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Cancer Risk Assessment for Chemical Mixtures at US EPA

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Office of Research and Development
National Center for Environmental Assessment

United States Environmental Protection Agency

Outline

1. Risk Assessment: Overview for Chemicals in Environment

2. Cancer Risk Assessment at EPA: Brief Overview
   A. Hazard Identification
   B. Dose-response Assessment

3. Component Methods for Cancer Assessment of Chemical Mixtures
   A. Mixture Components with same MOAs (Dose Addition)
   B. Mixture Components with Different MOAs (Response Addition)

Risk Assessment

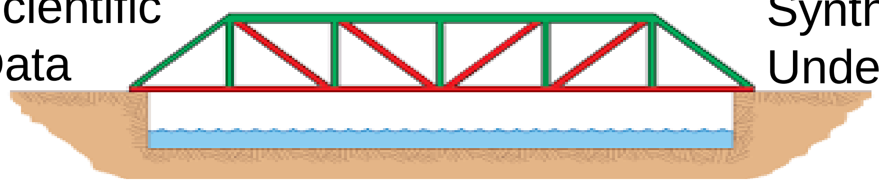
Systematic analysis, determines existence and extent of hazards to human health (outcome & magnitude), given available data

Goal: inform decision makers

- appropriately frame problem, identify relevant data
- clarify issues, scope assessment
- conduct assessment, characterize confidence (uncertainty)

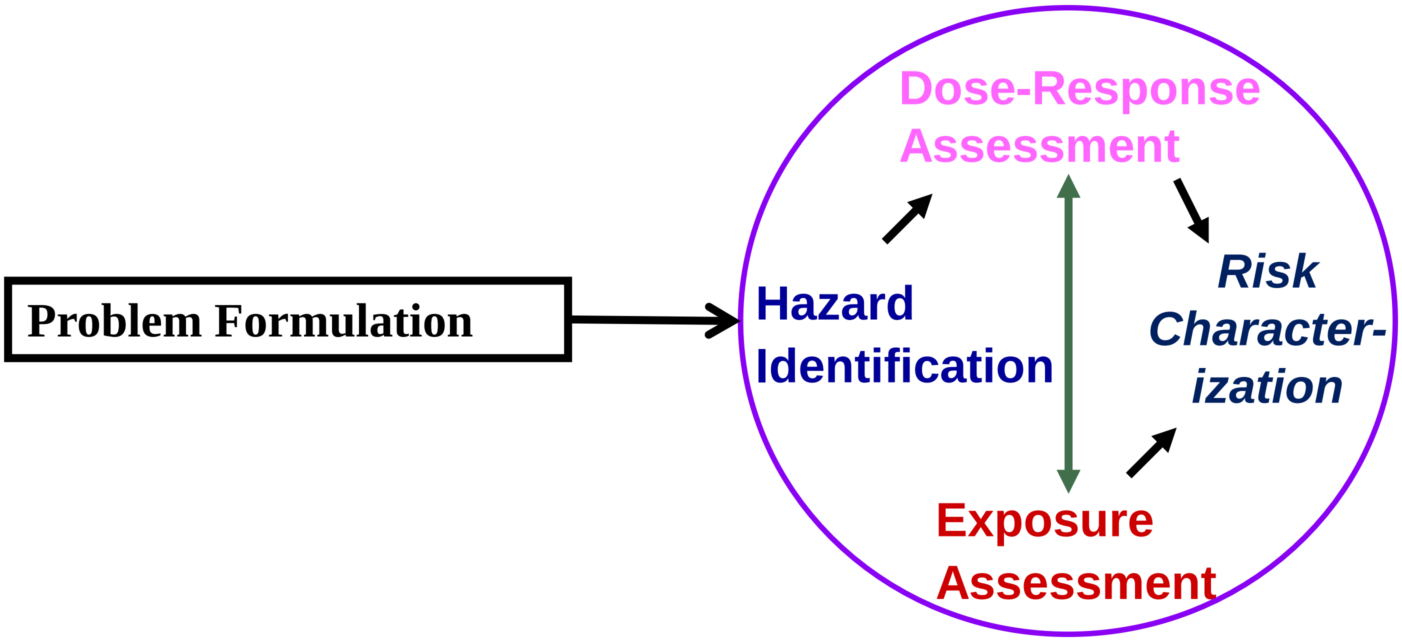
EPA decision-making typically informed by single stressor risk assessments

