Human Health Risk Assessment at EPA

FDA TPSAC meeting
08/16/13

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Disclaimer

- The views expressed in this presentation are those do the author and do not represent the policy of the U.S. EPA.

So What Is EPA Policy?

- Science Policy
  - Defaults, methods, Guidelines
  - Used when there are data or methodology gaps
  - Peer reviewed
  - Lots of documentation, which is publicly available
- Policy based on science
  - May be set by EPA Executive Level
  - Generally involves regulations or other risk management choices; science is peer reviewed, action involves public comment; May be subject to Federal Advisory Committee Act
  - Lots of documentation; may be docket; publicly available

Examples

- Science policy
  - *Cancer Guidelines* 2005
  - Set a reference dose for effects which are likely to have a threshold
  - Quantitative adjustment to cancer risk for early life exposure
  - Animal data are relevant to humans unless demonstrated otherwise

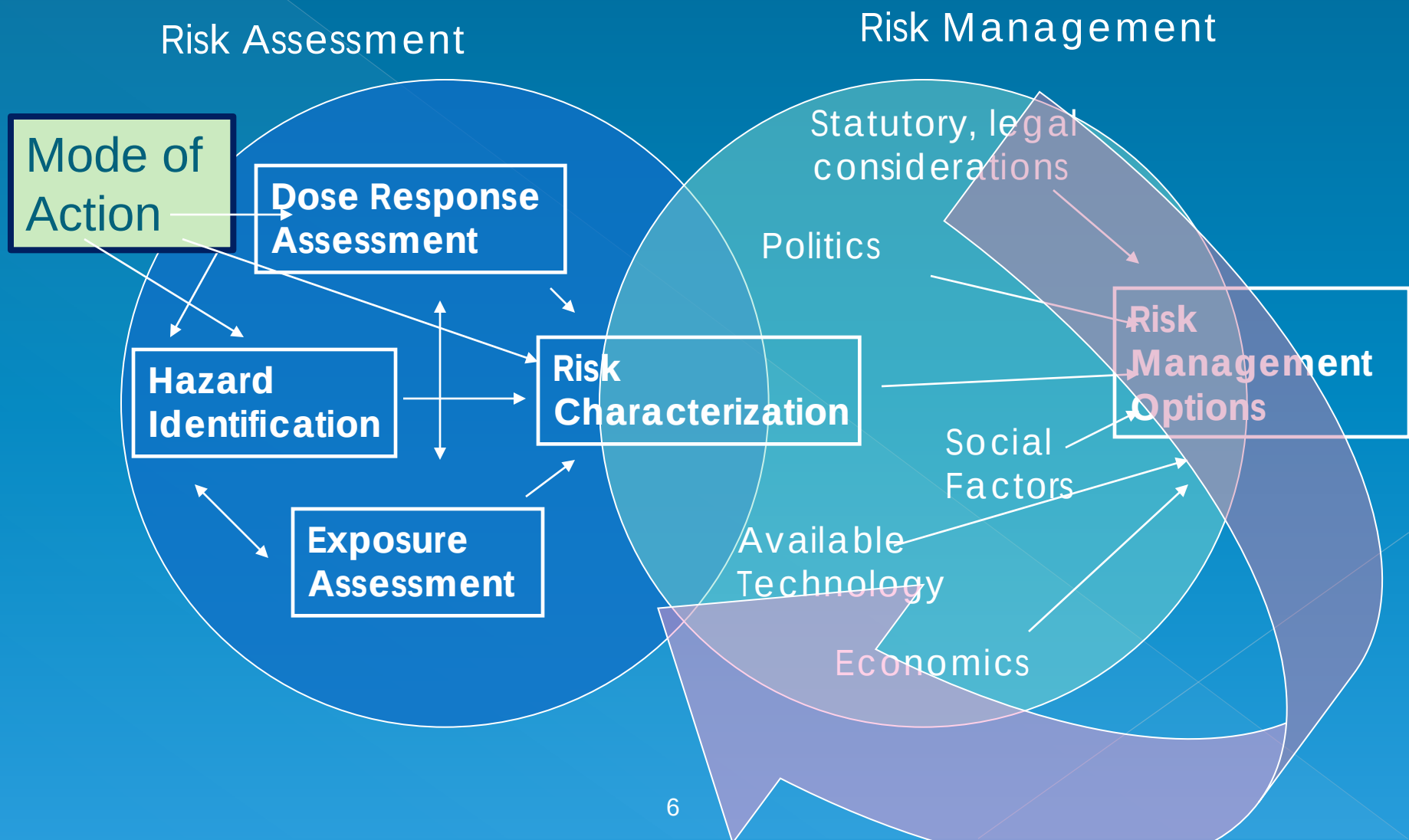
These all deal with risk assessment

Why Do Risk Assessment?

- "... risk assessment should be viewed as a method for evaluating the relative merits of various options for managing risk ..." (Science and Decisions 2009)
- To provide support for decisions to protect public health and the environment.
  - Complex and controversial
  - Risk assessment summarizes the science

5

'83 Risk Assessment Paradigm '13?



Acceptable Levels of Risk

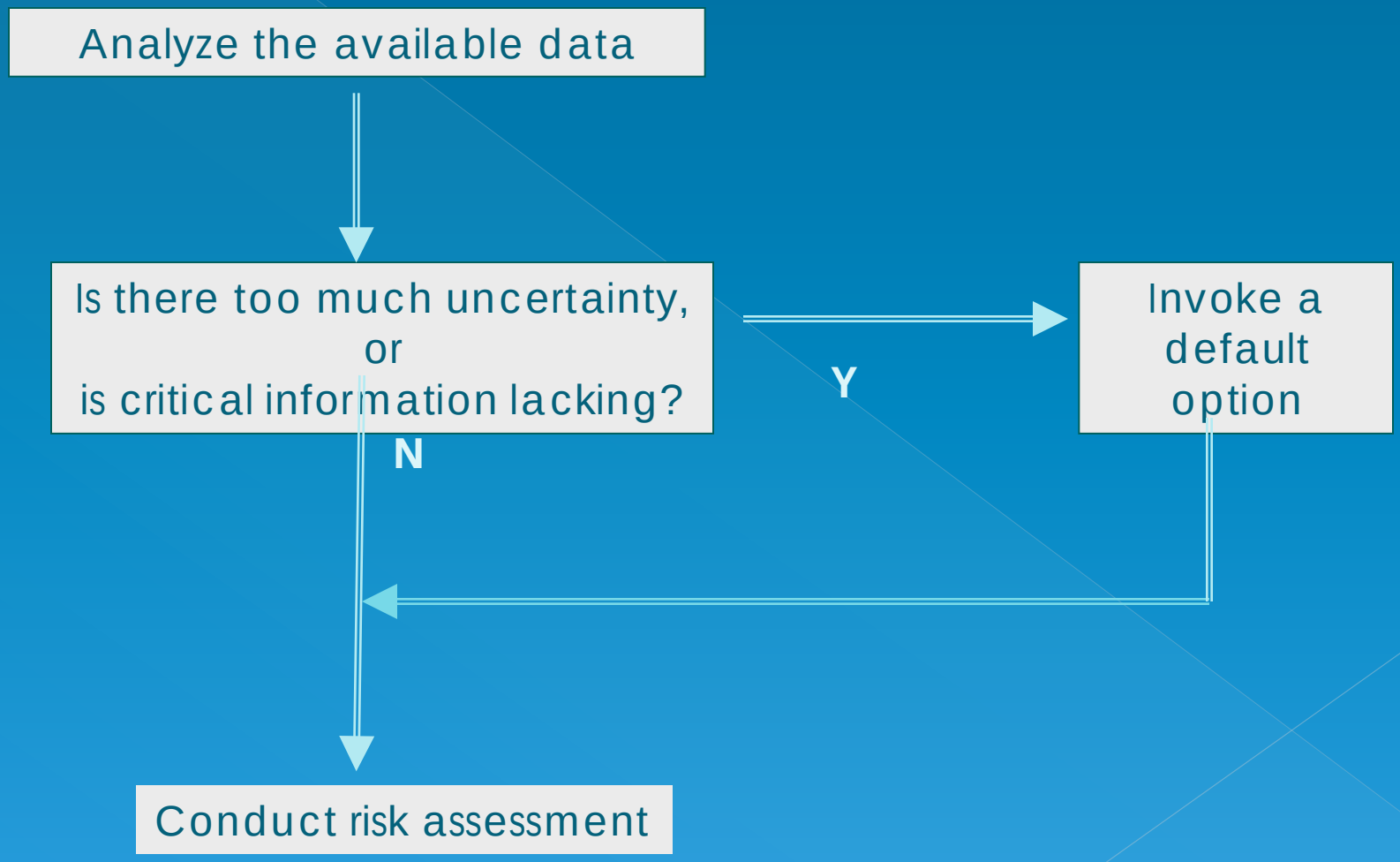
- TSCA . . . assure chemical substances and mixtures do not present an unreasonable risk of injury to health or the environment, §2(b)(3)
- FIFRA . . function without unreasonable and adverse effects on human health and the environment, §3
- RCRA . . . Necessary to protect human health and the environment, §3005 as amended
- NCP . . . provide the basis for the development of protective exposure levels, § 300.430(d)
- CWA . . . Adequate to protect public health and the environment from any reasonably anticipated adverse effect, §405(d)(2)(D)
- CAA varies within statute by source or contaminant

