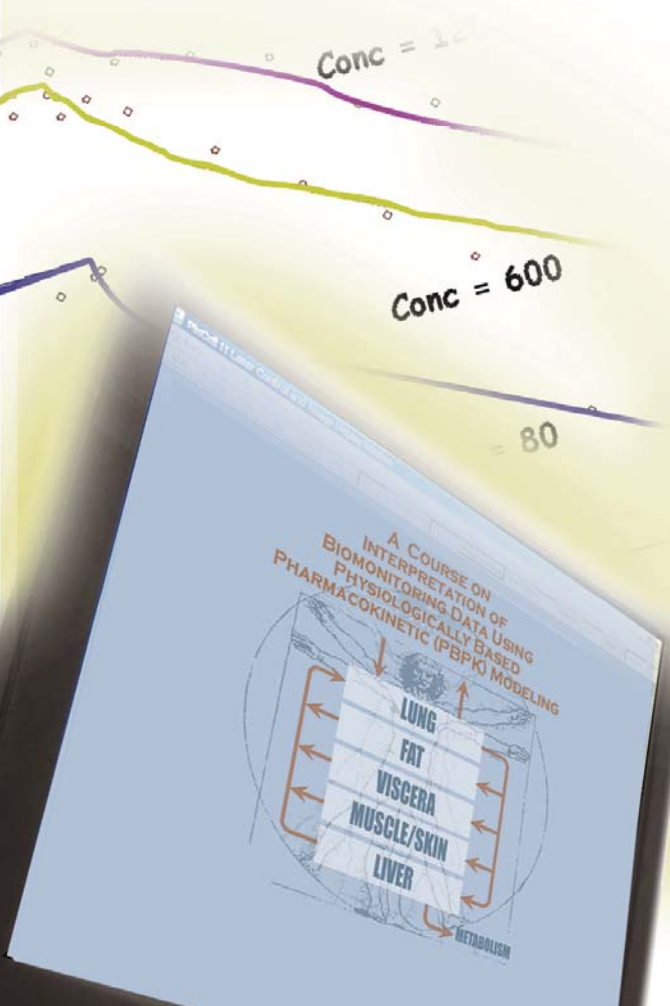


# Application of PBPK Modeling in Non-cancer Risk Assessment

Center for Human Health Assessment  
A Course on Physiologically Based Pharmacokinetic (PBPK)  
Modeling and Risk Assessment

February 11 – February 15, 2008



# Part 1: RISK ASSESSMENT

*“The characterization of the potential adverse effects of human exposures to environmental hazards.”*

- National Academy of Sciences, 1983

*All substances are poisons; there is none which is not a poison. The right dose differentiates a poison and a remedy.*

Paracelsus  
1493-1541

*Dancing with proper limitations is a salutary exercise, but when violent and long continued in a crowded room it is extremely pernicious, and has hurried many young people to the grave.*

A. Murray, M.D.  
1826

# Definition of Terms

## ***Risk Assessment:***

The qualitative or quantitative characterization of the potential adverse health effects to humans from exposures to environmental or occupational hazards.

## ***Risk Management:***

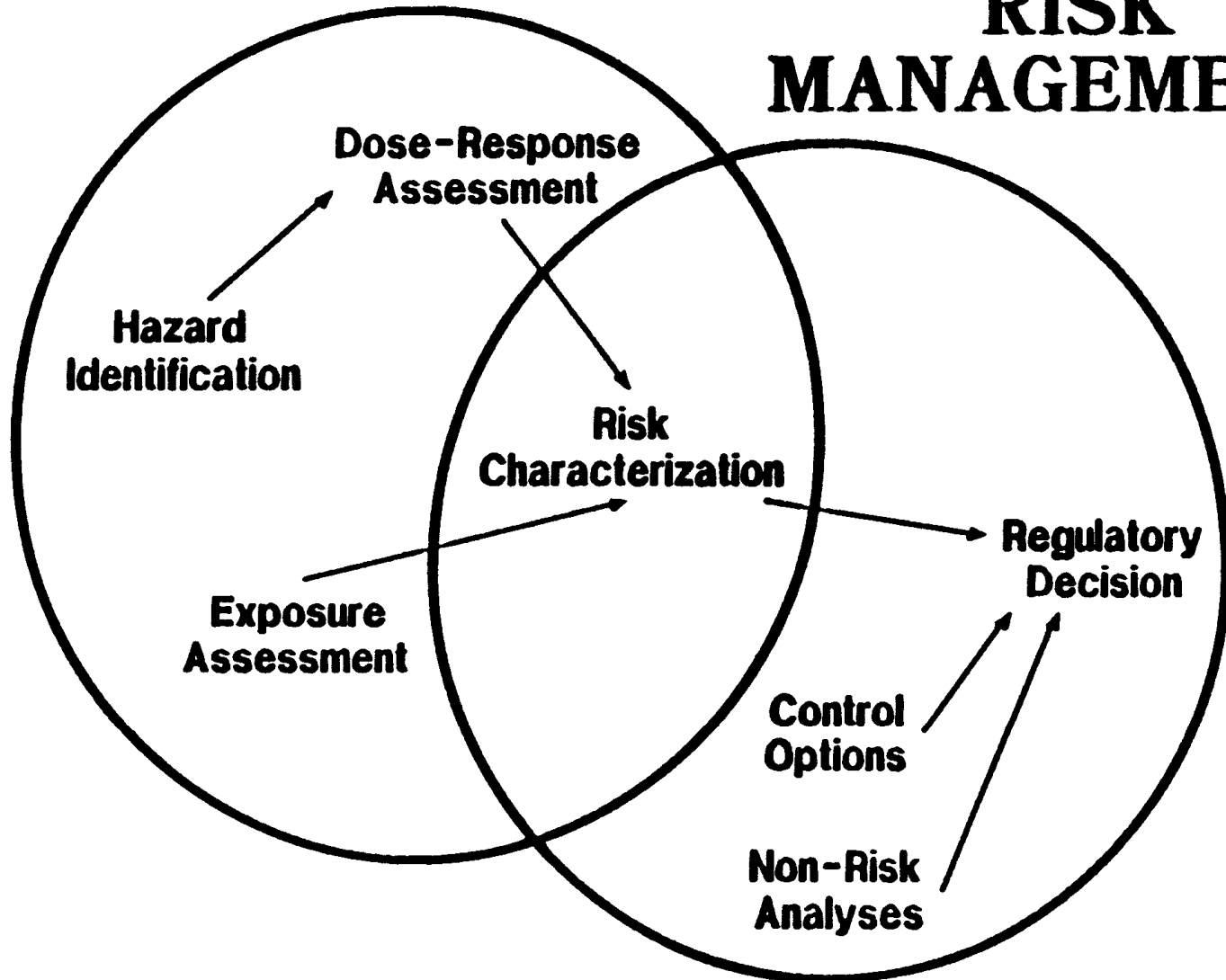
The process of evaluating alternative regulatory actions and selecting among them.