- Follow EPA statutes and guidelines



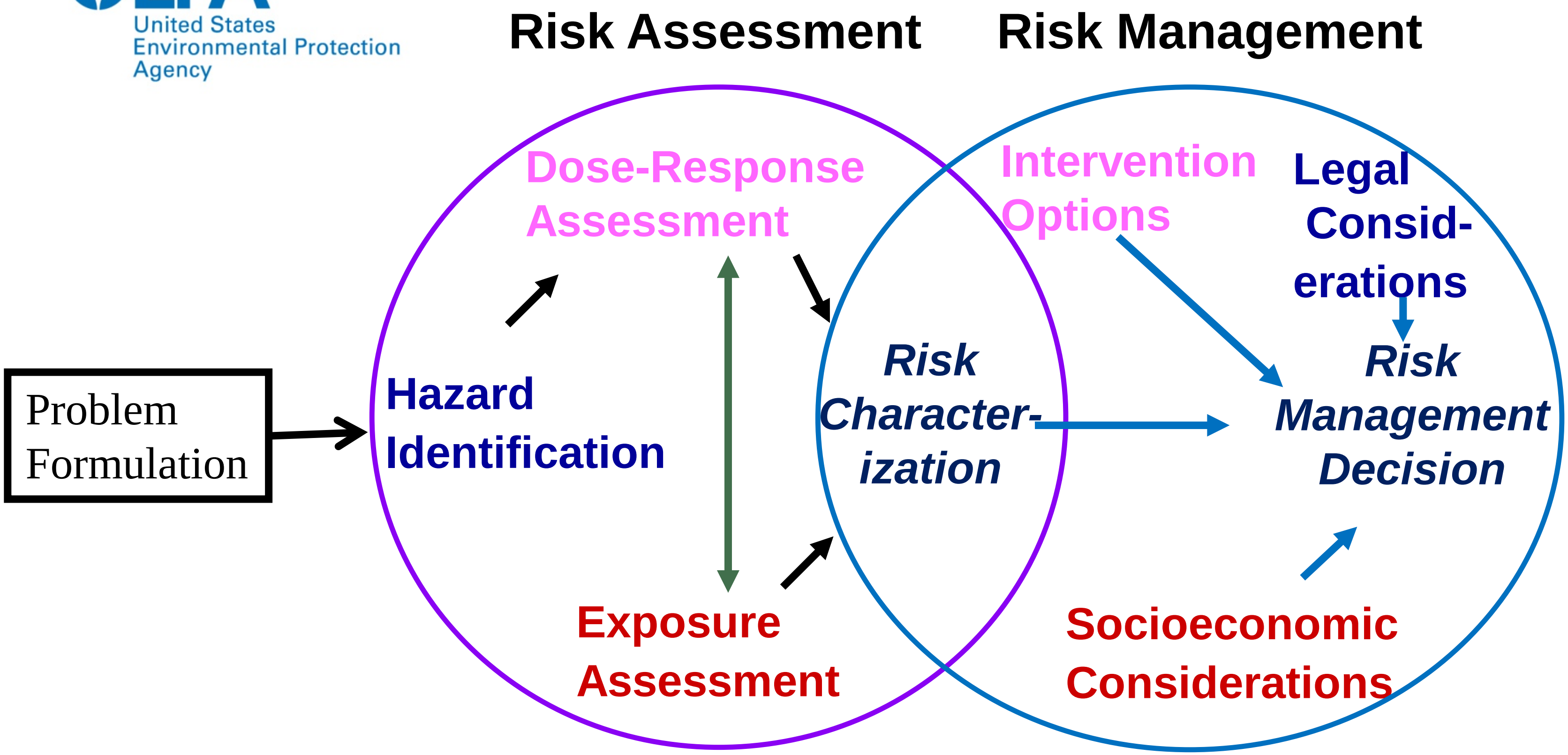
Sources: Society of Risk Analysis. Definitions
National Research Council. 1983. Risk assessment in the federal government. Managing the process. National Academy Press, Washington, DC

Human Health Risk Assessment Paradigm



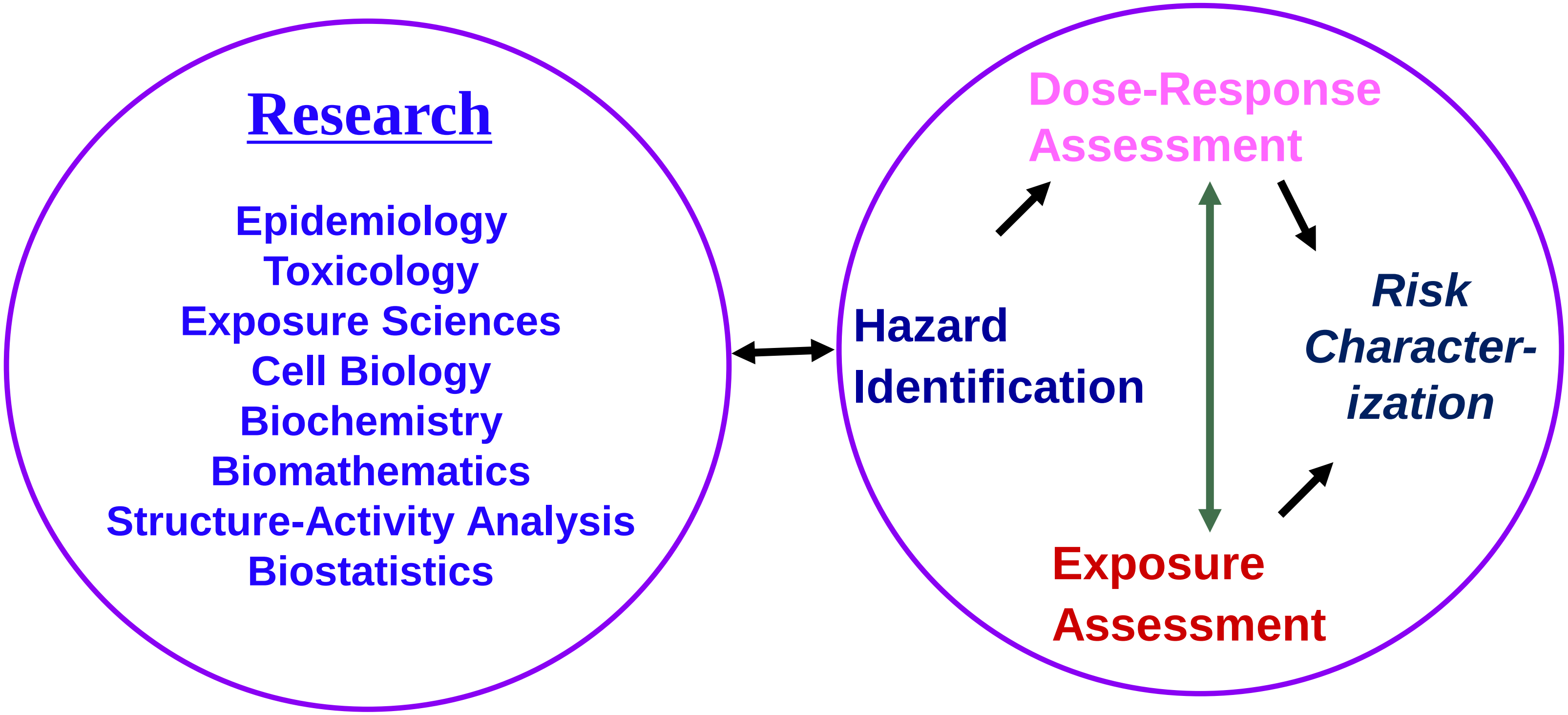
National Research Council. 1983. Risk assessment in the federal government. Managing the process. National Academy Press, Washington, DC
US EPA 1998. Ecological Risk Assessment Guidelines