We Cope By Applying Some Defaults

- For risk calculated to be linear at low dose, aim for risks between 10^{-6} and 10^{-4}
- For other endpoints, not thought to be linear at low dose, do a safety assessment (Reference Dose or Reference Concentration, MOE).

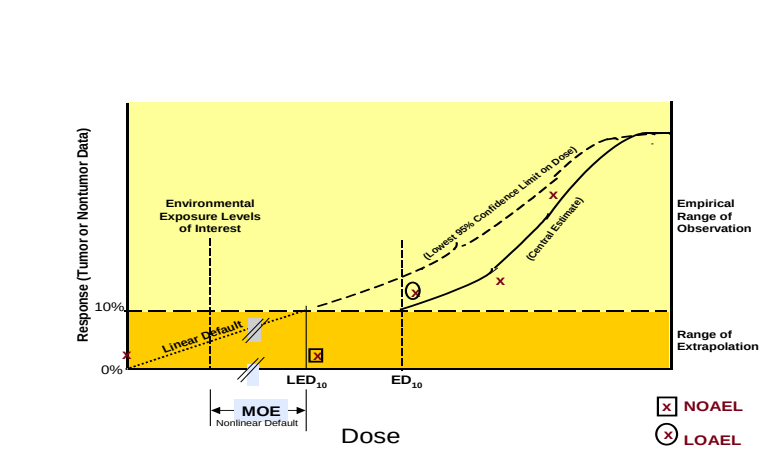
Risk Assessment Science

Use Data Before Invoking Defaults

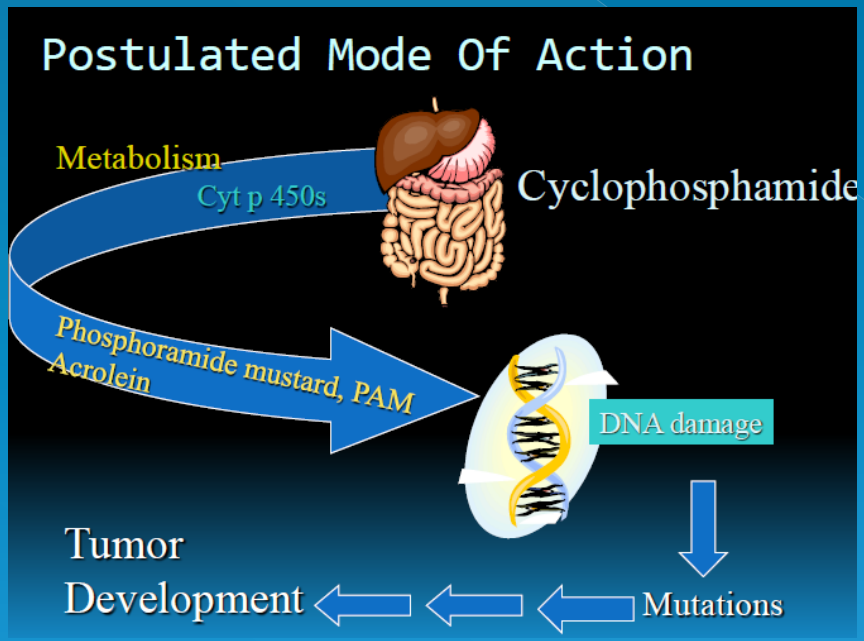


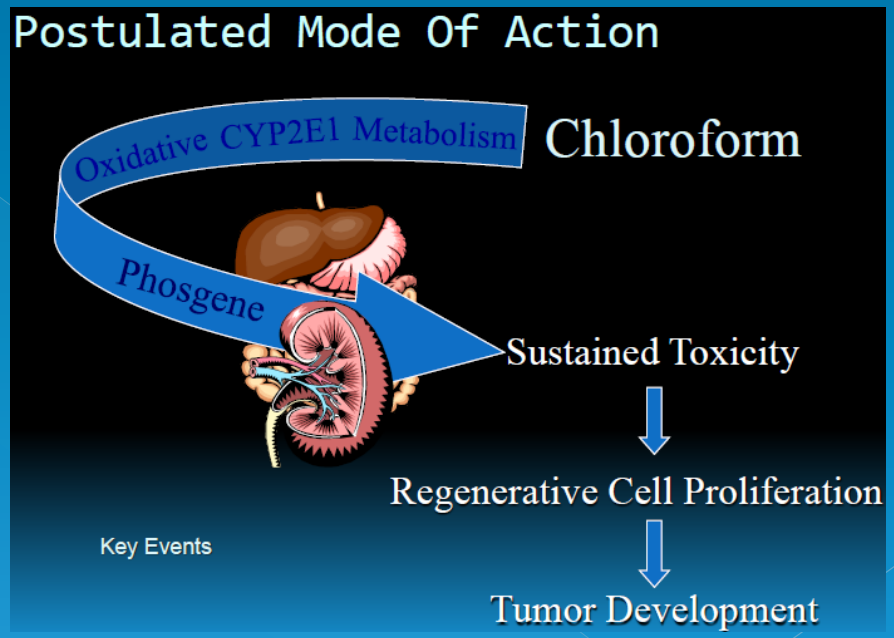
Why Do You Care about MOA ?

