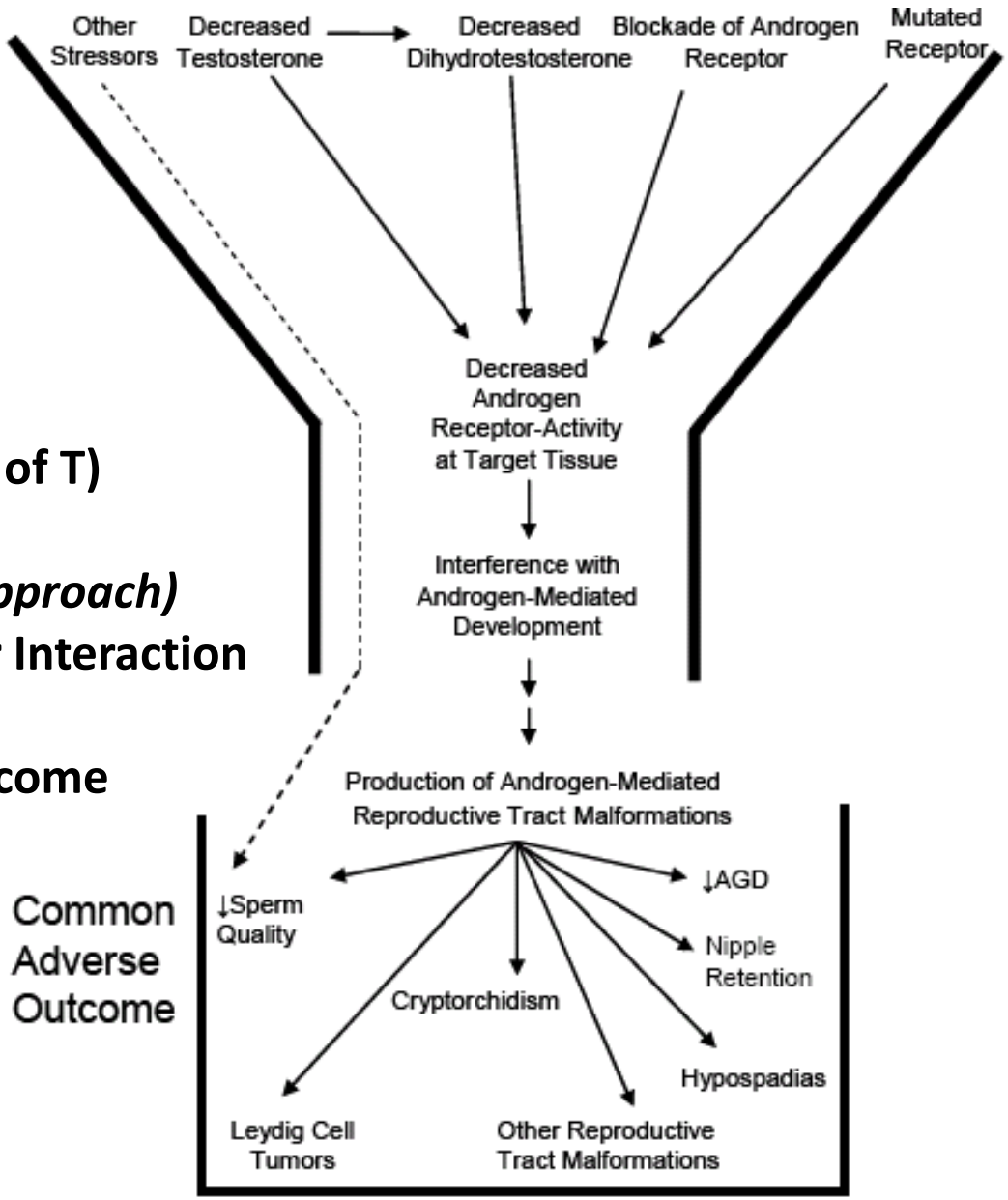


Similarity / Groupings: Options

By Mechanism of Action (e.g., decreased hydroxylation of T)