Decision Context of Risk Assessment



- Undertake assessments to determine if intervention needed and identify points where intervention could reduce likelihood of biological response
- Typical environmental and occupational interventions target release (e.g., vehicle emissions) or human contact with hazardous compounds (e.g., respirators, soil removal)
- Manufacturers identify hazardous chemicals used/formed/released in industrial processes with a risk management goal of reducing or eliminating them

Research Context of Risk Assessment



- Risk assessments rely on information from basic and applied sciences
- Risk assessments can identify needed research; provide context to its importance

Cancer Assessment for Chemicals at EPA: Overview

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Hazard Identification (Evaluate Data)

Animal or human

Exposure route

Exposure duration

Age

Gender

Confounders

Species and strain

Characterize Dose-Response Relationship

Conduct dose-response modeling

Identify critical effect level

Identify point of departure

Calculate Risk Values

Oral Slope Factor

Inhalation Unit Risk

EPA Hazard Identification for Carcinogenic Effects

Broadly, 3 sources of data:

(1) human data (primarily epidemiological);
(2) experimental animal bioassay data, primarily long-term; and
(3) supporting data e.g., short-term tests of genotoxicity and other relevant properties, pharmacokinetic & metabolic studies, mechanistic studies and SAR studies

EPA integrates information from these sources to characterize weight-of-evidence (WOE) regarding chemical's carcinogenic potential in humans for each relevant exposure route

WOE includes narrative and categories

EPA 5 standard WOE categories for carcinogens:

- Carcinogenic to Humans
- Likely to be Carcinogenic to Humans
- Suggestive Evidence of Carcinogenic Potential
- Inadequate Information to Assess Carcinogenic Potential
- Not Likely to be Carcinogenic to Humans

US EPA 2005 Guidelines for Carcinogen Risk Assessment

EPA Approach: Cancer Dose-response Assessment

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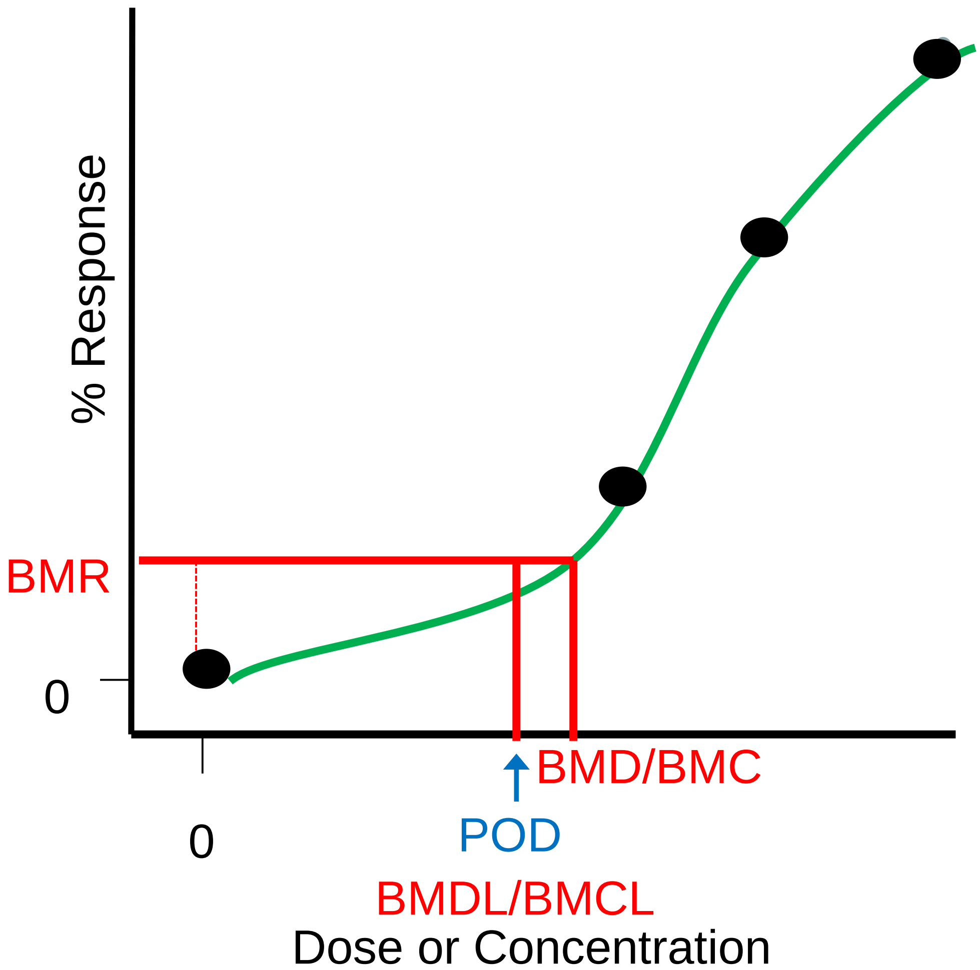