- MOA is key in Hazard Identification
  - Helps describe circumstances under which agent is carcinogenic (High dose? Route?)
  - Relevance of data for humans
- MOA determines choice of Low Dose Extrapolation
- Choice of biomarker
- Life stage risk



MOA


Postulated Mode Of Action
Metabolism
Cyt p 450s
Cyclophosphamide
Phosphoramide mustard, PAM
Acrolein
DNA damage
Tumor
Development
Mutations

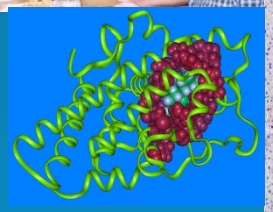

Postulated Mode Of Action
Oxidative CYP2E1 Metabolism
Chloroform
Phosgene
Sustained Toxicity
Regenerative Cell Proliferation
Key Events
Tumor Development

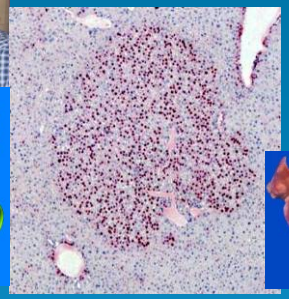
Application to Levels of Organization Based on Source to Outcome

Source

Environmental Contaminant

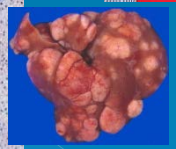
Exposure





Molecular Initiating Event

Cellular Effects



Individual

Population

Community

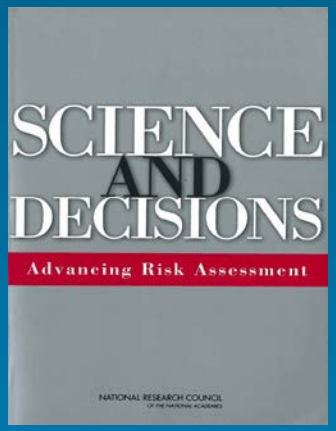
Toxicity Pathway

Mode of Action

Adverse Outcome Pathway

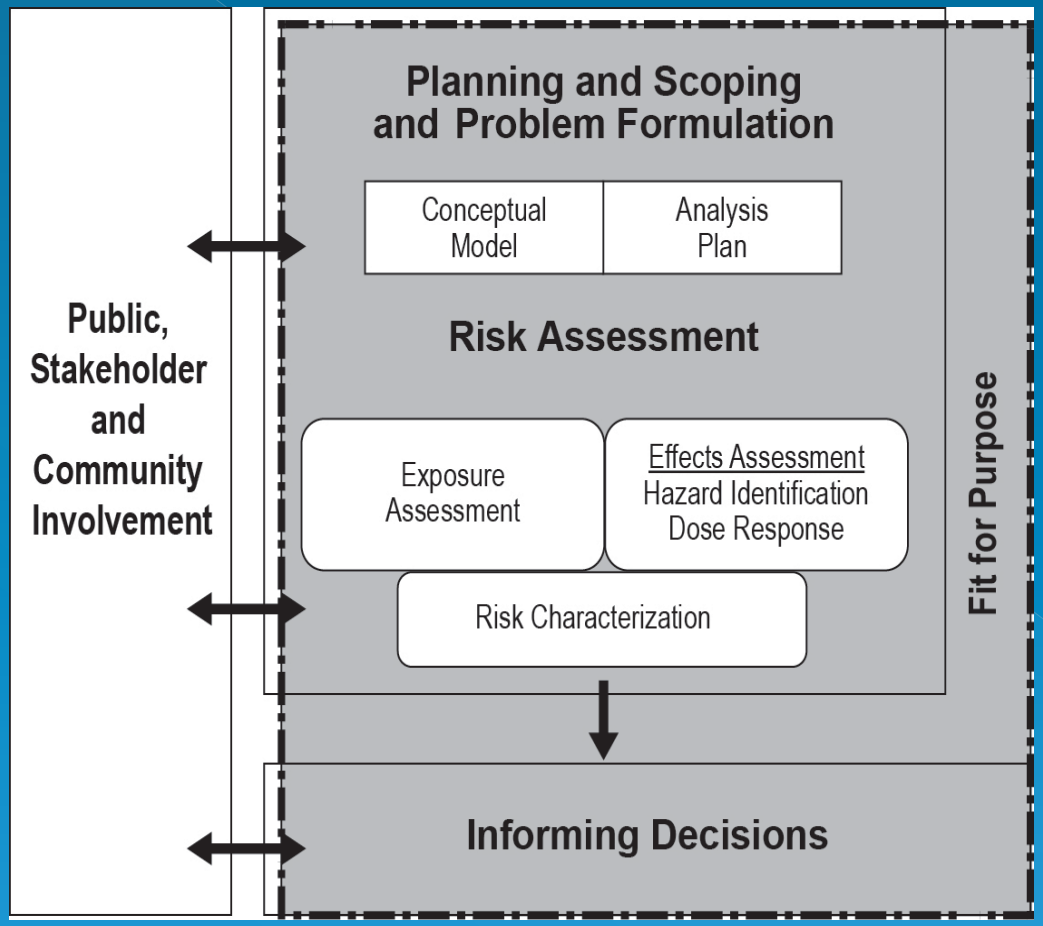
Source to Outcome Pathway

NRC Silver Book Recommendation

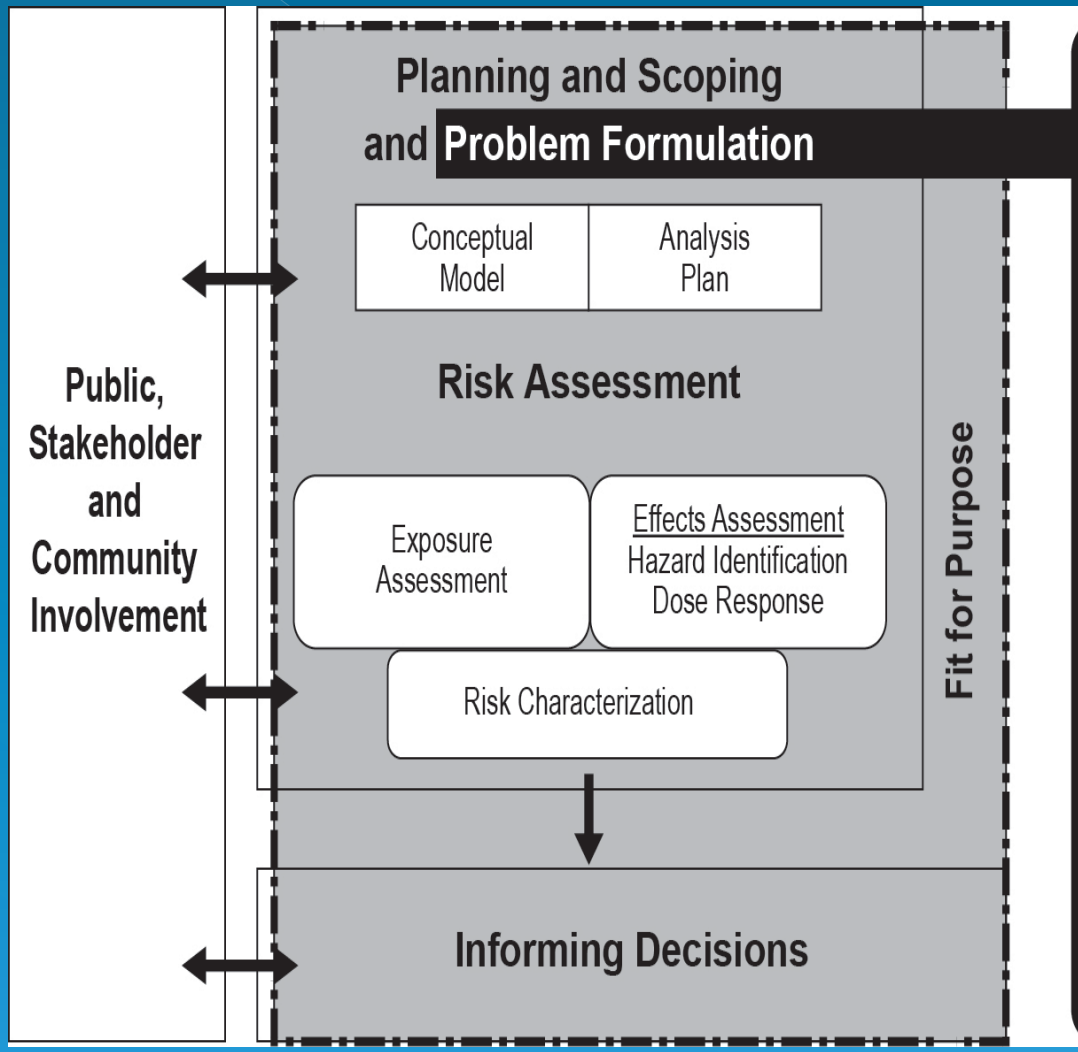


- NRC Silver Book recommendation (Chapter 8 "Improving Utility of Risk Assessment")
  - *To make risk assessments most useful for risk management decisions, the committee recommends that EPA adopt a framework for risk-based decision-making . . . that embeds the Red Book risk assessment paradigm into a process with initial problem formulation and scoping, upfront identification of risk-management options and use of risk assessment to discriminate among these options.*

Draft HHRA Framework



Silver Book on Utility
"Risk assessments should not be conducted unless it is clear that they are designed to answer specific questions, and that the level of technical detail and uncertainty and variability analysis is appropriate to the decision context" (NRC 2009, p. 247).



