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a nonprofit corporation dedicated to the best use of toxicity data for risk values

Air Toxics: Risk Based Analysis

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Lifeline

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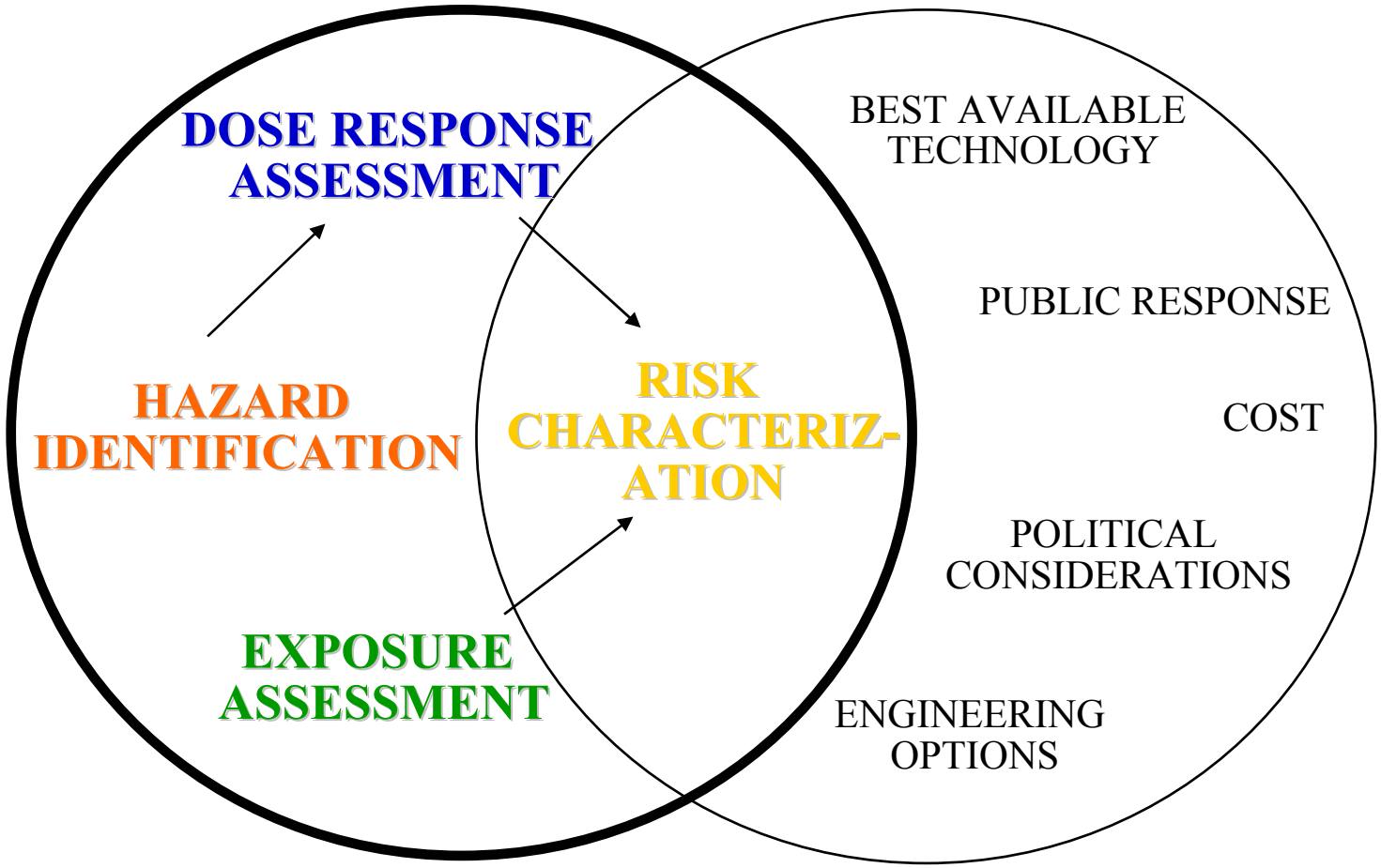
Risk Assessment/Management



NAS 1983

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The 4 Steps of the Risk Assessment Process

- **Hazard Identification:** Determine the nature & significance to human health of the observed effects. What does the chemical do?
- **Dose-Response Assessment:** Determine how the chemical causes effects in relationship to dose. How does the chemical do it?
- **Exposure Assessment:** Determine the characteristics, magnitude, and relevance of the experimental or observed routes of exposure. How are we exposed to the chemical?
- **Risk Characterization:** Integrate previous 3 steps into a format that promotes decision making. So what? What is the safe or de minimus level?

Communicate process to risk managers

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Hazard Identification and Dose Response Assessment = Health Assessment

Reference Dose (RfD) or Reference Concentration (RfC) is ...

an estimate (with uncertainty spanning perhaps an *order of magnitude*) of

a *daily* (for RfD) or *continuous* (for RfC) exposure to the human population (including *sensitive subgroups*)

that is *likely to be without* an appreciable risk of deleterious effects during a lifetime.