1. Conduct dose-response modeling
   Benchmark Dose Software
   Translate animal dose to a human equivalent dose (HED)
   [*not depicted in diagram*]

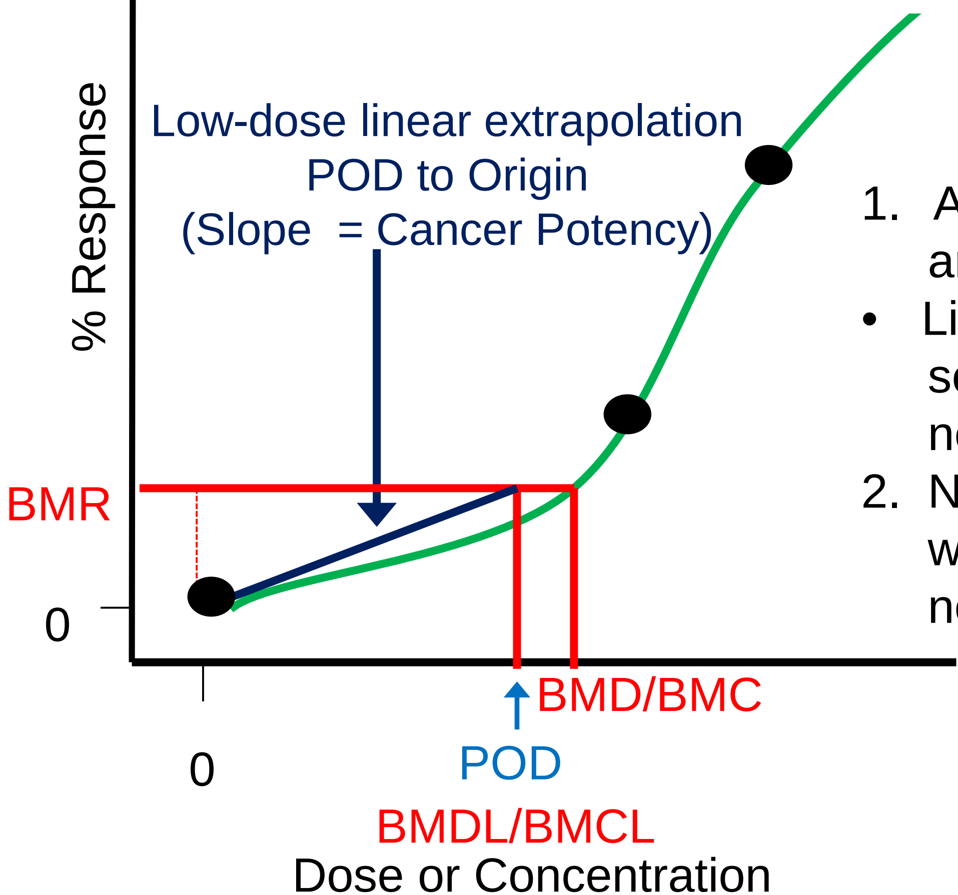
2. Identify critical effect level
- ED_{10} dose that causes 10% increase in tumor incidence
- LED_{10} lower 95% confidence limit on ED_{10}

3. Identify Point of Departure: LED_{10}

EPA. 1986. Guidelines for Carcinogen Risk Assessment. 51 FR 33992-34003
EPA. 2005. Guidelines for Carcinogen Risk Assessment. 70 FR 17765-17817

EPA Approach: Cancer Dose-response Assessment (2)

EPA Cancer Guidelines: developing a chemical's cancer dose-response function depends on what is known about carcinogenic mode of action and cancer dose-response curve shape



1. Assume linear approach when MOA is anticipated to be linear (e.g., DNA reactivity)
   - Linear approach used as a matter of science policy if carcinogenic MOA is not well understood
2. Nonlinear approach is appropriate when evidence sufficient to support a non-linear MOA

EPA. 1986. Guidelines for Carcinogen Risk Assessment. 51 FR 33992-34003
EPA. 2005. Guidelines for Carcinogen Risk Assessment. 70 FR 17765-17817

Chloroform Oral Cancer Assessment

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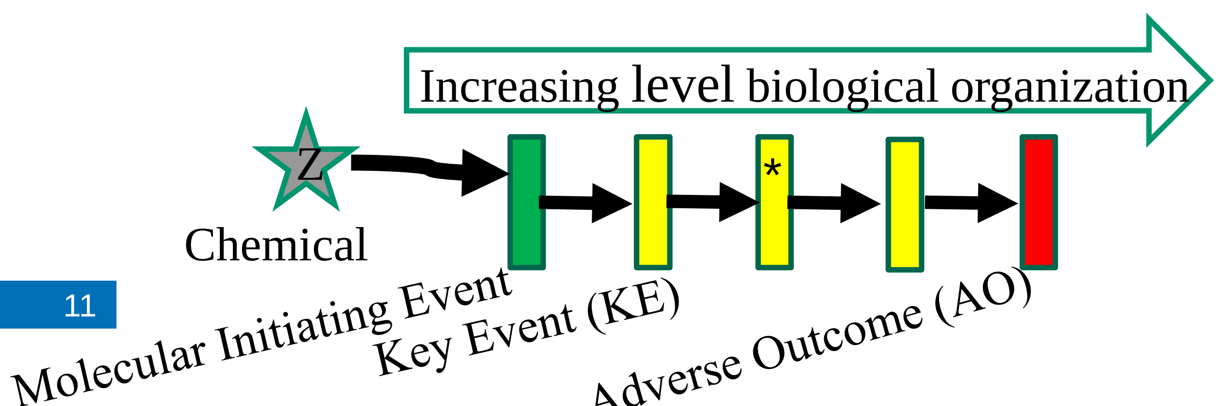
Several chronic bioassays: significantly increased incidence of liver tumors in mice (both sexes) and kidney tumors in male rats and mice