Key Considerations for Problem Formulation

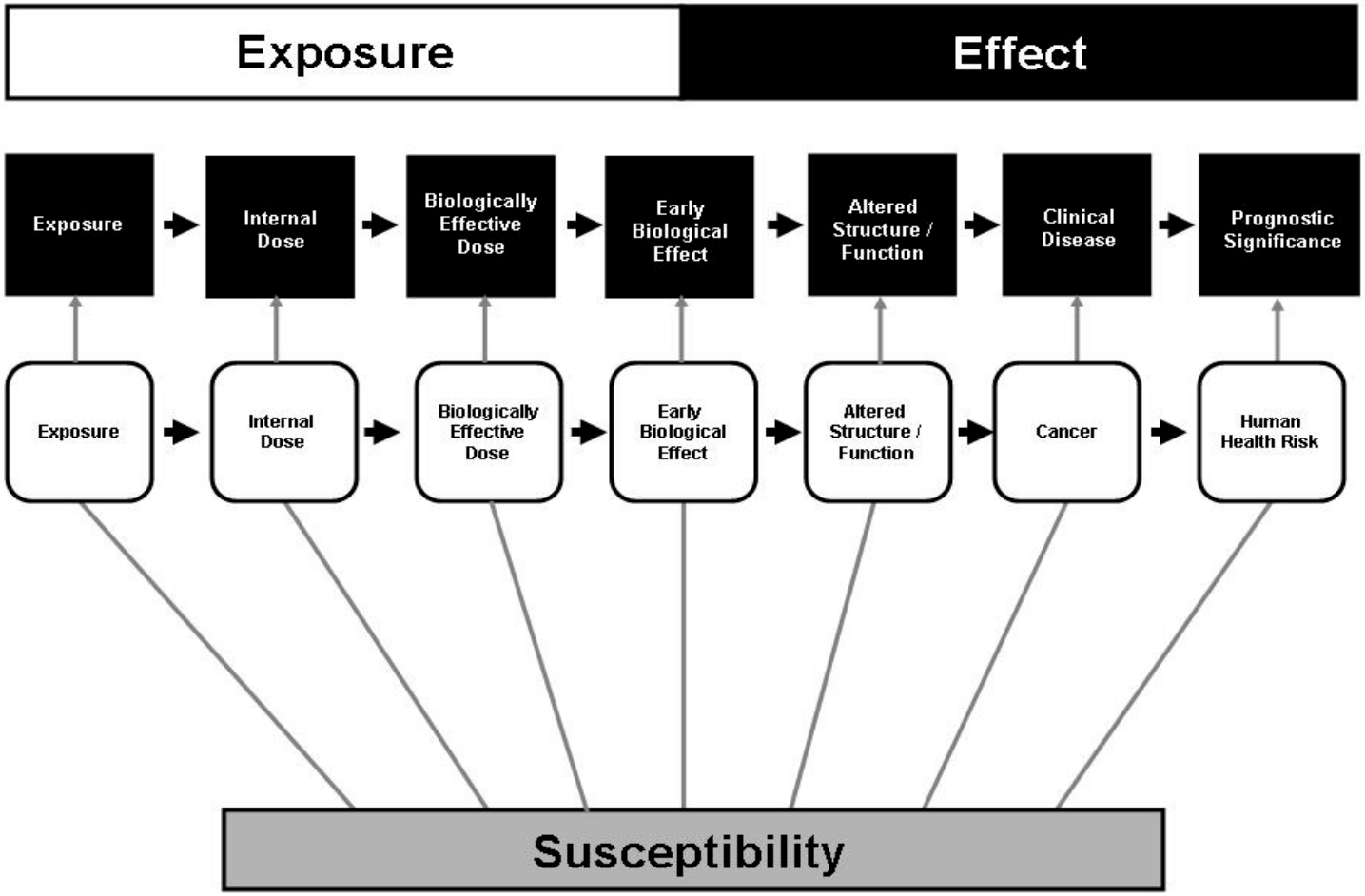
Conceptual Model

- What are the human health risk pathways for this problem, including the elements for each dimension (e.g., populations/lifestages at risk)?
- What factors and endpoints need to be analyzed?

Analysis Plan

- What approaches, methods and metrics will be used to assess exposures, effects and risk, including the associated uncertainty and variability?
- What is the strategy for developing new or using existing data?

NRC Scheme for Biomarkers (Schulte, 1989)



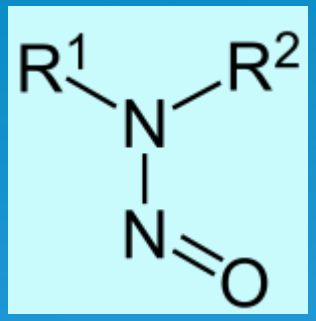
A Generalized Conceptual Model

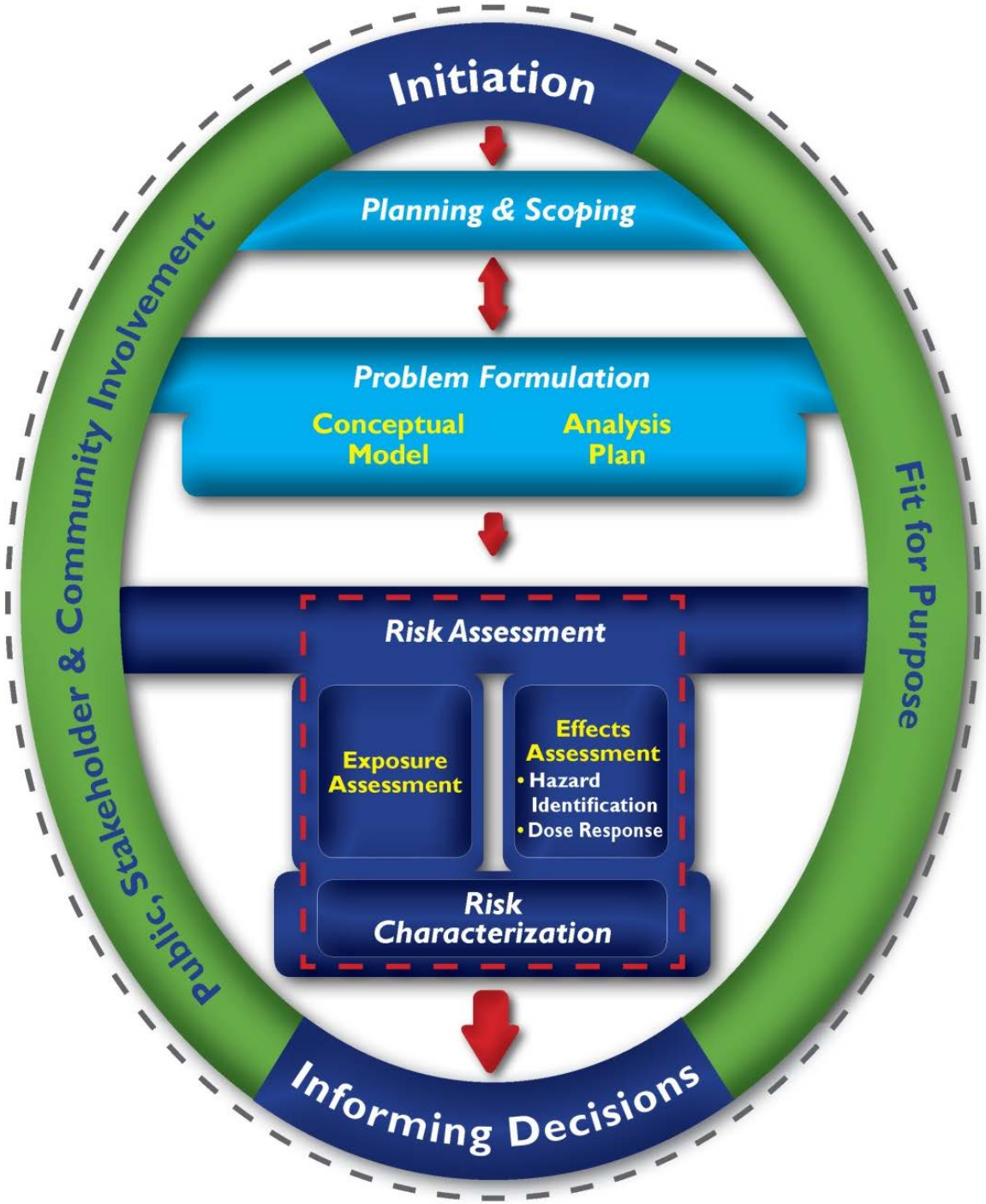
(adapted from USEPA, 2002; 2003)