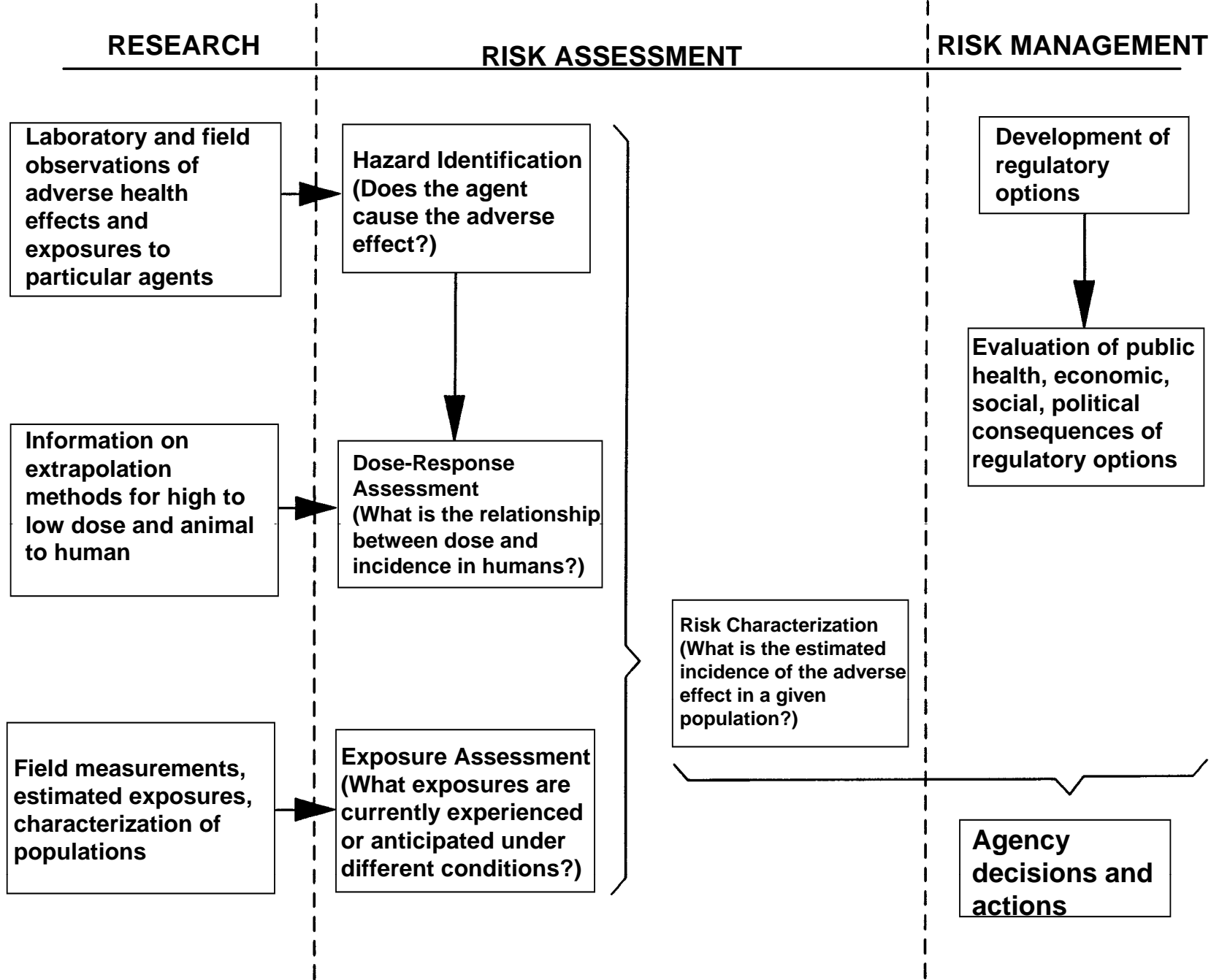
## ***Risk Perception:***

The general understanding of the relevance of risk to their particular situation.

# RISK ASSESSMENT

# RISK MANAGEMENT





**Elements of risk assessment and risk management**

# Risk Assessment Techniques Must Be Applied To A Wide Range Of Problems:

- Asbestos in buildings
- Contaminated drinking water
- Accidental releases
- Occupational exposure
- Leaching from a toxic waste dump
- Use of consumer products
- Pharmaceuticals

# Risk Assessment Is ...

- Part science and part policy
- Inherently conservative
- Inherently uncertain

# Cross-Species Extrapolation

<b>RELATIVE HUMAN RISK DEPENDS ON HOW DOSE RATE IS SCALED FROM EXPERIMENTAL ANIMALS TO HUMANS</b>				
	<b>Risk Projected for Humans When an Identical Dose is Scaled by Different Factors</b>			
<b>Experimental Animal</b>	<b>mg/kg bw/day</b>	<b>ppm in diet</b>	<b>mg/m<sup>2</sup>/day</b>	<b>mg/kg bw/lifetime</b>
<b>Mouse</b>	<b>1</b>	<b>6</b>	<b>14</b>	<b>40</b>
<b>Rat</b>	<b>1</b>	<b>3</b>	<b>6</b>	<b>35</b>

SOURCE: U.S. Congress Office of Technology Assessment (OTA)

# Approaches to Dealing with Uncertainty

- Assume “Worst Case” Values
  - Conservative Approach
- Use Uncertainty Factors
  - Intended to Provide Sufficient “Margin of Safety”