Carcinogenic MOA - reasonably well understood
- Not strong mutagen; unlikely produces rodent tumors via genotoxic MOA (ILSI,1997)
- Strong evidence: carcinogenic responses observed in animals associated with cytolethality/regenerative hyperplasia; only observed at doses above Reference Dose
- Doses below RfD do not result in cytolethality; no increased cancer risk
- Nonlinear approach considered "most appropriate" for cancer dose response

RfD (0.01 mg/kg-day) protects against noncancer effects (including cytolethality and regenerative hyperplasia) and against increased cancer risk



* If, in a well understood MOA, a KE does not occur below a certain dose, potential candidate for nonlinear approach

EPA. 2001. Toxicological Review of Chloroform

Risk Characterization: Cancer Risk

$$\text{Cancer Risk (Oral)} = \text{LADD}\left(\frac{mg}{kg-day}\right) \times \text{Oral Slope Factor}\left(\frac{mg}{kg-day}\right)^{-1}$$

LADD	Lifetime Average Daily Dose (mg/kg-day)
Oral Slope Factor	Proportion of population affected per (mg/kg-day)
Cancer Risk	Unitless

- Oral Slope Factor a plausible upper-bound estimate of cancer risk (i.e., the actual risk is likely lower)
- As oral slope factors include unquantifiable assumptions about effects at low doses, their upper bounds are not true statistical confidence limits
- Generally used in low-dose region of dose-response relationship, e.g., exposures correspond to risks less than 1 in 100 (e.g., 1 in 10,000)

Assessing Carcinogenesis

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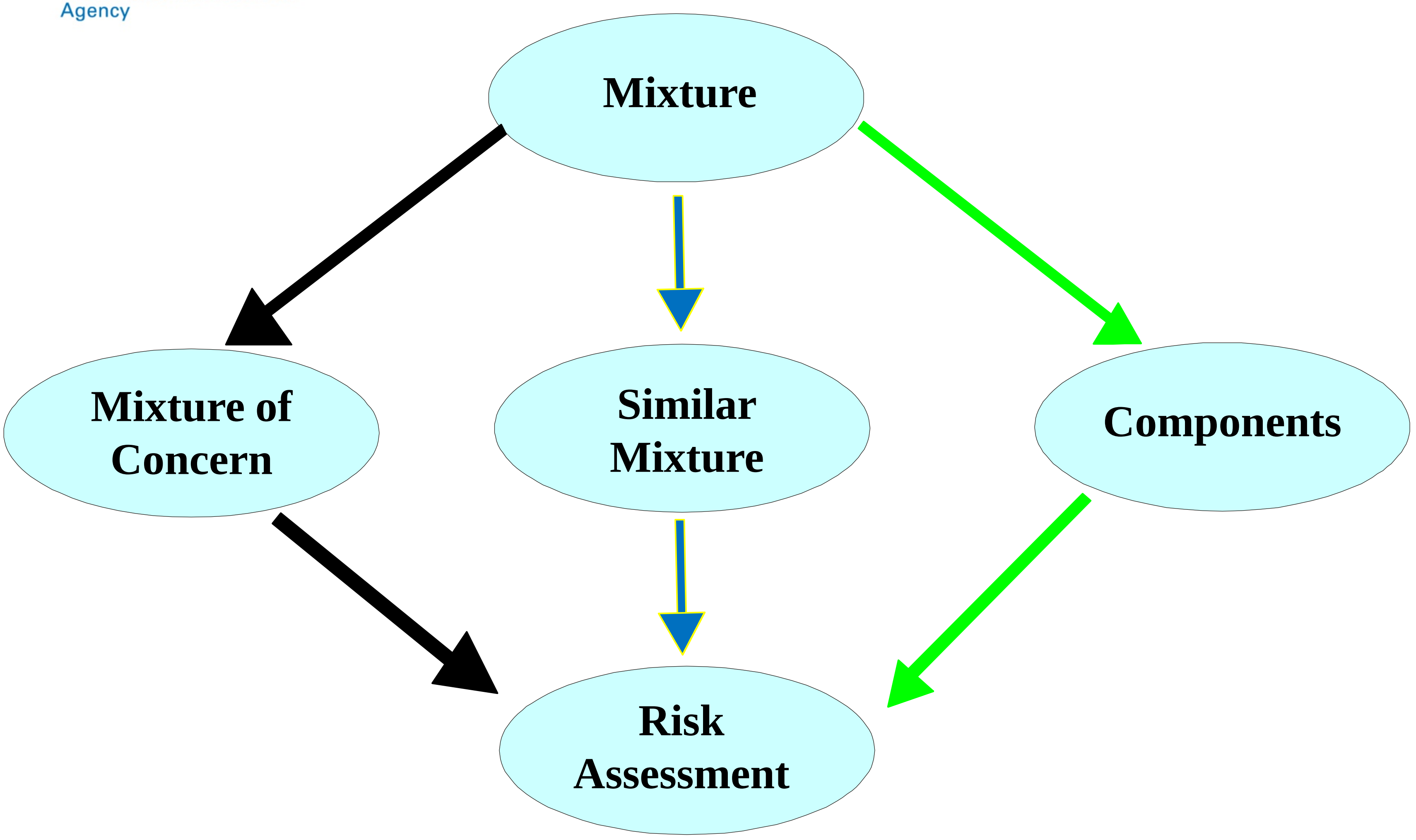
Qualitative Assessment of Risk