Sources	Stressors	Exposure Pathways/Routes	Receptors	Endpoints	Risk Metrics
Activities that generate/release Stressors or types of stressor releases	Chemical, physical or biological agents that cause an effect	Physical processes or interactions by which a stressor is brought into to contact with receptor	Populations and/or lifestages exposed to the stressor	Measures of stressor effects or biological systems affected	Metrics by which risk is quantified (e.g., disease cases, hazard quotients, magnitude of effect)

Conceptual Model
Nitrosamines in Drinking Water

Sources	Stressors	Exposure Pathways/ Routes	Receptors	Endpoints	Risk Metrics
Drinking water disinfection	Variable mixture nitrosamines; dependent on treatment & source water.	Ingestion of nitrosamine mixture in drinking water	Consumers of drinking water; includes sensitive populations &life stages	Cancer, any site or type	Combined risk of cancer from subset nitrosamines in mixture




Initiation
Planning & Scoping
Problem Formulation
Conceptual Model
Analysis Plan
Risk Assessment
Exposure Assessment
Effects Assessment
• Hazard Identification
• Dose Response
Risk Characterization
Informing Decisions
Public, Stakeholder & Community Involvement
Fit for Purpose

Guidance, No Definition of WOE, in 2005 Cancer Guidelines

- "weight-of-evidence evaluations based on the combined strength and coherence of inferences appropriately drawn from all of the available information." p. 2-1

- "The weight of evidence-of-evidence narrative should highlight:
  - the quality and quantity of the data;
  - all key decisions and the basis for these major decisions; and
  - any data, analyses, or assumptions that are unusual for or new to EPA." p. 2-50

Weight of Evidence Steps

- Assemble relevant data
- Evaluate data for quality and relevance
  - **All** relevant data evaluated
  - Guidelines describe data quality objectives
  - Provide guidance for weight to be given to types of data (e.g. human > animal, *in vivo* > *in vitro*)
  - Both negative and positive data considered in bottom line (vs. Strength of Evidence)
- Integration of the different lines of evidence to support conclusions concerning a property of the substance..

Weight of Evidence

- May or may not include categories
  - e.g. Likely to be carcinogenic to humans; robust demonstration of nonmonotonic dose response curve
- WoE considers both negative and positive studies, but it is not a simple tallying of the number of plusses and minuses.
- Issues, strengths, and limitations of the data and the uncertainties that deserve serious consideration are presented, and the major points of interpretation highlighted

EPA and FDA

- EPA generally evaluates involuntary risks
  - Water contamination vs. smoking
- Both evaluate mixtures

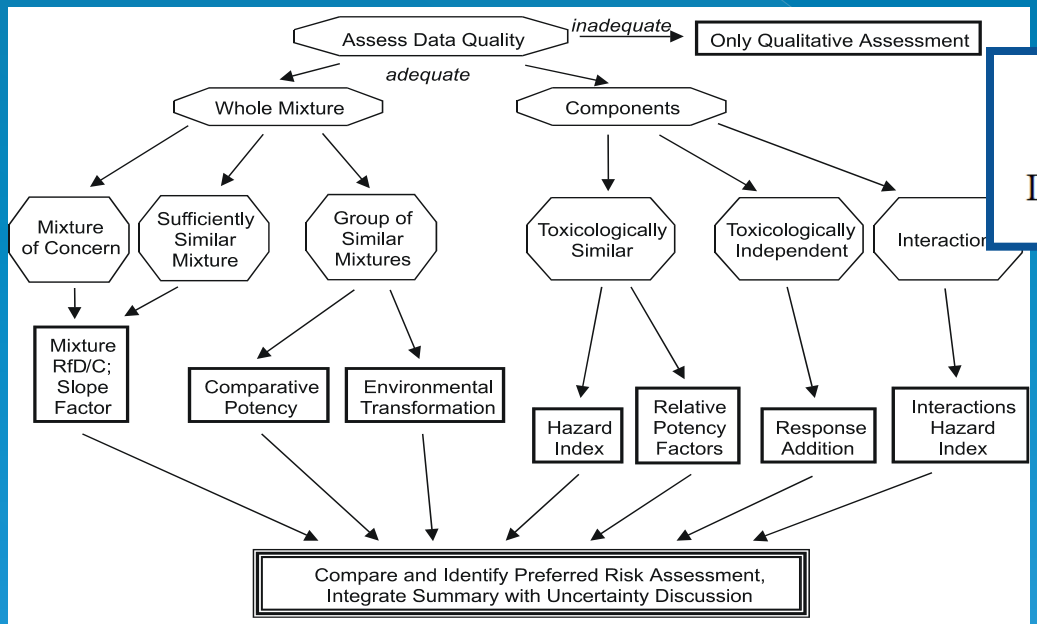
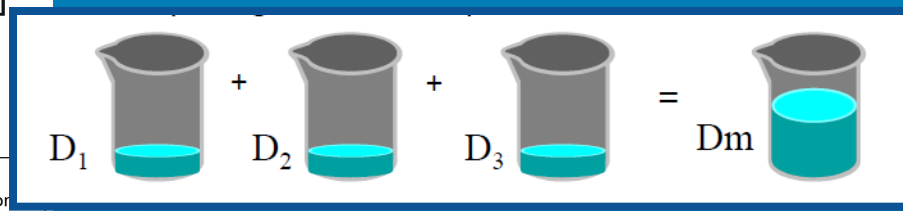
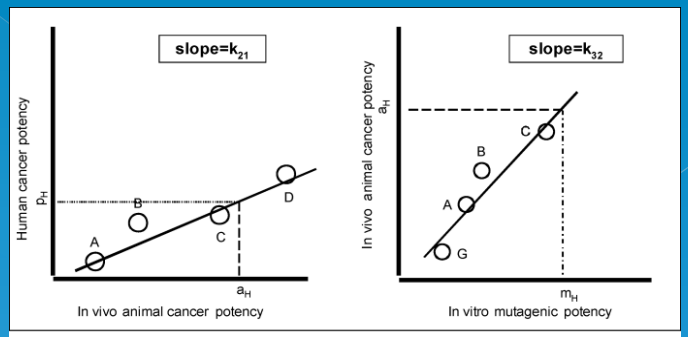


Figure 2-1. The different types of mixtures assessments based on the availability and quality of the data. All possible assessment paths should be performed.