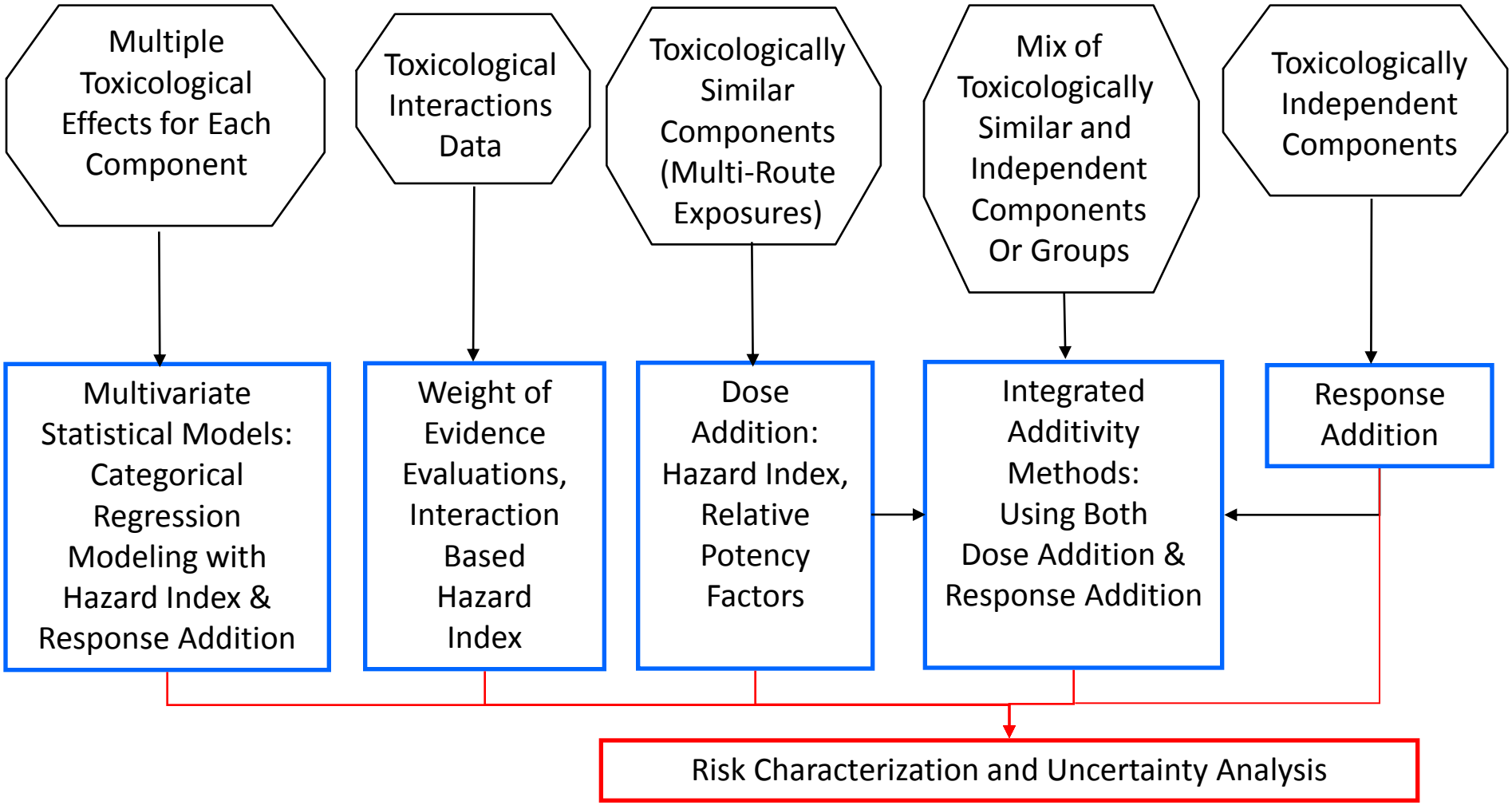
By Mode of Action *(Favored Approach)* Decreased Androgen-Receptor Interaction

By Target Tissue or Health Outcome



(Figure 3-4, NAS, 2008)

Component Based Methods for Chemical Mixtures Risk Assessment: Apply to Integrated Exposure/Toxicity Groups



Hazard Index (HI) Method (Based on Dose Addition)

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

Sums the exposure of each mixture component divided by an allowable level of that chemical. Interpreted as an indication of potential risk when HI $\geq$ 1