- **Weight-of-Evidence Narrative**
- **Weight-of-Evidence Descriptors**

Quantitative Estimates of Risk

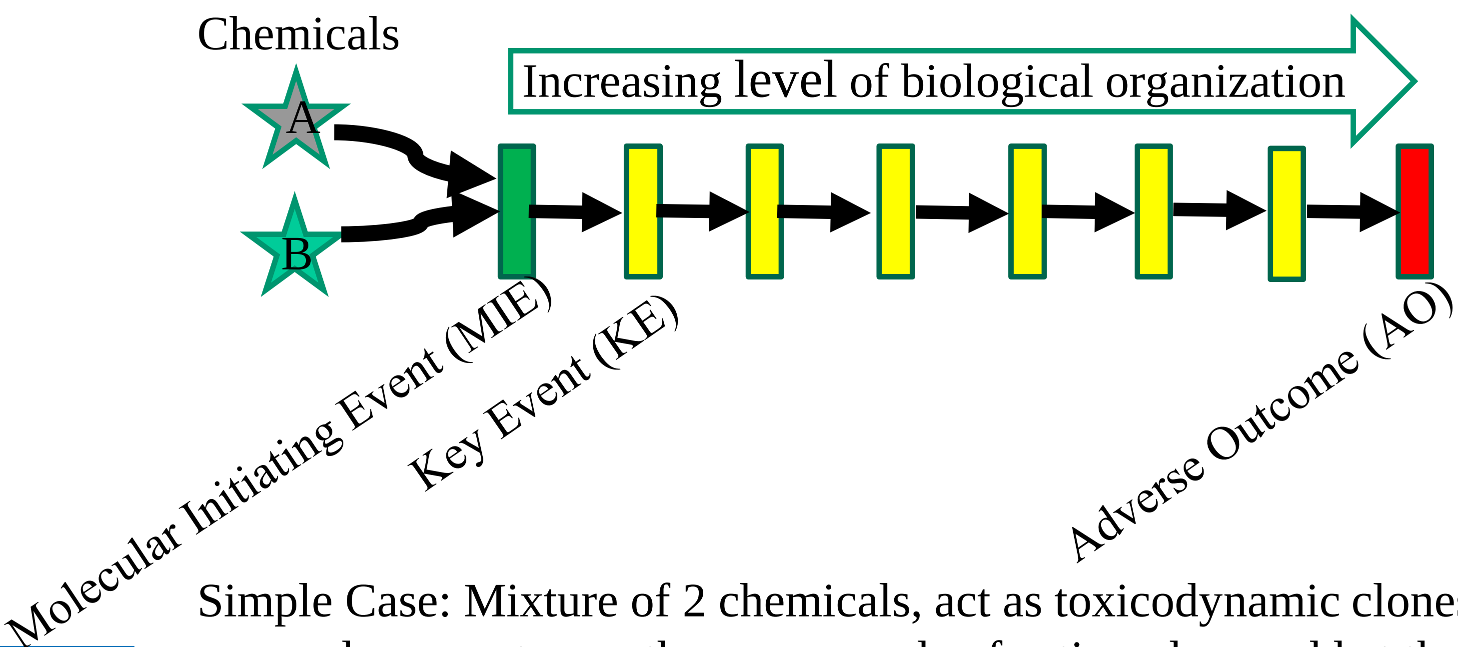
- **Dose-response Assessment**
  - Cancer Risk = Oral Slope Factor x Dose
  - Cancer Risk = Inhalation Unit Risk x Concentration
- **Risk Characterization Component**
- Concentration in air or water for “target” risk level
  - 1 person in 1,000,000 (10^{-6})
  - 1 person in 100,000 (10^{-5})
  - 1 person in 10,000 (10^{-4})

Mixture Approaches



KEY CONCEPT: ADDITIVE JOINT TOXIC ACTION OF MIXTURE COMPONENTS

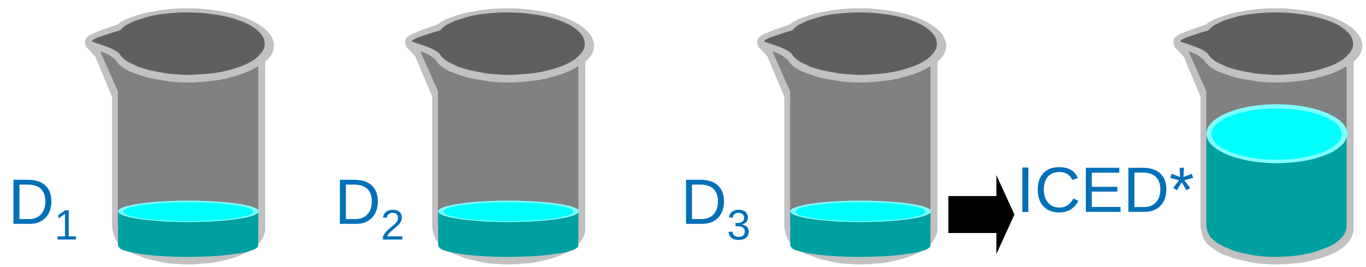
- Simple similar action
  - Dose addition—hazard index (HI), toxicity equivalence factors (TEFs), relative potency factors (RPFs)
    - Addition of component doses, scaled for relative toxicity
    - Assumes components affect same pathway of toxicity