# Chemical Risk Assessment: Historical Development

- Risk assessment for noncancer effects
  - Approach initially developed at FDA
  - Assumption of a threshold for toxic effects
  - Identify No Observed Adverse Effect Level (NOAEL)
  - Divide by Safety (Uncertainty) factors
- Cancer risk assessment
  - NAS “Redbook”: Assumption of non-threshold genotoxic mechanism
  - FDA: Delaney Clause
  - EPA: Quantitative risk estimates as alternative to “zero”
  - OSHA: Supreme court decision on benzene; *de minimis* risk
  - “Linearized” multistage model developed in 1980s

# Chemical Risk Assessment

## Lack of Uniformity

- Differences Across Chemical Uses
  - Pharmaceutical components: FDA
  - Workplace exposures: OSHA
  - Environmental exposures: EPA (IRIS)
  - Pesticides: EPA OPP
  - New commodities: EPA OPPT
  - Consumer products: CPSC
- Differences Across Jurisdictions
  - U.S. federal
  - States (e.g., California Prop. 65)
  - Canada
  - Europe (e.g., REACH)
  - Developing countries

# Chemical Risk Assessment: Regulatory Agency Differences

- Congressional mandates differ across agencies
  - FDA: safety vs. efficacy
  - OSHA: “material impairment” vs. achievability
  - EPA: protection of public health without consideration of cost
    - More recently, some requirement for cost-benefit analysis
- Risk assessment approaches reflect mandates
  - Non-cancer:
    - FDA: ‘Margin of Safety’ approach
    - OSHA: adopted 1968 ACGIH TLVs, no formal approach
    - EPA: formal NOAEL/UF approach
  - Cancer
    - FDA: linear risk estimate
    - OSHA: maximum likelihood risk estimate
    - EPA: upper bound risk estimate

# EPA Noncancer Risk Assessment Paradigm

- **Acceptable exposure** based on highest No-Observed-Adverse-Effect-Level (NOAEL) below lowest Effect-Level (LOAEL)
- **Cross-species equivalence** based on mg/kg/day for oral exposure or calculation of Human Equivalent Concentration (HEC) for inhalation
- **Uncertainty factors** applied for:

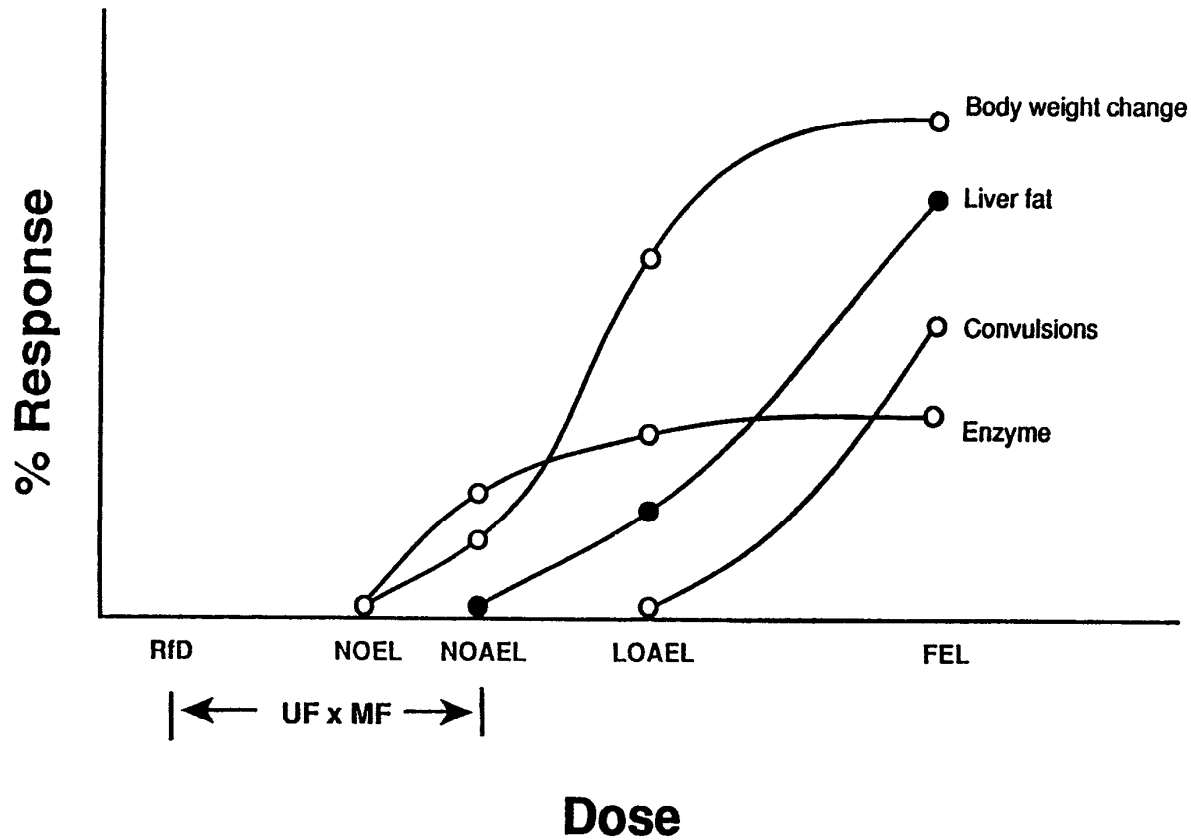
LOAEL to NOAEL	up to 10
short-duration to long	up to 10
animal to human	up to 10
human variability	up to 10
inadequate database	up to 10
maximum total:	3000

# Chronic Systemic Toxicity: Noncarcinogenic Health Effects

## Reference Dose (RfD)

“An estimate (with an uncertainty of one order of magnitude or more) of a lifetime dose which is likely to be without significant risk to human populations.”

# Estimating RfD from Experimental NOAEL



$$\text{RfC} = \frac{\text{NOAEL} * [\text{HEC}]}{\text{UF} \times \text{MF}}$$

Where:

NOAEL\*[HEC] = The NOAEL or equivalent effect level obtained with an alternate approach (\*), dosimetrically-adjusted to a human equivalent concentration [HEC],

UF = Uncertainty factor(s) applied to account for the extrapolation required from the characteristics of the experimental regimen to the assumed human scenario, and

MF = Modifying factor to account for scientific uncertainties in the study(ies) chosen as the basis for the operational derivation, e.g., poor statistical power or exposure characterization.