- In this case, the scaling factor t_i = (1 / RfD_i) for each chemical i, where RfD = NOAEL / Uncertainty Factors. Other toxicity-based scaling factors can be used.
- Same mode-of-action may be relaxed to same target organ
- Similarly shaped D-R curves not required
- Use at low exposures where interaction effects are unlikely

Hazard Index Approaches

Screening-Level
Hazard Index
Target Organ Toxicity Dose

Hazard Quotient, individual chemical
HQ = Exposure / Acceptable Limit

Hazard Index, sum of HQ values
for all components

Multiple Tissues Will Respond to Insult

Chemical	Developmental	Thyroid	Liver	Hematopoietic
A	5E-3 *	6E-3	8E-2	6E-3
B	6E-3	4E-3 *	2E-2	8E-3
C	Not Affected	4E-1	2E-3 *	4E-3
D	2E-2	5E-2	8E-3 *	1E-2
E	2E-2*	4E-2	4E-2	3E-2
F	1E-3	4E-3	6E-4*	8E-4
G	1E-1	4E-2*	8E-2	6E-2
H	Not Affected	8E-3*	8E-2	2E-2

*Reference Dose Value, Critical effect

**Reference Values are the Oral Reference Dose for the critical effect; and Target Organ Toxicity Dose, TTD, for effects other than the critical effect.

Screening Level Hazard Index Calculation*

Chemical	Exposure**	RfD**	Organ/Tissue	HQ
A	3E-3	5E-3	Developmental	0.60
B	2E-4	4E-3	Thyroid	0.05
C	8E-4	2E-3	Liver	0.40
D	1E-3	8E-3	Liver	0.125
E	7E-3	2E-2	Developmental	0.35
F	4E-5	6E-4	Liver	0.067
G	7E-3	4E-2	Thyroid	0.175
H	4E-4	8E-3	Thyroid	0.05
			Screening HI= 1.82	

*U.S. EPA (1989)-EPA/540/1-89/002

**Both exposure and RfD are in units of mg/kg-day

Hazard Index Calculation

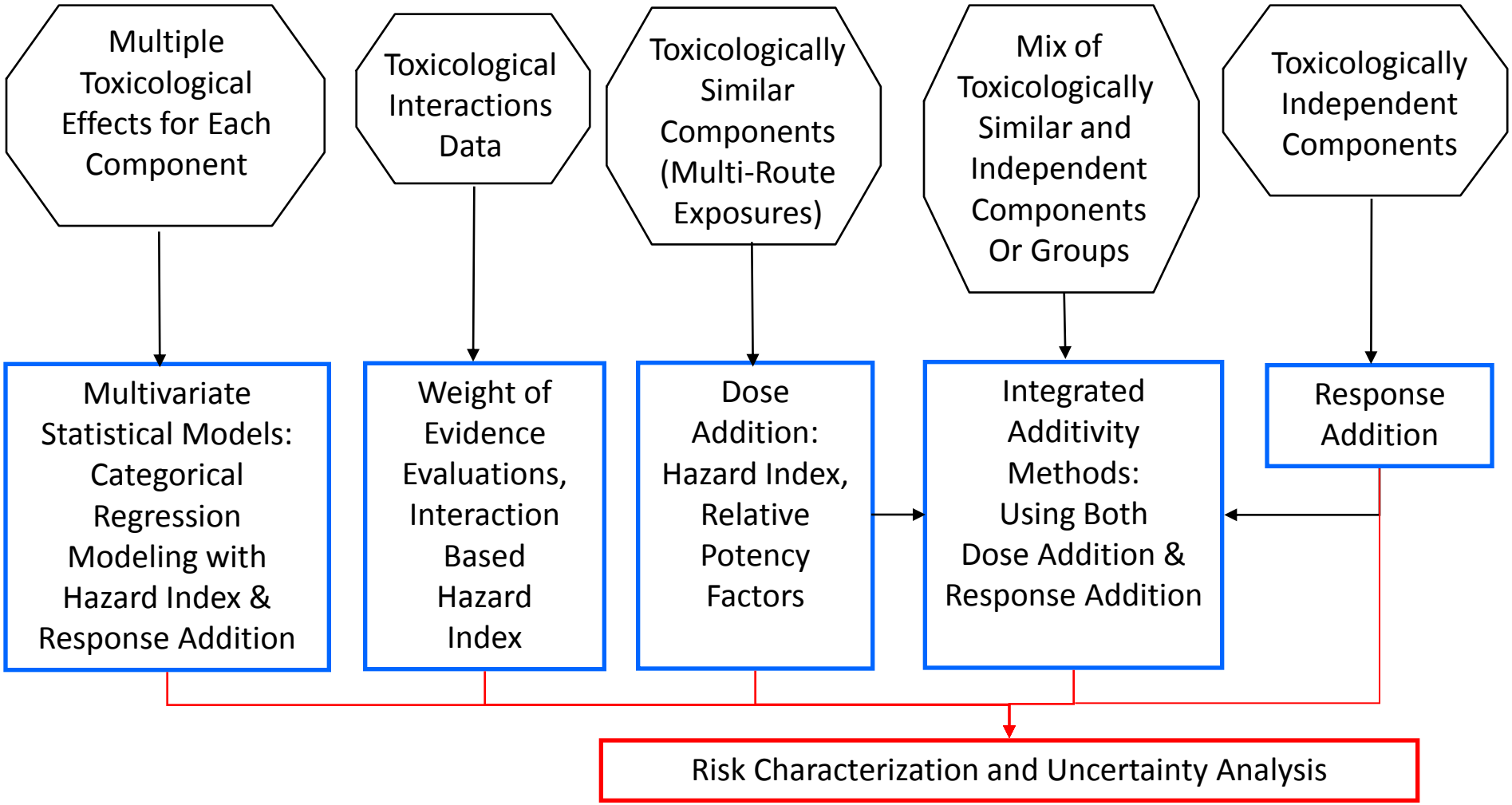
Chemical	Exposure**	RfD**	Organ/Tissue HQ			
			Developmental	Thyroid	Liver	Hematopoietic
A	3E-3	5E-3	0.60	-	-	-
B	2E-4	4E-3	-	0.05	-	-
C	8E-4	2E-3	-	-	0.40	-
D	1E-3	8E-3	-	-	0.125	-
E	7E-3	2E-2	0.35	-	-	-
F	4E-5	6E-4	-	-	0.067	-
G	7E-3	4E-2	-	0.175	-	-
H	4E-4	8E-3	-	0.05	-	-
		HI=	**0.95**	**0.28**	**0.59**	-