Hypothetical comparative potency example using proportionality constants with two assays.
(Left) Human potency estimated from animal data for four mixtures.
(Right) Animal potency estimated from in vitro data for four mixtures.
p_H = human potency for mixture H estimated not from the animal data but from the estimated animal potency for H, a_H, which is estimated from the in vitro potency, m_H, so that $p_H = k_{21} * k_{32} * m_H$.

Figure 3-2. Comparative potency method - three assays.

EPA and FDA

- Both may do risk / risk comparison

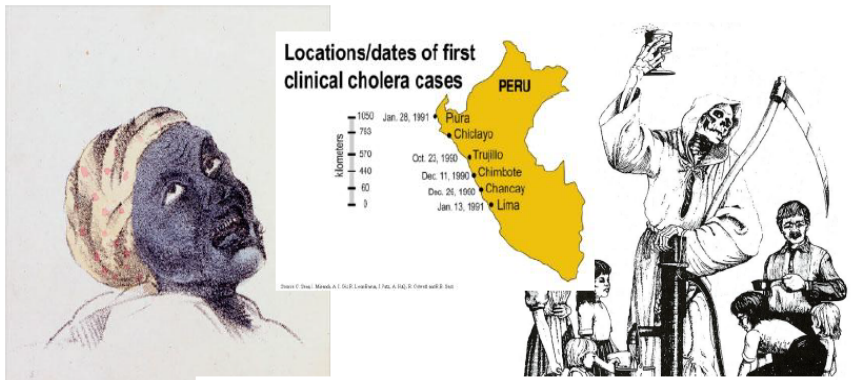


Table 3: Estimates of Water-Related Mortality

Source	Deaths per Year
World Health Organization 2000	2.2 million (diarrheal diseases only)
World Health Organization 1999	2.3 million
WaterDome 2002	more than 3 million
World Health Organization 1992	4 million
World Health Organization 1996	more than 5 million
Hunter et al. 2000	more than 5 million
UNDP 2002	more than 5 million
Johannesburg Summit 2002	more than 5 million
Hinrichsen et.al, 1997	12 million

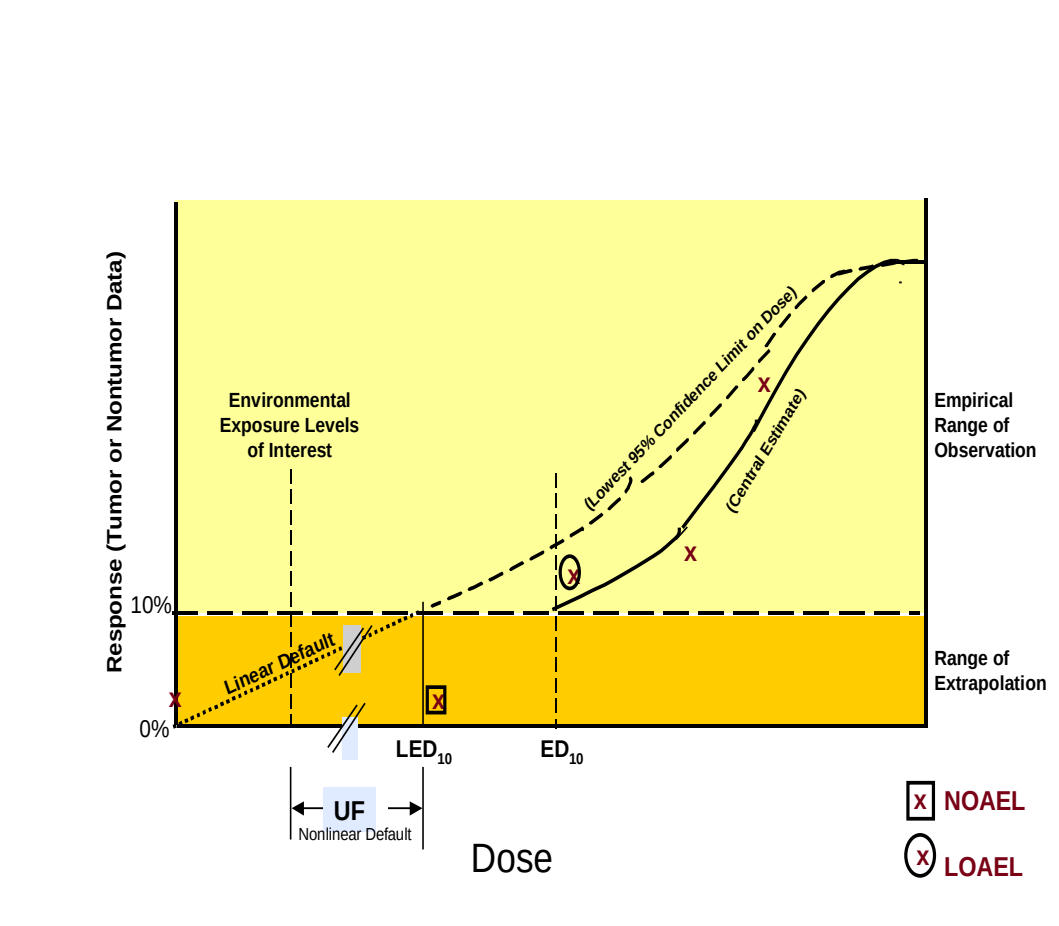
1998 DBP1 -- 11 DBPs Regulated – to reduce risk of cancer

- Bromate
- THM
  - Chloroform
  - Dibromochloro-methane
  - Dichlorobromo-methane
  - Bromoform
- Chlorite
- Haloacetic acids
  - Chloroacetic acid
  - Dichloroacetic acid
  - Trichloroacetic acid
  - Bromoacetic acid
  - Dibromoacetic acid

These are meant to serve as indicators of all DBPs -- identified or not

3

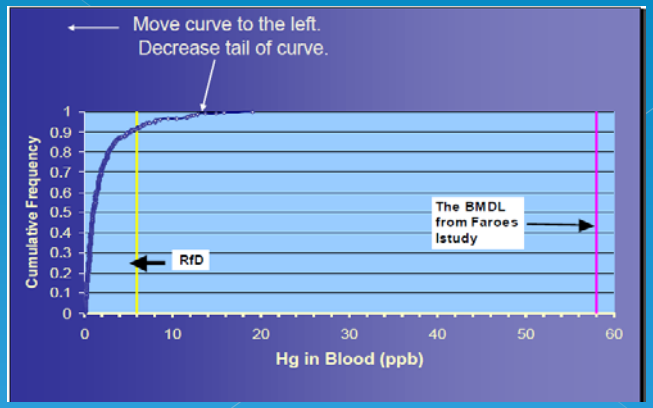
EPA does a lot of quantitative risk estimation



- Model data in the observed range – to a point of departure
- Extrapolate below the POD

A Thought

- Can not predict an individual's risk
  - e.g. mine or yours
- Both "individual risk" and "population risk" are modeling constructs
- Risk = hazard x exposure.