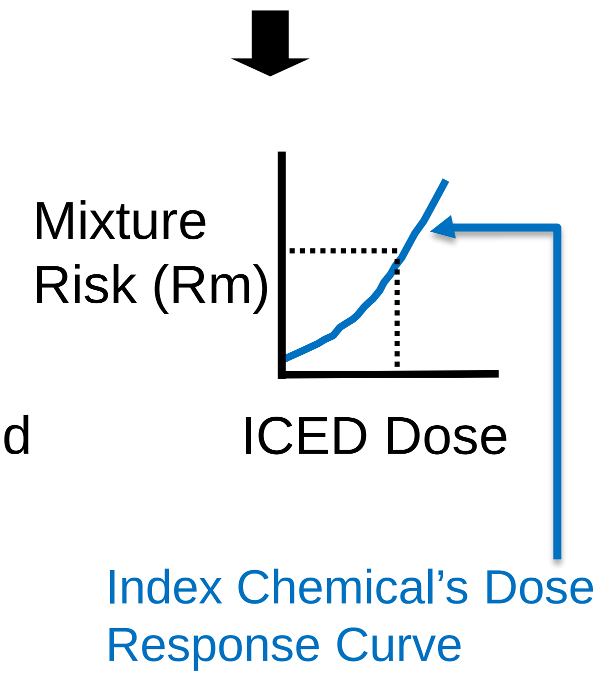
Simple Case: Mixture of 2 chemicals, act as toxicodynamic clones, affect same adverse outcome thru same mode of action; doses add at the MIE

Adapted from US EPA (2017) Adverse Outcome Pathway (AOP) Factsheet
https://www.epa.gov/sites/production/files/2017-03/documents/aop_research_brief_03_2017.pdf

Dose Addition Method using Relative Potency Factors (RPFs): Generalized Index Chemical Method



Dose Addition:
Assumes common mode of action



RPF Method

$$Rm = f_1(D_1 + RPF_2D_2 + RPF_3D_3\ldots) = f_1(ICED)$$

where RPF_i scales the doses of chemicals 2 and 3 for relative potency to index chemical 1

*ICED = Index Chemical Equivalent Dose

US EPA, 2000

Methods to Calculate RPFs

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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.,

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

ED_x = The “Effective Dose” at which an x% response is observed.

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

$$RPF_i = \frac{Dose\ Coefficient(Chemical_i)}{Dose\ Coefficient(Index\ Chemical)}$$

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RPF Example: Toxicity Data for a 3 Chemical Mixture

Chemical	Study ED_{10} (mg/kg/day)	Test Species	Duration Critical Study	Overall Data Set Characteristics
Chemical 1	5	Rat	90 days	Poor. Few poor studies.
Chemical 2	25	Rat	90 days	Extensive. Human confirmation of effects, dose-response data, similar structure to other chemicals in group.
Chemical 3	40	Rat	90 days	Good. Several good studies, multiple species. Some Dose-response data.

RPF values for a set of chemicals could differ depending on the effect of interest.

RPF Example: Calculation of RPFs and ICED

Chemical	Rat ED_{10} Oral (mg/kg-d)	RPF (oral dose)	Human Intake (mg/kg-d)	ICED (mg/kg-d)	Total ICED (mg/kg-d)	% of Total ICED
Chemical #1	5	5.0	0.002	0.01		91
Chemical #2 Index Chemical	25	1.0	0.0007	0.0007	0.011	6
Chemical #3	40	0.63	0.0004	0.00025		2

$RPF = ED10_{IC} \div ED10_{i}$

$ICED = RPF \times \text{Human Intake}$

RPF Example: Cancer Risk Estimate Using the ICED when the Index Chemical is analyzed using a Linear Non-Threshold Model

Index Chemical Comparison	Total ICED = 0.011 (mg/kg-d) Conduct Assessment Using Index Chemical Dose Response Information	Potential Risk
Cancer Risk for the Mixture (Rm)	Oral Slope Factor = 6.2×10^{-2} per mg/kg-d (liver tumors) Rm = 0.011 mg/kg-day × 6.2×10^{-2} per mg/kg-d	Rm = 6.8×10^{-4}