Target Organ Toxicity Dose Calculation

	Developmental			Thyroid			Liver			Hematopoietic		
Chem	TTD	Exp.	HQ	TTD	Exp.	HQ	TTD	Exp	HQ	TTD	Exp.	HQ
A	5E-3*	3E-3	0.60	6E-3	3E-3	0.50	8E-2	3E-3	0.0375	6E-3	3E-3	0.50
B	6E-3	2E-4	0.033	4E-3*	2E-4	0.05	2E-2	2E-4	0.01	8E-3	2E-4	0.025
C	N/A	8E-4	N.D.	4E-1	8E-4	0.002	2E-3*	8E-4	0.40	4E-3	8E-4	0.20
D	2E-2	1E-3	0.05	5E-2	1E-3	0.02	8E-3*	1E-3	0.125	1E-2	1E-3	0.10
E	2E-2*	7E-3	0.35	4E-2	7E-3	0.175	4E-2	7E-3	0.175	3E-2	7E-3	0.23
F	1E-3	4E-5	0.04	4E-3	4E-5	0.01	6E-4*	4E-5	0.067	8E-4	4E-5	0.05
G	1E-1	7E-3	0.07	4E-2*	7E-3	0.175	8E-2	7E-3	0.0875	6E-2	7E-3	0.12
H	N/A	4E-4	N.D.	8E-3*	4E-4	0.05	8E-2	4E-4	0.005	2E-2	4E-4	0.02
TTD= 1.14				**TTD= 0.98**			**TTD = 0.91**			**TTD= 1.25**		

*RfD Value
N/A = developmental effects not indicated in the absence of maternal toxicity
N.D. = calculation of TTD for this chemical/endpoint not warranted, value is zero

Component Based Methods for Chemical Mixtures Risk Assessment: Apply to Integrated Exposure/Toxicity Groups



