# Uncertainty in Mixtures and Cumulative Risk Assessment

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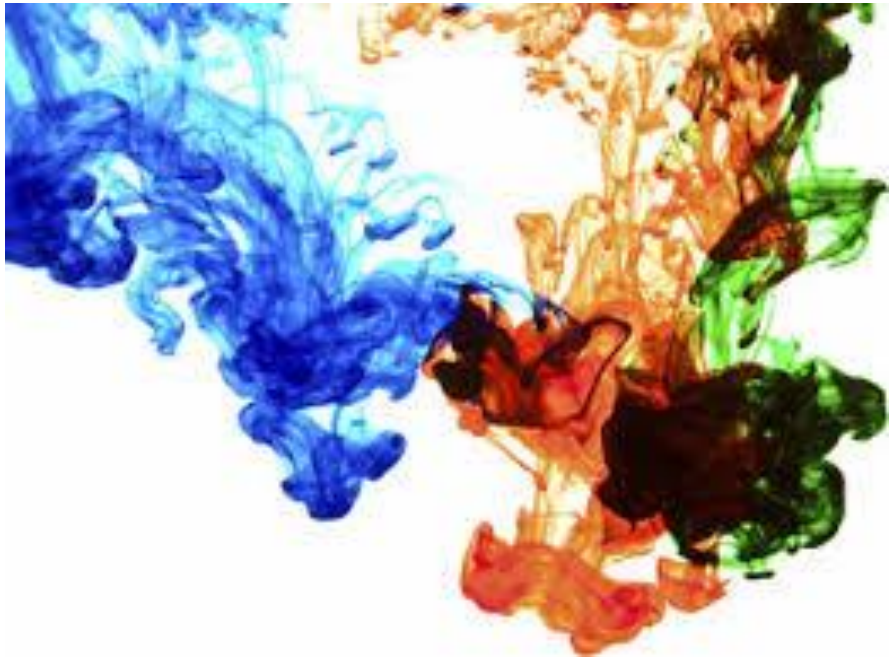
Natural Resources
Goods Production
Economic Interests
Public Health
Ecosystems