# Minimum Data Base for Both High and Low Confidence in the Inhalation RfC

(Rationale: address all critical life stages)

<b>Mammalian Data Base</b>	<b>Confidence</b>	<b>Comments</b>
<b>A. Two Chronic Inhalation Bioassays in Different Species</b>  <b>B. One 2-Generation Reproductive Study*</b>  <b>C. Two Developmental Toxicity Studies in Different Species*</b>	<b>High</b>	<b>Minimum Data Base for High Confidence</b>
<b>One Subchronic Inhalation Bioassay that Adressed Respiratory Tract and other Parameters</b>	<b>Low</b>	<b>Minimum Data Base for Estimation of an RfC</b>

# Dosimetric Adjustments to Derive HEC

- Type of Chemical: Particle or Gas
- Type of Effect: Respiratory or Extrarespiratory
- Type of Model: Optimal or Default

# Adjustment for Exposure Regimen

$$\text{NOAEL}_{\text{ADJ}}(\text{mg}/\text{m}^3) =$$

$$\text{Exposure Concentration} \times \frac{\text{Hours per Day}}{24} \times \frac{\text{Days per Week}}{7}$$

(mg/m<sup>3</sup>)

Note: It has been a common practice not to apply duration-adjustment to exposures associated with developmental toxicity.

# HEC Default Approach Particles

$$\text{NOAEL}_{\text{HEC}}(\text{mg}/\text{m}^3) = \text{NOAEL}_{\text{ADJ}}(\text{mg}/\text{m}^3) \times \text{RDDR}_r$$

$$\text{RDDR}_r = \frac{(\text{RDD})_A}{(\text{RDD})_H} = \frac{(10^{-6}C_i)_A}{(10^{-6}C_i)_H} \times \frac{(\text{Normalizing Factor})^*_H}{(\text{Normalizing Factor})_A} \times \frac{(\dot{V}_E)_A}{(\dot{V}_E)_H} \times \frac{(F_r)_A}{(F_r)_H}$$

RDDR = Regional Deposited Dose Ratio

RDD = Regional Deposited Dose

A = animal, H = human

r = Region of observed toxicity for extrapolation (e.g., tracheobronchial region)

\* = surface area for respiratory effects, body weight for remote effects

$C_i$  = Inhaled concentration ( $\text{mg}/\text{m}^3$ )

$V_E$  = Total ventilation rate ( $\text{m}^3/\text{hr}$ )

$F_r$  = fractional deposition

# HEC Default Approach

## Category One Gases: Extrathoracic Region

$$\text{NOAEL}_{\text{HEC}}(\text{mg}/\text{m}^3) = \text{NOAEL}_{\text{ADJ}}(\text{mg}/\text{m}^3) \times \text{RGDR}_{\text{ET}}$$

$$\text{RGDR}_{\text{ET}} = \frac{\left( \frac{C_i \dot{V}_E}{SA_{\text{ET}}} \right)_A}{\left( \frac{C_i \dot{V}_E}{SA_{\text{ET}}} \right)_H}$$

RGDR = Regional Gas Dose Ratio  
HEC = Human Equivalent Concentration  
ADJ = adjusted to continuous exposure  
A = animal, H = human  
 $C_i$  = Inhaled concentration ( $\text{mg}/\text{m}^3$ )  
 $V_E$  = Total ventilation rate ( $\text{m}^3/\text{hr}$ )  
SA = surface area

# Extra-respiratory Effects

## Category 3 Gases

$$\text{NOAEL}_{\text{HEC}} (\text{mg}/\text{m}^3) = \text{NOAEL}_{\text{ADJ}} (\text{mg}/\text{m}^3) \times \frac{\lambda_{\text{A}}}{\lambda_{\text{H}}}$$

HEC = Human Equivalent Concentration

ADJ = adjusted to continuous exposure

A = animal, H = human

Where  $\lambda$  = Blood:Air Partition Coefficient

If  $\lambda_{\text{A}} > \lambda_{\text{H}}$  or if  $\lambda$  values are unknown, the default for this ratio = 1.0.

# Human Occupational Default

$$\text{NOAEL[HEC]} = \text{NOAEL(TWA)} \times \frac{10 \text{ mg/m}^3}{20 \text{ mg/m}^3} \times \frac{5 \text{ days}}{7 \text{ days}}$$