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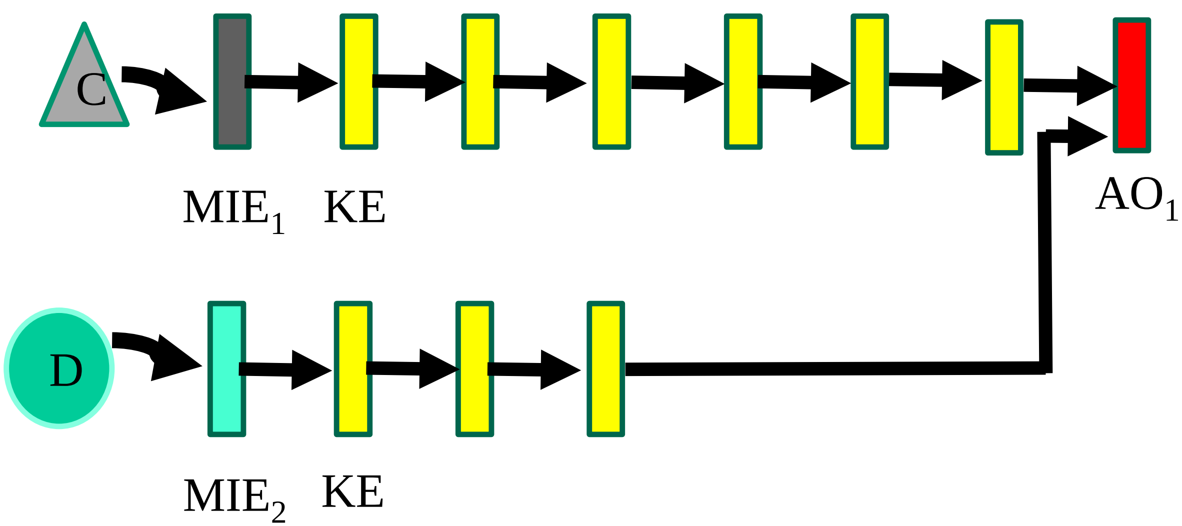
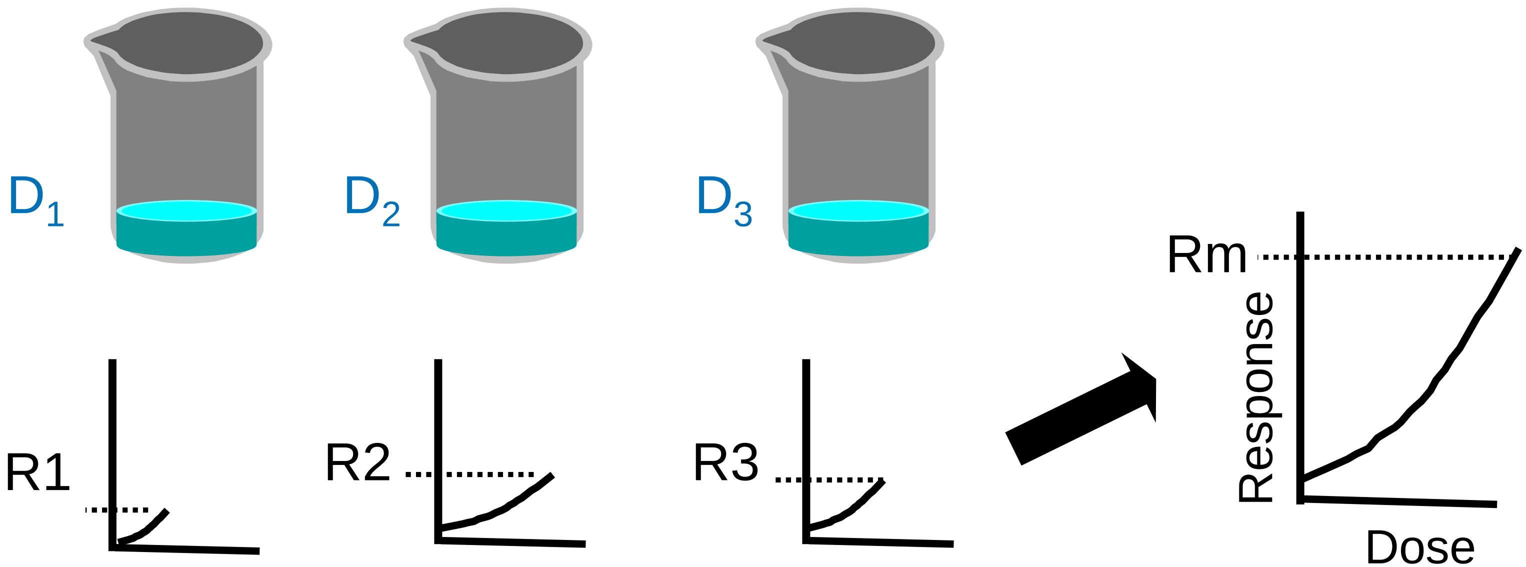
KEY CONCEPT: ADDITIVE JOINT TOXIC ACTION OF MIXTURE COMPONENTS

- Simple dissimilar action
  - Response addition—cancer risk sums
    - Addition of component risks
    - Assumes toxicological and statistical independence
  - Effects addition—cumulative effects
    - Addition of biological responses across components
    - Assumes toxicologic similarity across components



Mixture of 2 toxicologically independent chemicals affect same adverse outcome thru different pathways

Response Addition: Applied Extensively to Estimate Mixture Risk (Rm) for Carcinogens



Response Addition: Independence of Toxic Action

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

For a common health outcome, the toxicity caused by the first chemical has no impact on the toxicity caused by the second chemical (and so on for more chemicals).

Response Addition Example Calculations for Oral Cancer Risk

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Chemical	Unit Risk	Intake	r_i	Organ	Class
	(per µg/L)	(µg/L)			
Chemical 1	5.0 E-05	3.0 E-03	1.5E-7	Dermal	Carcinogen
Chemical 2	1.0 E-05	9.0 E-05	9.0E-10	Liver	Likely
Chemical 3	1.3 E-04	6.0 E-03	7.8E-7	Liver	Likely
Total Excess Lifetime Cancer Risk per the Exposure =			9.3E-7		

Assumes Toxicological and Statistical Independence

Uncertainties: Cancer data are 95% upper bound slope factors; Most of the risk is from chemicals with a cancer weight of evidence descriptor of “likely to be carcinogenic in humans”, rather than chemicals designated “human carcinogen”; Toxicological independence is uncertain, given that the primary target organ contributing to risk is the liver.

Conclusions

1. Cancer risk assessment of environmental chemical mixtures is critical to protecting human health
2. Best evidence supporting mixture cancer assessments often obtained from epidemiological studies
   - Epi studies resource intensive; but can evaluate chemical mixtures in relevant exposure range and species (humans)
3. Toxicological evidence potentially important source of mechanistic information for multiple stressors and cancer slope estimates
   - Often basis of component analyses
4. Opportunities through "–Omics" data to better inform
   - hazard assessment
   - kinetic analyses
   - mode of action analyses
   - eventually, inform quantitative risk estimates

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SUPPLEMENTAL SLIDES

Formula for the Index Chemical Equivalent Dose (ICED)

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

$$ICED = \sum_{i=1}^{n} \left[RPF_i \; X \; D_i \right]$$

where,

ICED = mixture dose expressed as dose of the index chemical

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

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

Choice of Index Chemical

- Well studied with well characterized dose-response function for effect of interest
- Structurally and Toxicologically similar to other chemicals in group
- Confirmation of effects in humans, if data exist
- Data available to compare relative toxicity between index chemical and other chemicals in group
- Confidence increases if typically found in large percent of environmental concentrations as compared with other chemicals in group