Dose Addition Theory: Relative Potency Factors

Assuming same mode-of action, similarly shaped D-R curves, for exposure to a mixture of n chemicals:

$$Rm = f_1\left(\sum_{i=1}^{n}\left(D_1 + t_i * D_i\right)\right)$$

Interpreted as:
mixture response = sum(doses scaled for relative potency), evaluated using the dose-response curve of the index chemical 1

Where: R_m = mixtures response
D_i = exposure dose of chemical i
t_i = potency of chemical i relative to chemical 1
f_1 = d-r curve for the index chemical 1

Relative Potency Factor (RPF) Method

Given that mixture risk (Rm) is:

$$R_m = f_1\left(D_1 + RPF_i * D_i\right),$$

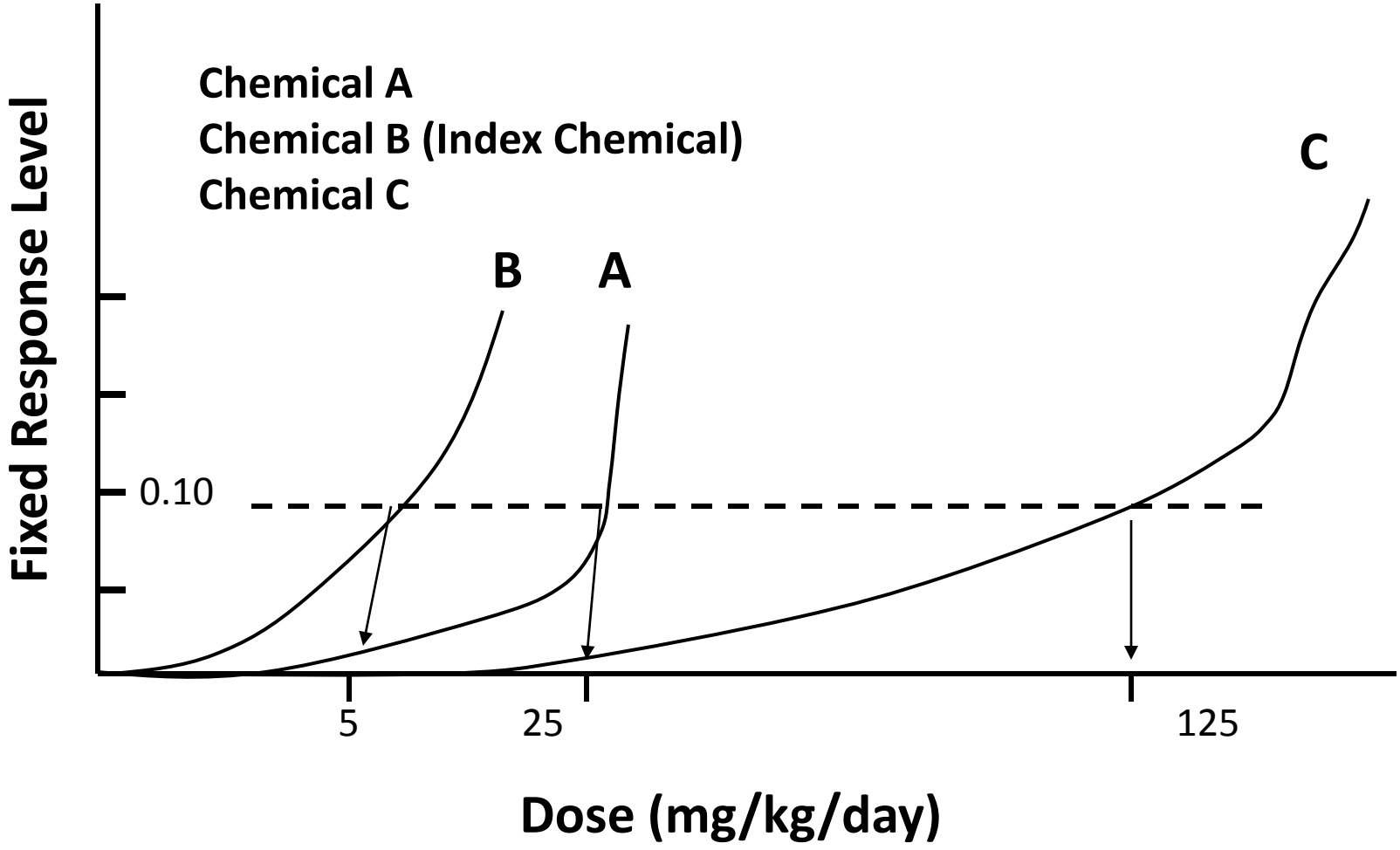
for a given chemical i with Dose (D_i) and Index Chemical 1 at Dose D_1, the RPF_i may be estimated as a ratio of equally toxic doses of the 2 chemicals, e.g.,