Conclusions

- Risk assessment should be designed to inform risk management decisions
- WOE processes are integral to risk assessment
- Difficult choices must be made
  - Neither EPA nor FDA may choose not to choose

Benzene MoA

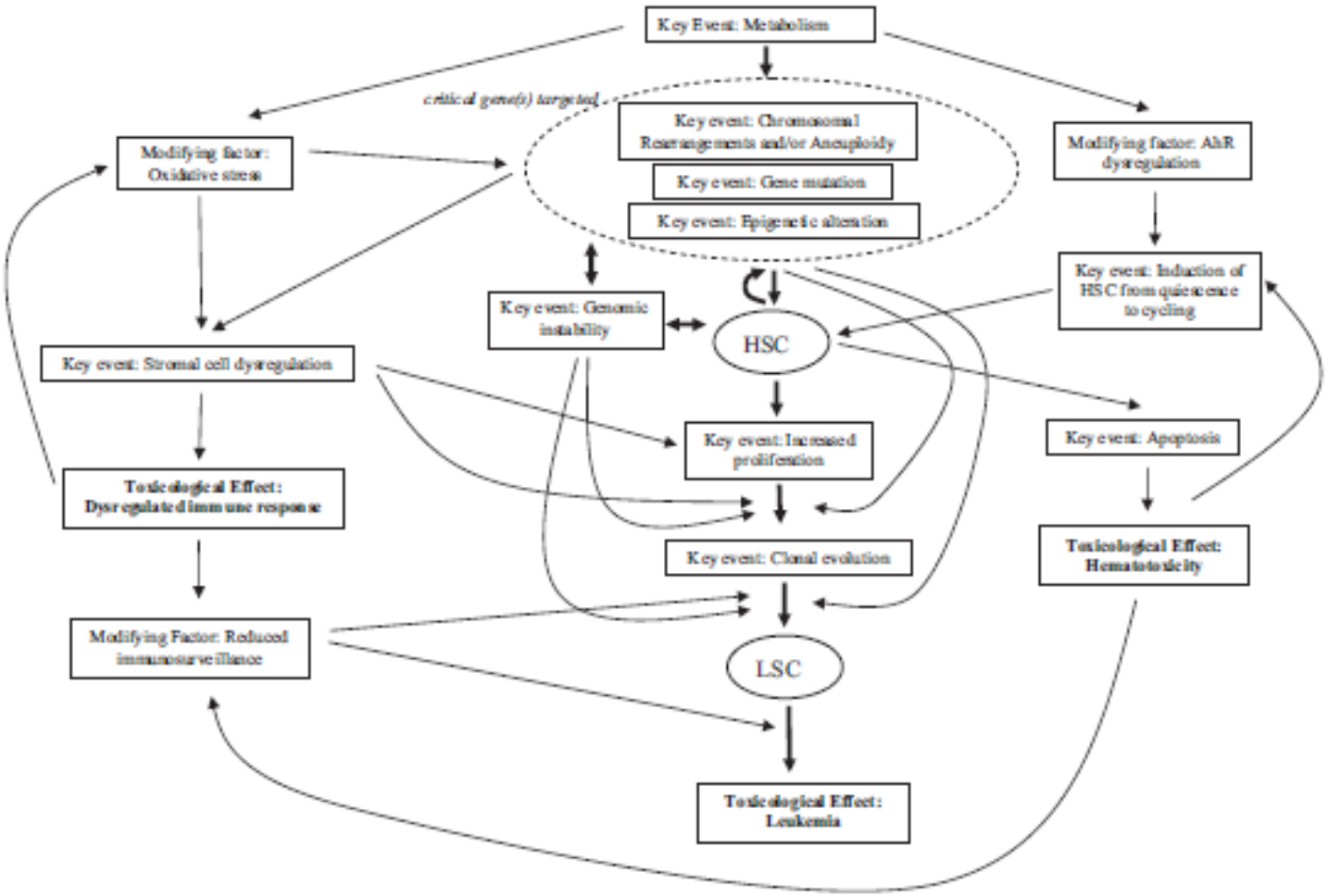


Fig. 2. Probable mechanism of benzene-induced leukemia.

Smith *et al.* 2011

Benzene Data

McHale *et al.* 2011

Table 2. Summary of GO categories overrepresented at each benzene exposure category.

GO ID[a]	GO term	Total no. of genes[b]	Very low ($n = 29$) No. genes	Very low ($n = 29$) p-Value[c]	Low ($n = 30$) No. genes	Low ($n = 30$) p-Value[c]	High ($n = 11$) No. genes	High ($n = 11$) p-Value[c]	Very high ($n = 13$) No. genes	Very high ($n = 13$) p-Value[c]
GO:0006412	translation	456	64	2.0E-06	93	1.2E-03				
GO:0006512	ubiquitin cycle	480	48	7.5E-04	98	1.6E-05				
GO:0006917	induction of apoptosis	216	27	4.1E-04	49	1.6E-04	19	1.5E-03[d]		
GO:0006955	immune response	653	58	3.7E-03[d]	124	4.6E-05	54	4.9E-06	97	1.1E-04
GO:0015986	ATP synthesis coupled proton transport	40	11	2.2E-05	14	5.0E-04			11	1.8E-03
GO:0006915	apoptosis	804	80	5.6E-03	158	9.2E-04			107	2.7E-03
GO:0030301	cholesterol transport	8	5	4.4E-05	4	1.5E-02[d]			4	5.5E-03[d]
GO:0006954	inflammatory response	318			60	4.6E-03[d]	34	2.8E-05		

[a]GO categories that are significant at ≥ 2 doses. [b]Number of annotated genes included on the chip. [c]p-Values were determined using the elim method in TopGO, which computes the statistical significance of a parent node dependent on the significance of its children by Fisher's exact test; nodes are significant if the p-value is smaller than a previously defined threshold (Alexa et al. 2006), 0.01 divided by the number of nodes in the GO graph with at least one annotated gene. [d]Significantly enriched term in classic analysis (which does not take GO hierarchy into account) but not in elim analysis in TopGO. Complete GO data are available in Supplemental Material, Table 9 (doi:10.1289/ehp.1002546).

Global Gene Expression Profiling of a Population Exposed to a Range of Benzene Levels