Chemicals & Chemical Mixtures

- Additives
- Byproducts
- Contaminants

Exposures
Species
Populations

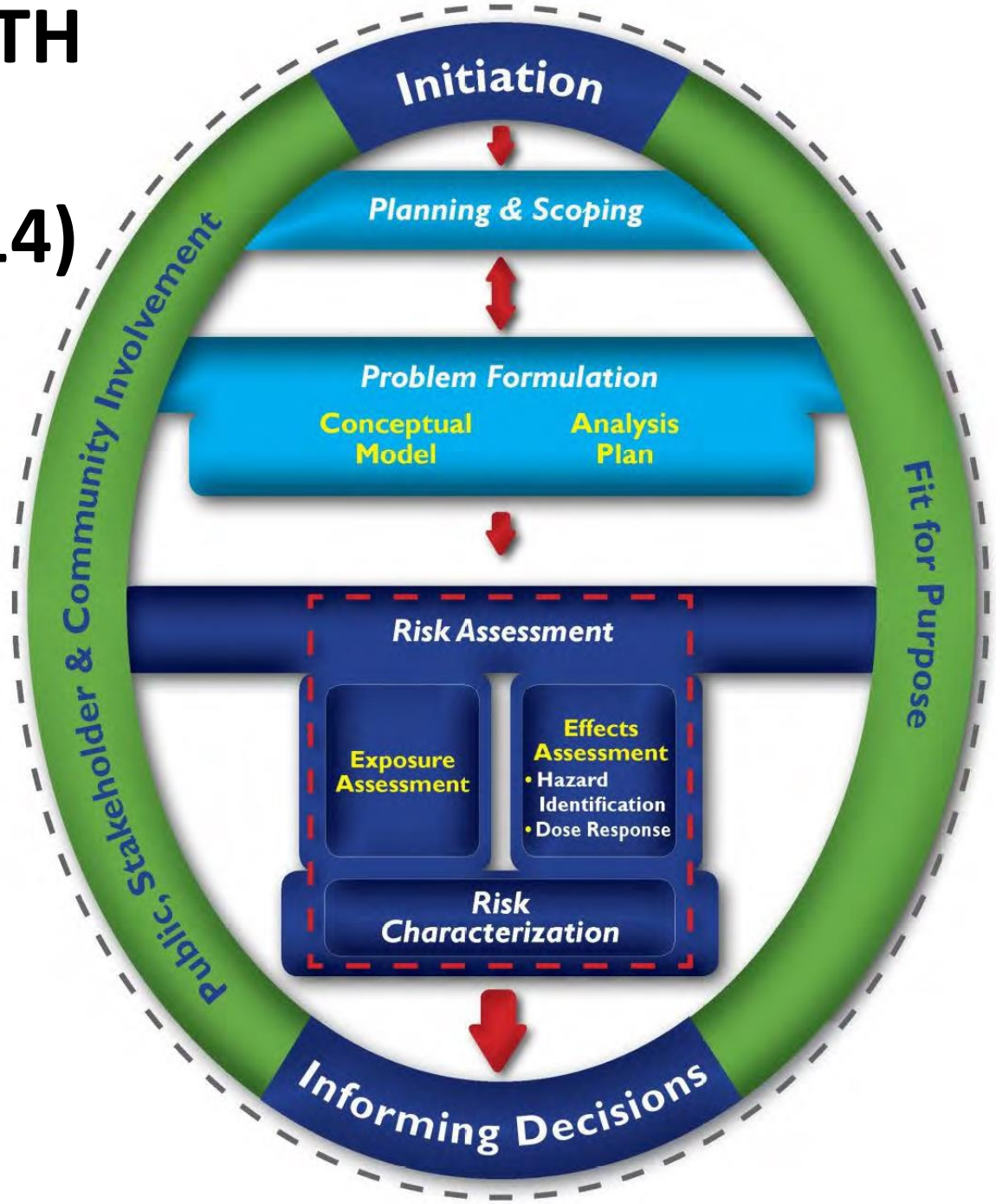


# FRAMEWORK FOR HUMAN HEALTH RISK ASSESSMENT TO INFORM DECISION MAKING (U.S. EPA, 2014)

RISK ASSESSMENT:
Exposure Assessment
Effects Assessment
- Hazard Identification
- Dose Response
  - Data
  - Science Policy Decisions
  - Models
  - Multiple Chemicals, Mixtures

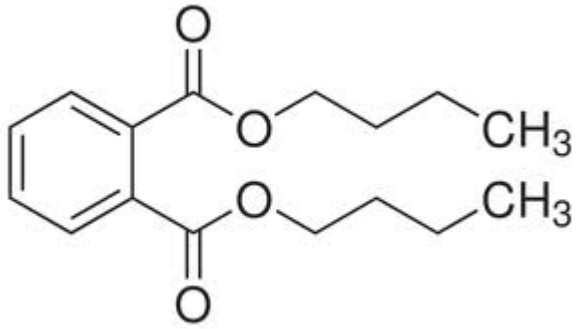
Risk Characterization

http://www.epa.gov/raf/frameworkhhra.htm



## Ecological Risk Assessment

## Human Health Risk Assessment




# Uncertainty *versus* Variability

**<u>Uncertainty</u> is a property of the observer, may be reduced by additional research, but cannot be verified**

**<u>Variability</u> is a property of nature, cannot be reduced by additional research, but can be verified and estimated with greater accuracy**

**Some sources of uncertainty:**

- **Conceptual model – problem formulation**
- **Information & data – resources may constrain availability**
- **Stochasticity – level of certainty regarding natural variability**
- **Error – in experimental design or data analysis procedures**