$$RPF_i = \left(\frac{ED_{10}(IndexChemical)}{ED_{10}(Chemical\,i)} \right)$$

Note: EDx = the "Effective Dose" at which an x% response is observed. This method can be extended to evaluate mixtures of many chemicals.

The sum of the scaled doses forms the Index Chemical Equivalent Dose (ICED). The ICED is evaluated using the dose response information of the Index Chemical.

Relating Potency: Rat Toxicity Studies

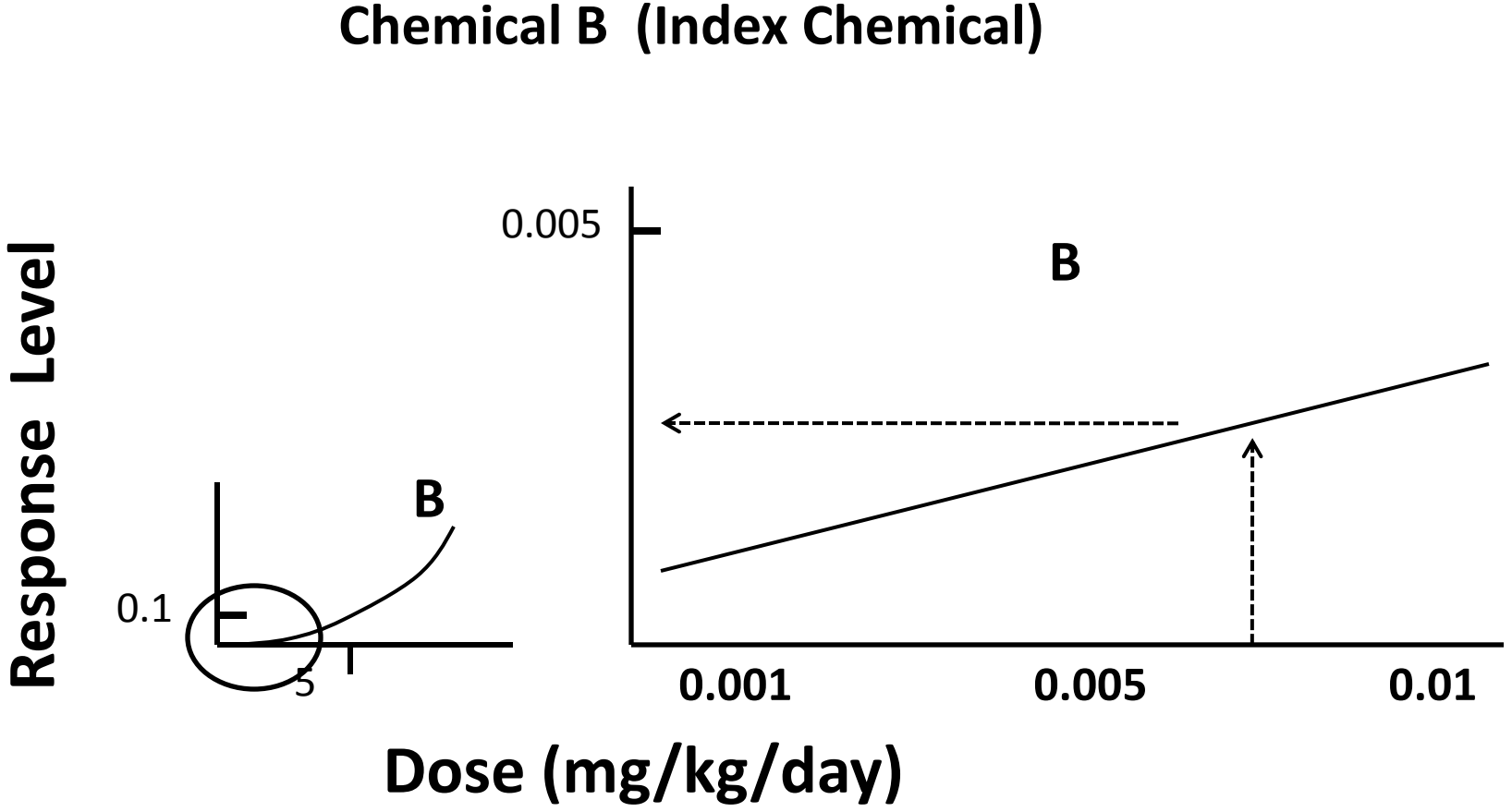


Computing Relative Potency

Fixed response level, same measurement technique

Chemical	Rat ED 10 Oral Dose	RPF Oral Dose	Human Dose (mg/kg/day)	ICED*** (mg/kg/day)	% of Subgroup ICED