Oil Dispersants

Judson *et al.* 2010

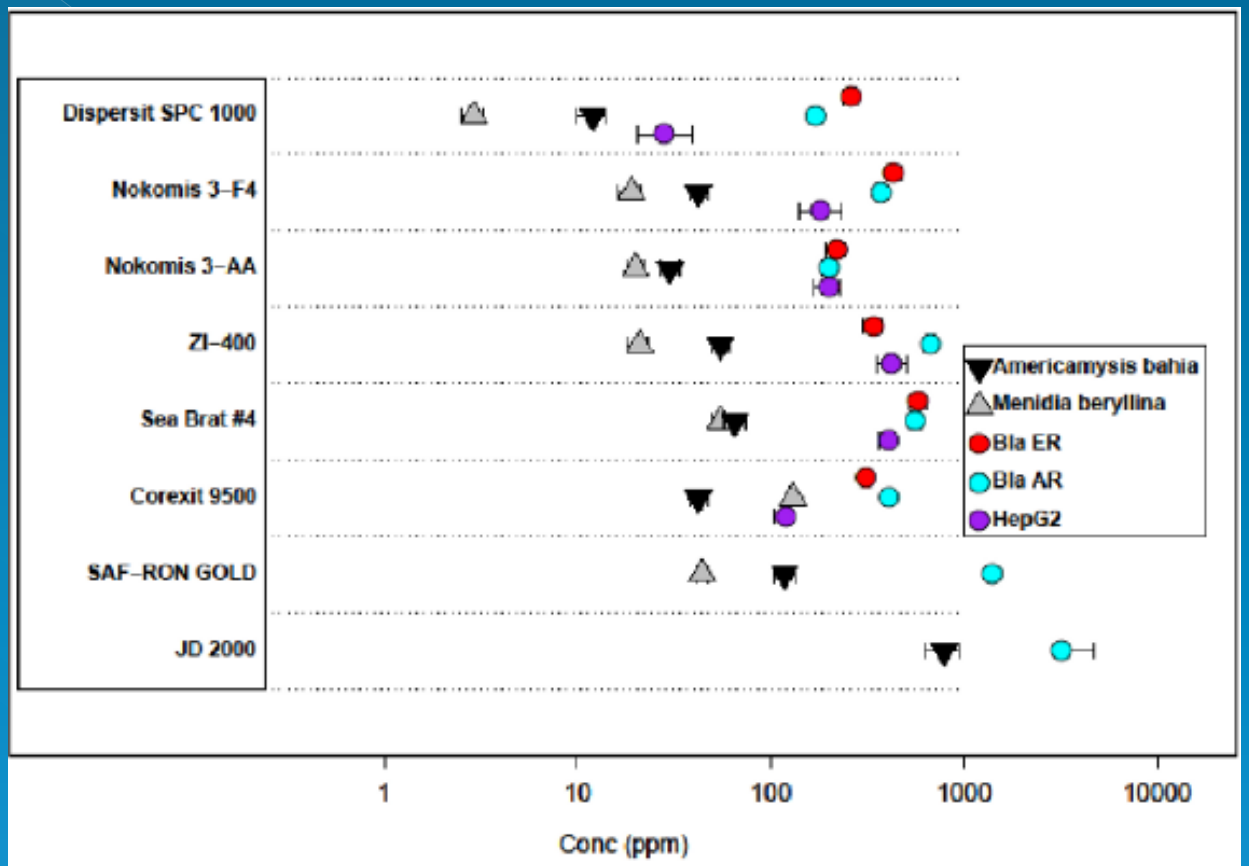
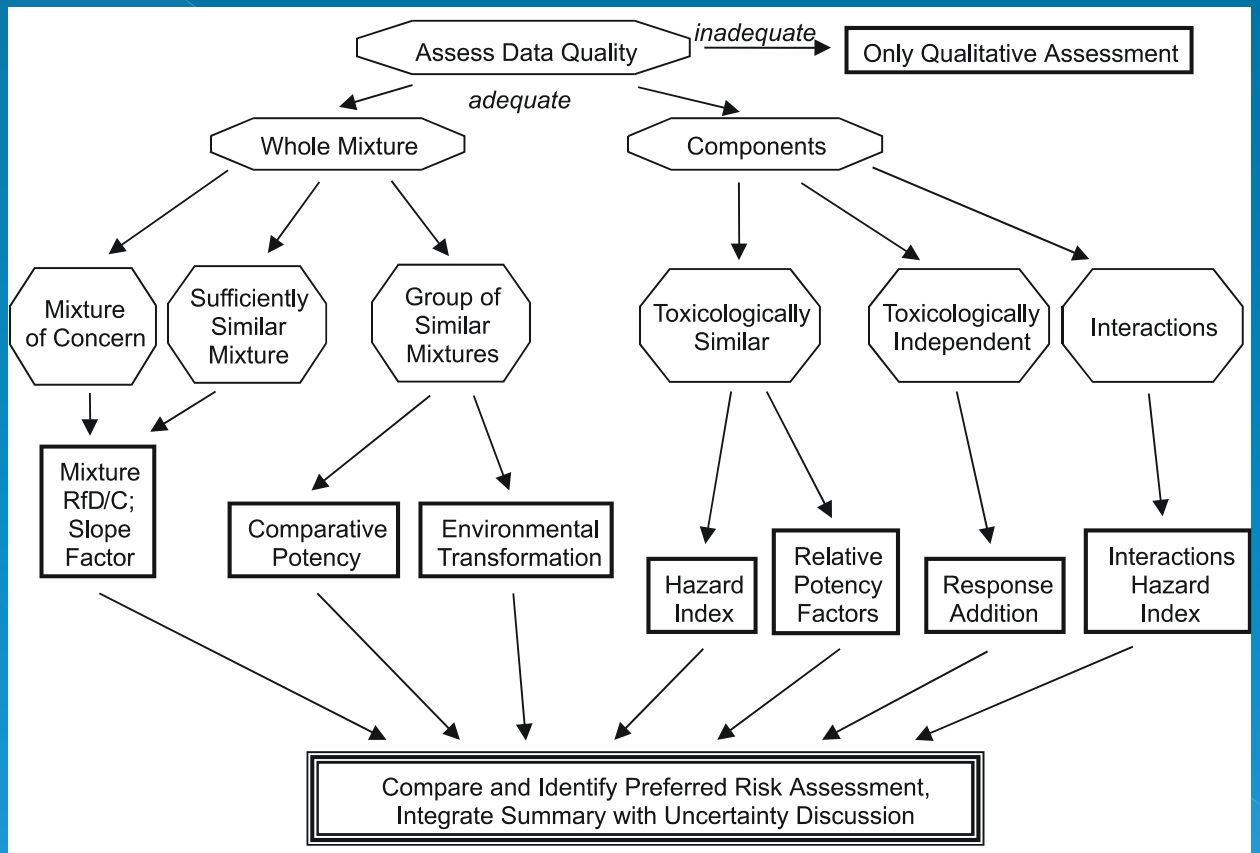


Figure 1.
Toxicity data for the dispersants, combining data from 3 cell-based assays with data on aquatic species [12]. Each horizontal band shows the data for one dispersant. Cell-based LC50 values (concentration at which 50% lethality or effect is observed) are indicated by circles. Aquatic species LC50 values are indicated by triangles. Note that all dispersants were tested in all assays, and missing data points indicate that no toxicity was seen in that assay at the highest concentration tested (1000 ppm). 95% confidence intervals are shown for all assays.



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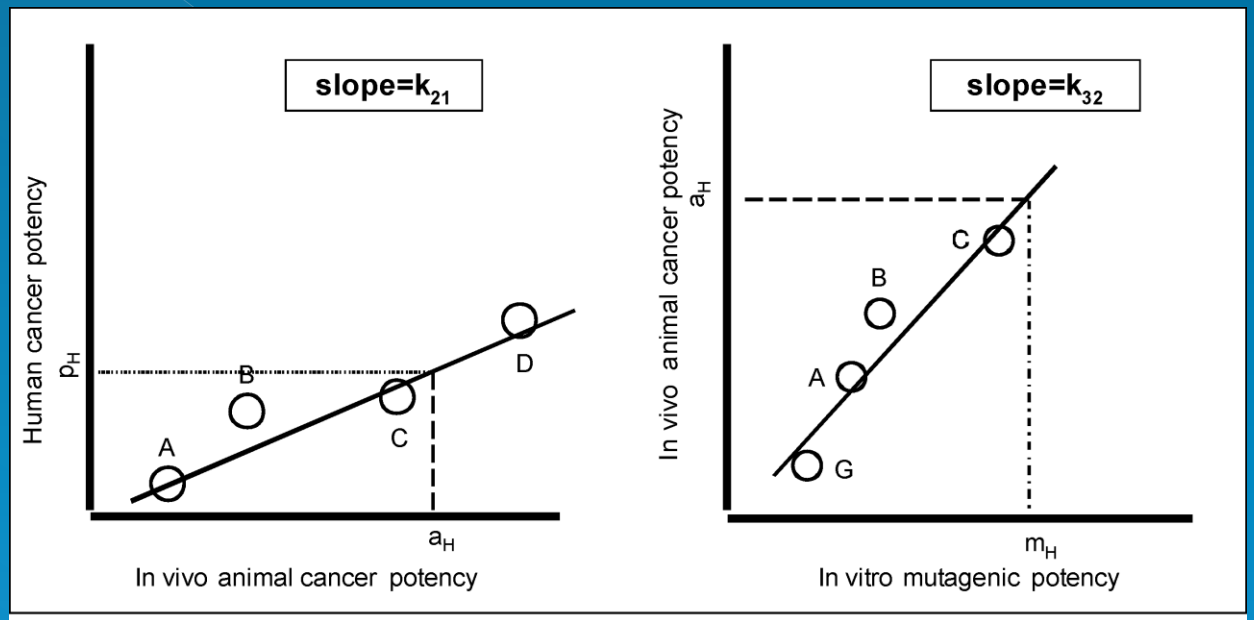

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