# Human Health Risk Assessment
# Toxicity Testing

**Risks to human population**

**Reference Value = POD / UF**

**Sensitivity of Effect**

Critical Effect

Secondary Effect

Mortality

**Likelihood of Effect**

Relevant Species
Relevant Response
Relevant MOA

Point of Departure

$BMD_L$
NOAEL
LOAEL

$UF_A$
$UF_H$
$UF_S$
$UF_L$
$UF_D$

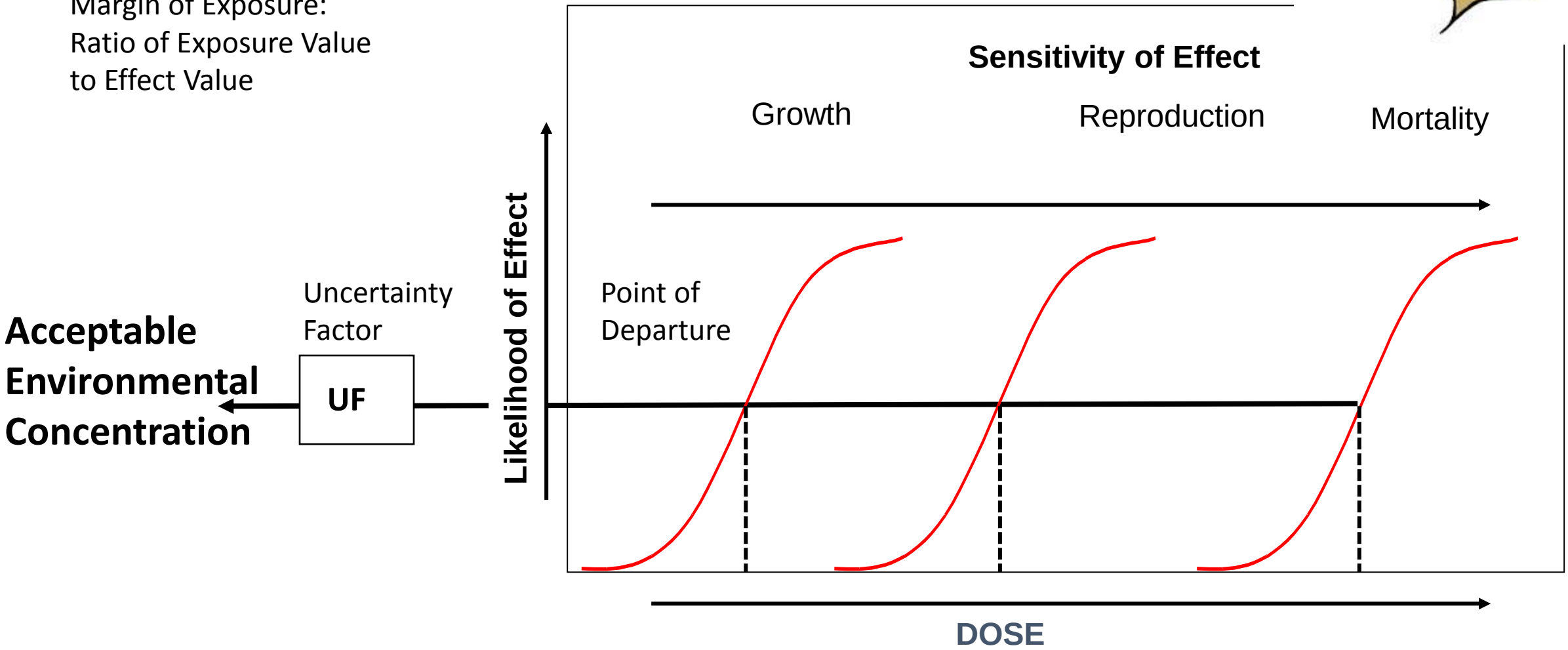
**Human Exposure Limit**

**DOSE**

# Ecological Risk Assessment
# Toxicity Testing

**Population and community risks**

Margin of Exposure:
Ratio of Exposure Value
to Effect Value



# Uncertainties in Mixtures Risk Assessment

Are we focused on …

The correct chemical or mixture?

- Whole mixture?
- Similar mixture?
- Component data?

A sensitive or representative species?

A/the sensitive (critical) effect?