# Disadvantages of NOAEL- Uncertainty Factor Approach

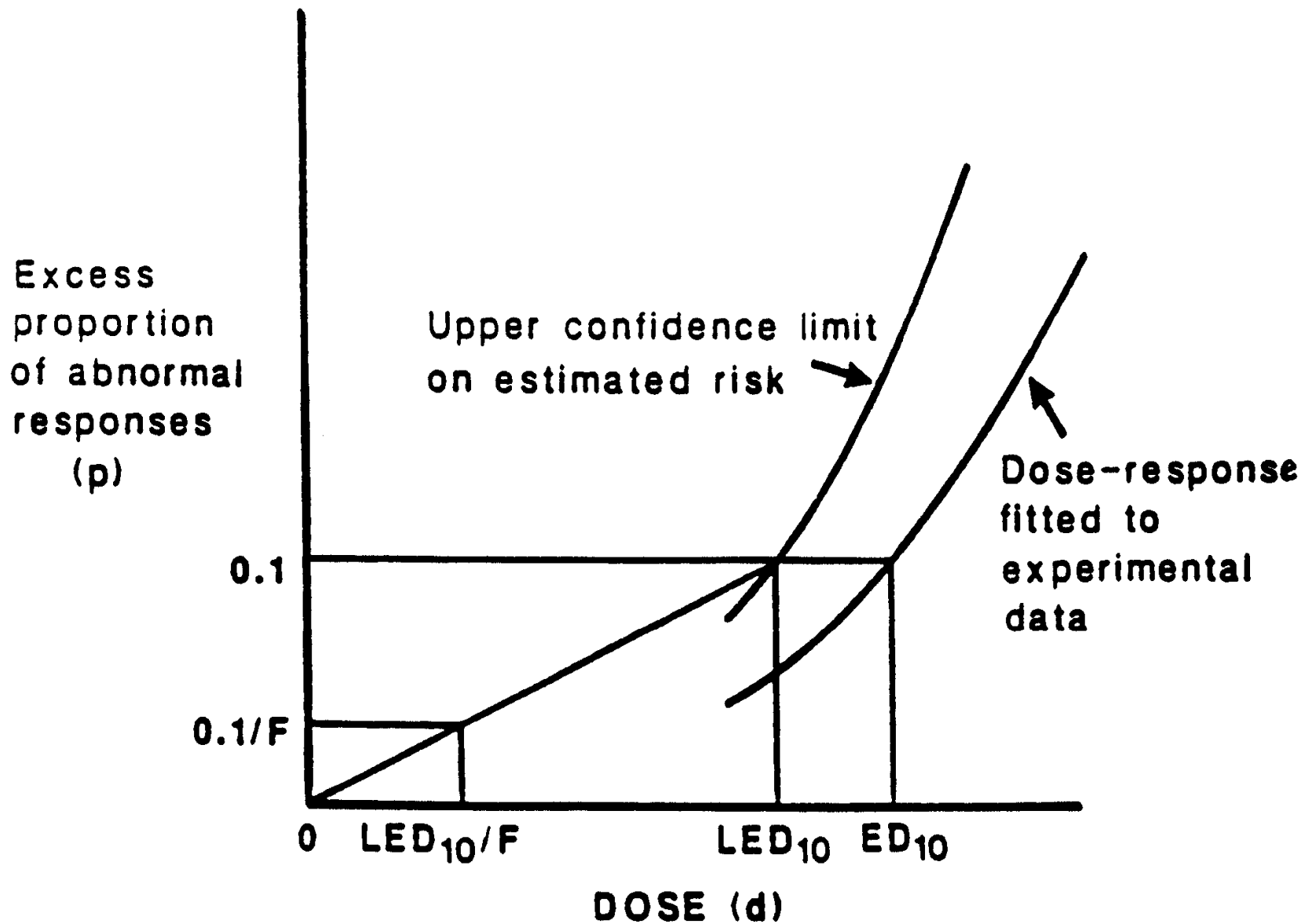
- Arbitrariness of uncertainty and modifying factors
- Discourages use of larger sample sizes
- May entail additional experimentation and expense
- Ignores dose-response relationships

# Benchmark Dose Analysis

## Methodology

- Benchmark Dose (BMD) = dose (or exposure) predicted to result in a specified increase in risk: the benchmark risk (BR)
- Calculated using a statistical dose-response model (e.g., polynomial or Weibull) applied to either experimental or epidemiological data
- Statistical lower bound on the Benchmark Dose (BMDL) has been proposed as a replacement for the NOAEL

# BENCHMARK APPROACH



# Benchmark Dose Analysis

## Ratios of NOAEL to BMDL<sup>a</sup>

Additional Risk	Mean Ratio NOAEL/BMDL ( $\pm$ SD)	Percentiles of Ratios						
		5th	10th	25th	50th	75th	90th	95th
0.1	2.9 ( $\pm$ 3.9)	0.49	0.66	1.1	2.0	3.8	5.2	7.2
0.05	5.9 ( $\pm$ 8.4)	0.87	1.1	1.7	4.0	7.8	11	15
0.01	29 ( $\pm$ 44)	2.2	2.9	6.6	19	40	56	80

Source: Faustman et al. (1994).

<sup>a</sup>95% lower statistical confidence bounds on lifetime dose corresponding to given level of additional risk

# Benchmark Dose Analysis

## Advantages over NOAEL/LOAEL

- Can estimate a NOAEL for a study in which only a LOAEL has been identified
- Provides comparability across studies with different dose-spacing and number of animals
- Does not require arbitrary categorization of the data in epidemiological studies
- Statistical lower bound appropriately reflects the sample size of the study and the variability of the data

Conjecture

~~Rule~~

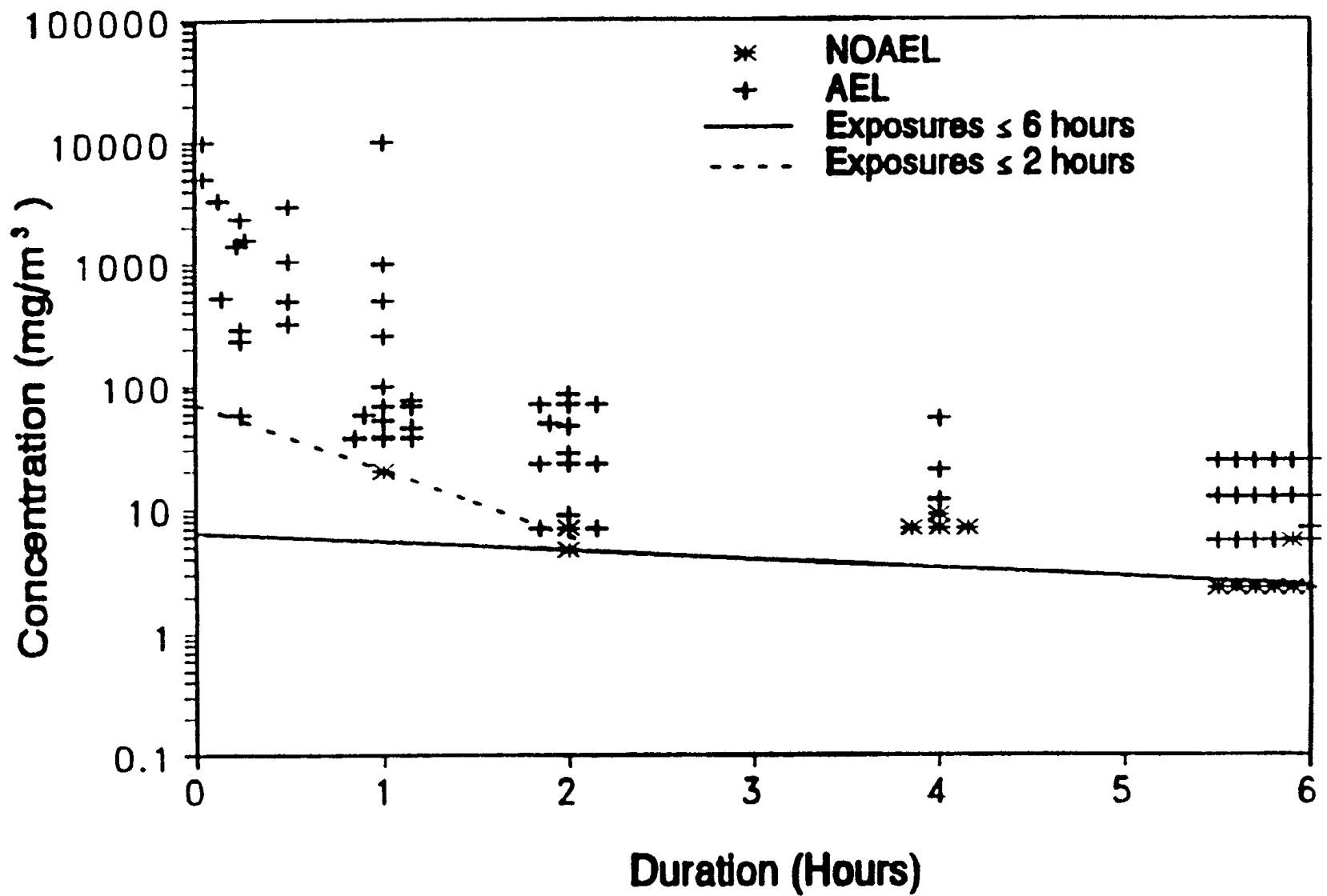
Haber's ~~Law~~:

$$D = C \times T$$

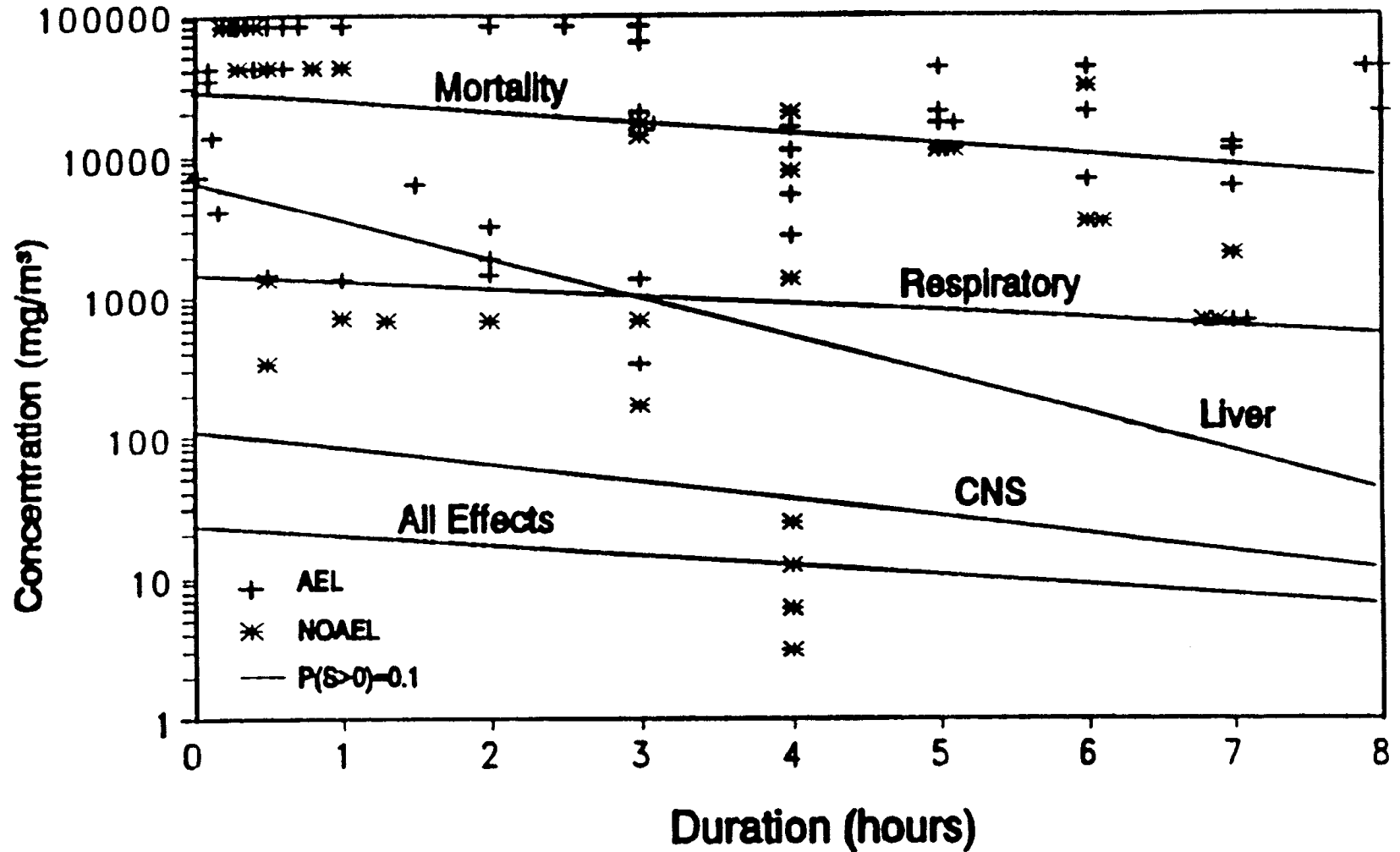
Across Species:

$$D = C \times V \times T$$

# A Chemical Can Have Different Concentration – Time Relationships Over Different Exposure Periods



# Different Effects of the Same Chemical Can Have Different Concentration – Time Relationships



# Chemical Risk Assessment

## Recent Trends and Future Directions

- Recent Trends: Greater Use of Chemical-Specific Data
  - Physiologically Based Pharmacokinetic Modeling
  - Use of chemical-specific mode of action information
- Growing Concern: Interpretation of Biomonitoring Data
  - CDC data on blood concentrations of chemicals in U.S.
  - Environmental monitoring of persistent compounds
- Future Directions: Computational Toxicology
  - Biologically Based Dose-Response Modeling
  - Use of genomic data
  - Modeling of cellular response (toxicity pathways)

# Part 2: Role of PBPK Modeling in Risk Assessment

Define the relationship between external concentration or dose and an internal measure of (biologically effective) exposure:

- in experimental animals
- in subjects from human studies
- in the population of concern

# Key Definitions In Contemporary Human Health Risk Assessment

(from the new USEPA Cancer Guidelines)

***Default*** – A generic, no-information approach, the use of which must be justified on the basis of the lack of necessary data to conduct a chemical-specific approach

***Mode of Action*** - in a broad fashion, the critical steps involved in the causation of specific biological responses.