A	25	5/25 = 0.2	0.002	0.0004	5
B Index Chemical	5	5/5 = 1	0.005	0.005	67
C	150	5/150 = 0.03	0.07	0.0021	28
			Total ICED	0.0075	

Estimate Mixture Response



Response Addition Method

$$R_m = \sum_{i=1}^{n} r_i$$

Where:

R_m = mixtures risk

n = number of components

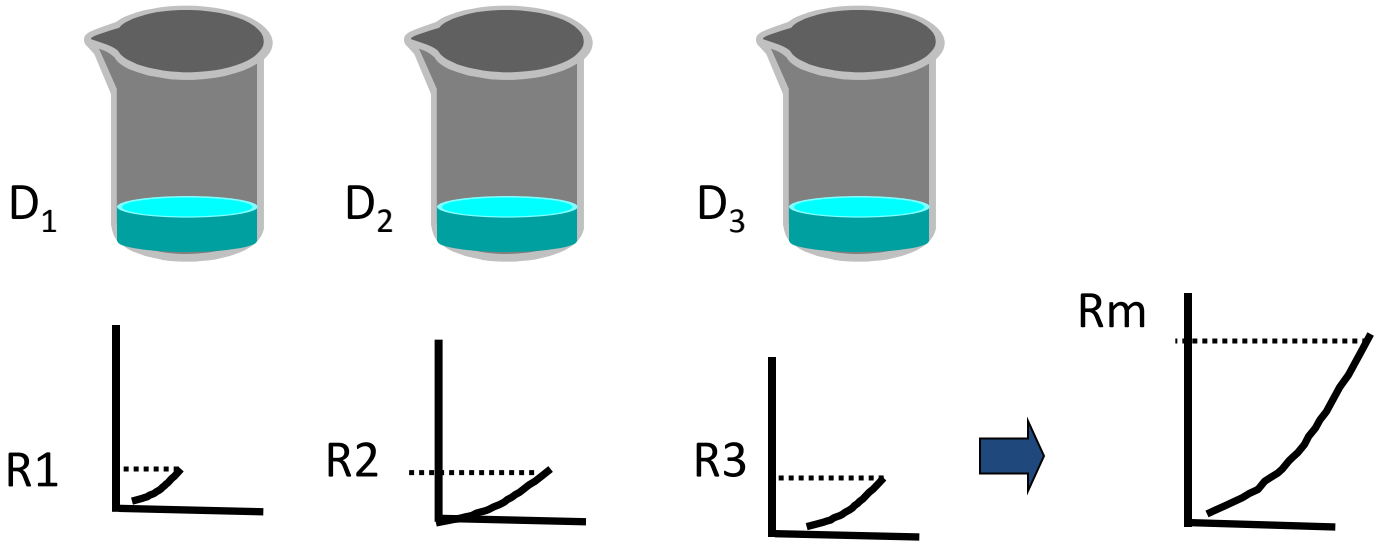
r_i = component risks

Assumes biological and statistical independence of action

Use is appropriate at low doses where

- interaction effects are less likely, and
- risks are small, so cross-products are negligible

Response Addition: How to Estimate Response?