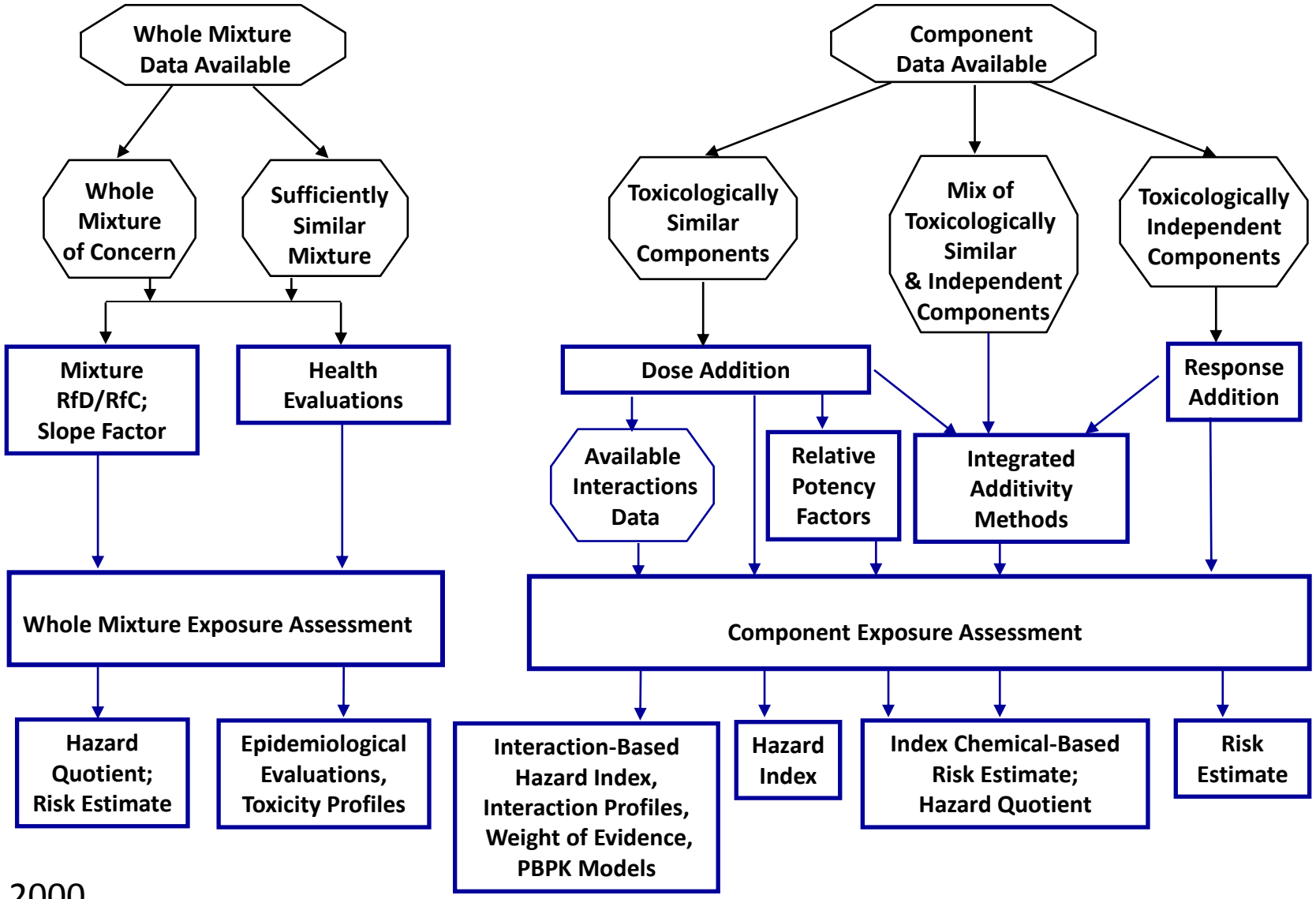
- In a sensitive life stage?
- For a duration representative of a lifetime exposure?
- At an appropriate response level?

# Uncertainties in Mixtures Risk Assessment

What do we know about …

Concentrations of multiple chemicals in the environmental media?
Contact with the environmental medium?
Temporal fluctuations in environmental concentrations?
The impact of fluctuations on exposure and toxicity?
Durations of exposure?
Necessity of duration adjustments?
Absorption, bioavailability, bioconcentration?
Dose additivity?