***Dosimetry*** – Estimation of the target tissue exposure to the form of the chemical that is most directly related to the tissue responses.

***Mode of Action Statement*** - expresses the biological basis of the response and the form of chemical involved in causing the response.

# Value of PBPK Modeling in Chemical Risk Assessment

**Exploratory** - Calculate alternative measures of tissue dose and correlate with toxic effects.

**Mechanistic** - Characterize relationships between potential dose measures and early biochemical responses and determine consistency with mode-of-action hypotheses.

**Interpretive** - Use selected dose metric to determine relationship of tissue dose to response for evaluating acceptable exposure levels based on extrapolation across dose, dose-route, and species.

# Applications of PBPK Modeling in Human Risk Assessment by Regulatory Agencies

- Methylene Chloride (EPA, OSHA, ATSDR, Health Canada)
- 2-Butoxy Ethanol (EPA, Health Canada)
- Vinyl Chloride (EPA)
- Chloroform (Health Canada)
- Dioxin (EPA)
- Trichloroethylene (EPA)
- Perchloroethylene (EPA)
- Isopropanol (EPA)

# Steps for Incorporating PBPK Modeling in Human Health Risk Assessment

- Identify toxic effects in animals or human populations
- Evaluate available data on mode(s) of action, metabolism, for compounds and related chemicals
- Describe potential mode(s) of action
- Propose relationship between response and tissue dose
- Develop/adapt an appropriate PBPK model
- Estimate tissue dose during toxic exposures with model
- Estimate risk in humans based on assumption of similar tissue response for equivalent target tissue dose

# Application of Pharmacokinetics in Risk Assessment

## Underlying Assumption: Tissue Dose Equivalence

- Effects occur as a result of tissue exposure to the toxic form of the chemical.
- Equivalent effects will be observed at equal tissue exposure/dose in experimental animals and humans.
- Appropriate measure of tissue dose depends critically on the mode of action for the effect of the chemical.

# Mode of Action Considerations

- **Parent Chemical** (ethylene oxide)
  - vs. Stable Metabolite (2-butoxyacetic acid from EGBE)
  - vs. Reactive Metabolite (methylene chloride)
- **Physical** (acute neurotoxicity of solvents)
  - vs. Reactivity (formaldehyde)
  - vs. Receptor Binding (dioxin)
- **Direct Genotoxicity** (mutations from vinyl chloride adducts)
  - vs. Indirect (oxidative stress from NO donors)
  - vs. Nongenotoxic (arsenic inhibition of DNA repair)

# Implications of Cellular Interactions

- Chemical Reactivity:



- Receptor Binding:

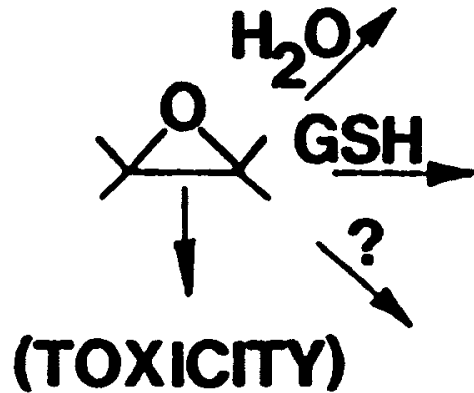


# Dose Metrics

## General Principles

- Stable Chemicals (Parent or Metabolite):
  - Area Under the Curve ( $C \times T$ )
  - Peak Concentration
- Acute Toxicity:
  - $C^n \times T$
- Reactive Intermediates:
  - Amount Produced / Tissue Volume

- Parent Chemical Example: Ethylene Oxide

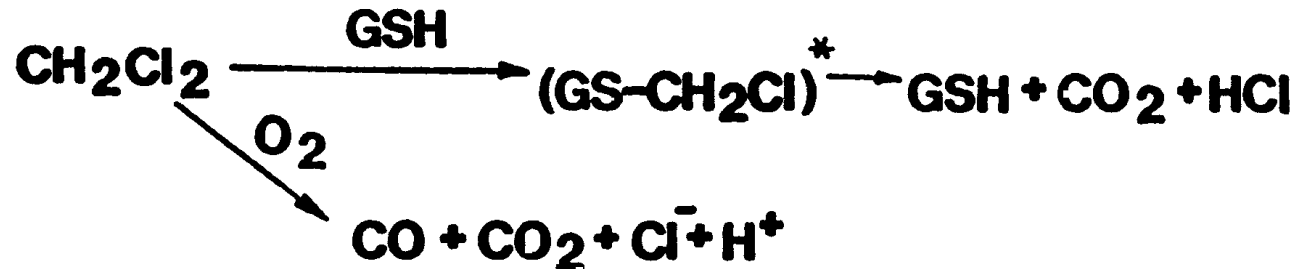


- Tissue dose related to integrated tissue exposure (i.e., area under curve)

$$\text{dose} = \int ( \text{ethylene oxide} ) dt$$

- Pharmacokinetic factors indicate tissue dose should increase with body size.

- **Reactive Metabolite Example: Methylene Chloride**



- **TISSUE DOSE =  $\int (\text{GSCH}_2\text{Cl}) \cdot dt$**

- Cannot measure (GS-CH<sub>2</sub>Cl). Dose is related to rate of formation and tissue volume if further steps are concentration independent.

- Pharmacokinetic factors indicate tissue dose should decrease with increasing body size.