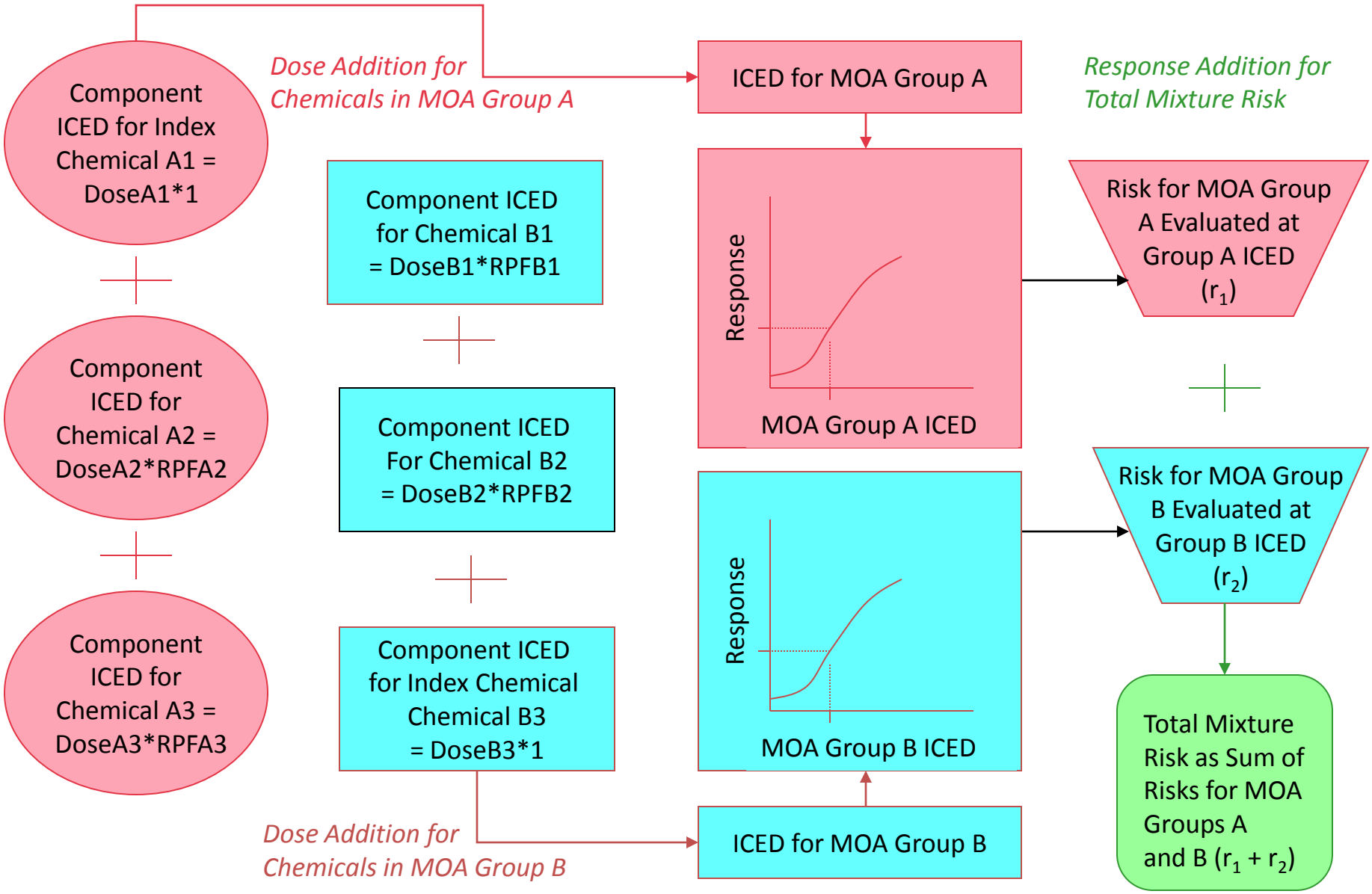


Response Addition:

Independence of Action

$$Rm = f_1(D_1) + f_2(D_2) + f_3(D_3) = R_1 + R_2 + R_3$$

Cumulative RPF Analysis - Sum MOA Groups A and B Risks



U.S. EPA, 2003

In Conclusion, CRA ……

- Is solidly based on Mixtures Toxicology concepts and practice,
- Is established and the practice is codified,
- Addresses population (community) -based risk,
- Requires exposure assessment and dose-response data,
- Optimally includes information on mode of action,
- Can characterize or confirm susceptibility,
- Can identify major agents or sources for remediation, and
- Can be an effective tool to prioritize community-based health improvement activities.

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