# Flow Chart for Evaluating Chemical Mixtures




Adapted from U.S. EPA, 2000

# Dose Additive Models

Hazard Index Approaches

- Exposure / Acceptable Exposure Limit
- Exposure data for components
- Response data for components

Relative Potency Factor Approaches

- Based on Point of Departure
- Index Chemical
- Similarity of effect(s)
- Exposure data for mixture
- Response data for components
- Quantify potency at fixed response level

# Relative Potency Factor Formula

Index Chemical Identified: overall representativeness, data completeness

RPF formula for expressing the mixture dose in terms of the index chemical:

$$D_m = \sum_{i=1}^{n} [RPF_i \times D_i]$$

where,

$D_m$ = mixture dose expressed as dose of index chemical (index chemical equivalent dose = ICED)

$D_i$ = dose of the $i^{th}$ mixture component (i = 1,…,n), and

$RPF_i$ = toxicity proportionality constant relative to index chemical for the $i^{th}$ mixture component (i = 1,…,n)

# Formula for Mixture Risk using RPF Values

$$R_m = f_1 (D_m)$$

where,

$R_m$ = risk posed by chemical mixture

$f_1$ (*) = dose-response function of index chemical

$D_m$ = mixture equivalent dose as index chemical

**Choice of Index Chemical:**

- **How good is the dose-response function, $f_1$ ?**
- **How similar are the other chemicals to the index chemical?**

# Hazard Index

Hazard Index = Σ HQ; HQ = E / AL

E = Exposure (Concentration, duration, absorption)

AL = Acceptable Exposure Limit (POD / UF)

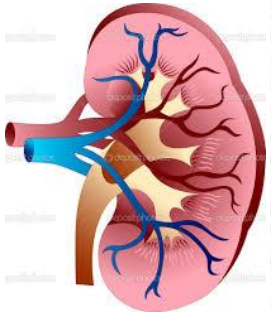
There is No Index Chemical

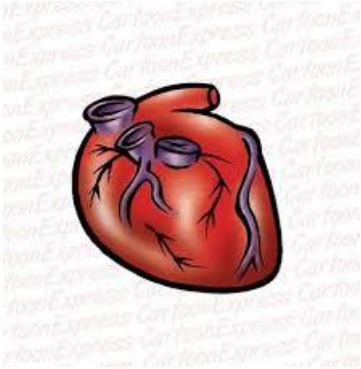
**Screening Hazard Index**

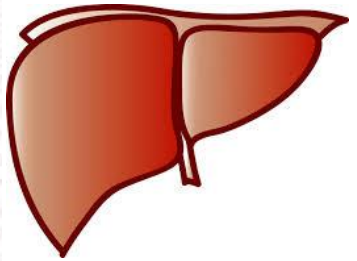
- Single critical effect

**Hazard Index**

- Single critical effect
- Segregated by organ







**Target Organ Toxicity Dose**

- Critical & Secondary effects
- Segregated by organ

# Mixtures Uncertainty Factor

**In some regulatory settings, it may be deemed desirable to derive exposure standards that … take account of cumulative exposures. In such cases, tolerable daily exposures to individual chemicals could be corrected downward by incorporating an additional "mixture uncertainty factor." The additional uncertainty factor would have to take account of the number of chemicals to which simultaneous effective coexposure is deemed likely (NAS, 2008; p. 133).**

- **There are unique uncertainties associated with mixtures.**
- **Additivity Approaches rely on single chemical RFVs. These are generally developed to be conservative estimates of risk.**
- **Exposure assessments are often conservative (e.g., drinking water consumption rates).**
- **Inputs to additivity models appear to be sufficiently conservative.**

U.S. National Academies of Science. Phthalates and cumulative risk. National Research Council, National Academies press, Washington, D.C., 2008.

# Conclusions

Human/ecological exposure: concentration, duration, bioavailability

Experimental species: relevant, sensitive

Experimental endpoint: representative, protective, sensitive

Experimental exposures:  representative of real-world exposures

Preference: Whole mixture, similar mixture, component data

- Availability of Mode of Action information
- Choice of additivity models