# Human Equivalent Concentrations Based on Pharmacokinetic Dose Metrics for Three Volatile Chemicals<sup>1</sup>

## Inhalation Exposure

- Toxicity Due to **Parent Chemical Exposure** (MC, TCE, VC):
  - PBPK HEC *similar* to default
- Toxicity Due to **Reactive Metabolite** (MC, VC):
  - PBPK HEC 5 - to 25-fold *higher* than default
- Toxicity Due to **Stable Metabolite** (TCE):
  - PBPK HEC *similar* to 10-fold *lower* than default

<sup>1</sup> Based on PBPK model calculations for methylene chloride (MC), trichloroethylene (TCE), and vinyl chloride (VC)

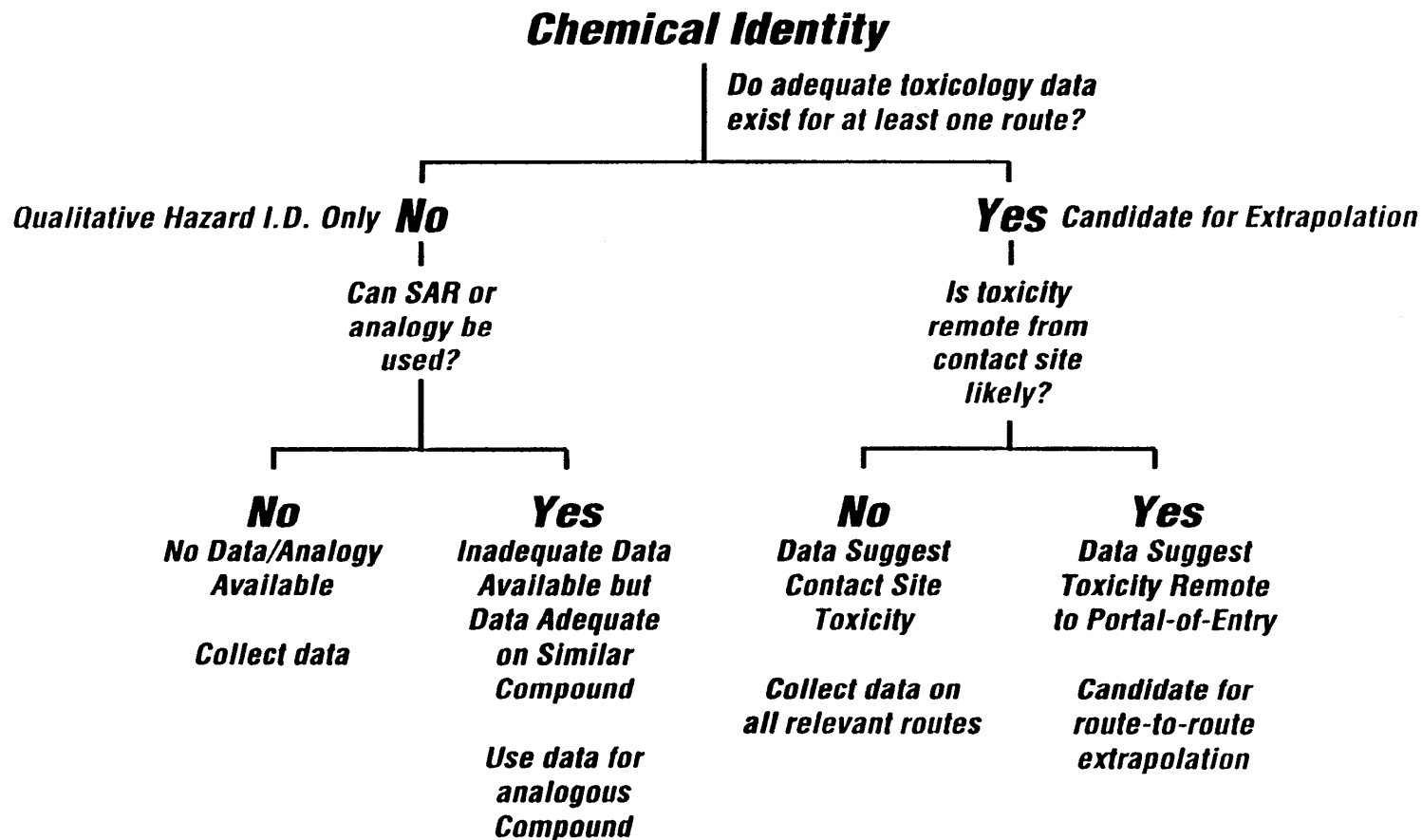
# Human Equivalent Concentrations Based on Pharmacokinetic Dose Metrics for Three Volatile Chemicals<sup>1</sup>

## Oral Exposure:

- Toxicity Due to **Parent Chemical Exposure** (MC, TCE, VC):
  - PBPK human dose 10- to 100-fold *lower* than RfD default
- Toxicity Due to **Reactive Metabolite** (MC, VC):
  - PBPK human dose *similar* to RfD default
- Toxicity Due to **Stable Metabolite** (TCE):
  - PBPK human dose 15- to 60-fold *lower* than RfD default

<sup>1</sup> Based on PBPK model calculations for methylene chloride (MC), trichloroethylene (TCE), and vinyl chloride (VC)

# Decision Tree for Route-to-Route Extrapolation



*(Source: U.S. EPA/LSI Workshops on Principles of Route-to-Route Extrapolation for Risk Assessment, 1990)*

# Decision Tree for Route-to-Route Extrapolation

## Option 4: Data Suggest Toxicity Remote to Portal-of-Entry

- Use of Default Absorption Values
- Direct Measure of Absorption Efficiency
- Measure of Bioavailability by Internal Marker
- Development of a Comprehensive Delivered Dose Description

**(Source: U.S. EPA/LSI Workshops on Principles of Route-to-Route Extrapolation for Risk Assessment, 1990)**

# Summary: Use of PBPK Modeling in Risk Assessment

- **Most important impact:** Estimating cross-species and route-to-route equivalence
- **Challenge:** Selection of dose metric based on mode of action
- Pharmacokinetic principles can be applied without full PBPK model (e.g., IRIS entry for Boron compounds)
- Can develop categorical pharmacokinetic defaults for cross-species extrapolation (Beck et al. 2001):

Compound	Oral Scaling	Inhalation Scaling
Parent	$BW^{3/4}$	BW
Circulating Metabolite	$BW^{3/4}$	BW
Reactive Metabolite	BW	$BW^{-3/4}$