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Health Assessment (non-cancer)

$$\text{RfD or RfC} = \frac{\text{NOAEL, LOAEL or BMD}}{\text{UF}}$$

NOAEL = The No Observed Adverse Effect Level
LOAEL = The Lowest Observed Adverse Effect Level
BMD = Benchmark Dose
UF = Uncertainty factor(s) applied to account for the extrapolation required from the characteristics of the experimental regimen to the assumed human scenario

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Several Judgments Are Needed

such as...

the choice of the most appropriate No-Observed-Adverse-Effect Level (NOAEL) or benchmark dose (BMD) of the critical effect, usually from experimental animal data, and

the choice of the appropriate uncertainty factors based on a review of the entire data base.

Critical effect is first adverse effect
or its known precursor.

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What is the Critical Effect?

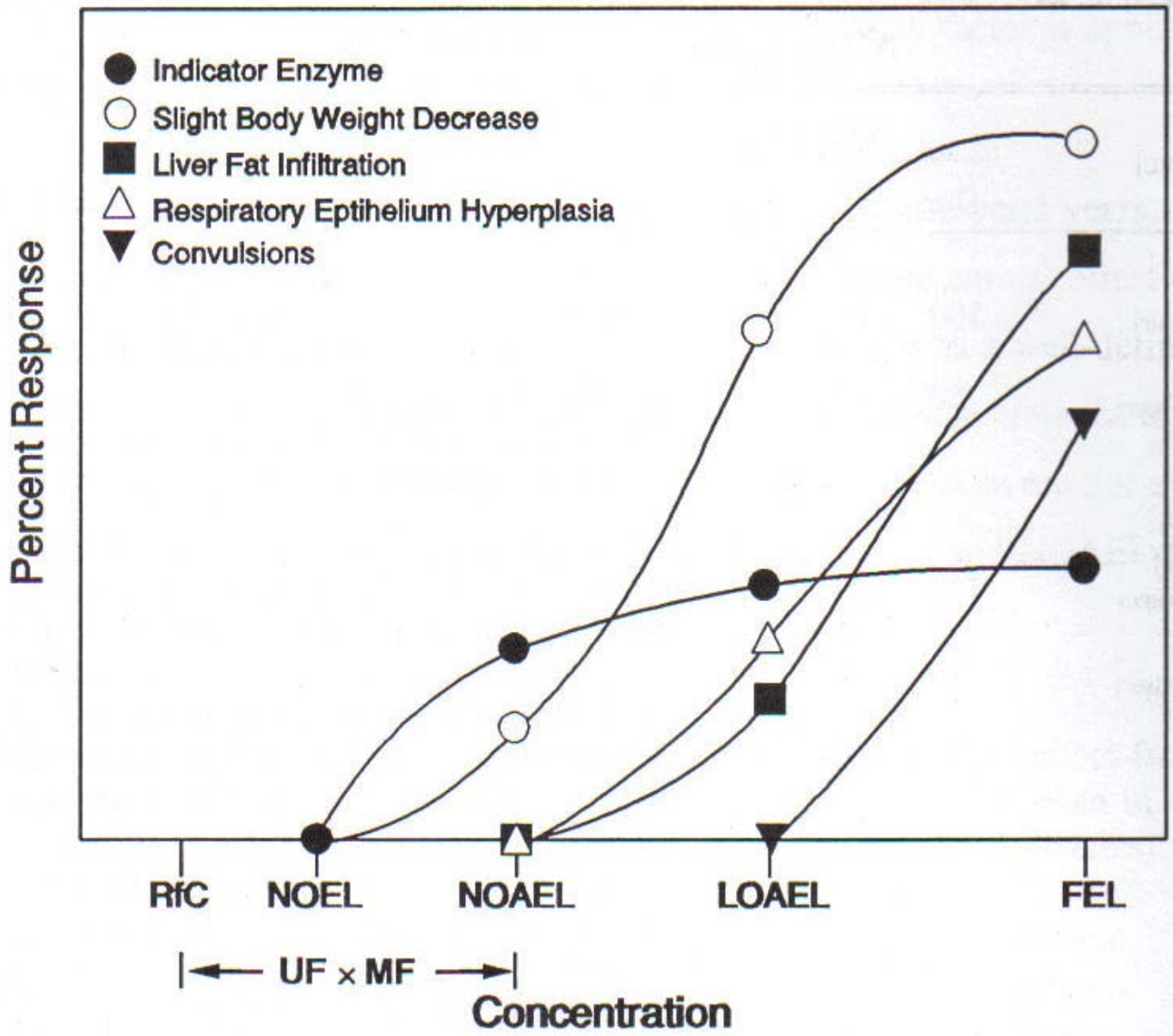

Figure 4-11. Example data array and inhalation reference concentration (RfC) derivation.

U.S. EPA , 1994

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Uncertainty and Variability

- Uncertainty = lack of knowledge
  - In toxicity from studies of different lengths
  - Of doses or exposures showing no effect
  - In toxicity in younger or older individuals
- Variability = differences in response due to kinetics and/or dynamics
  - From experimental animals to humans
  - Among humans

Kinetics = what you do to the chemical

Dynamics = what the chemical does to you

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Uncertainty Factors in the Development of RfDs or RfCs

Ufs	Health Canada	IPCS	RIVM	ATSDR	EPA
Interhuman	10 (3.16 x 3.16)	10 (3.16 x 3.16)	10	10	10
Animal to Human	10 (2.5 x 4.0)	10 (2.5 x 4.0)	10	10	10 (RfD) 3 (RfC)
Subchronic to chronic	1-100	1-100	10	NA	≤ 10
LOAEL to NOAEL			10	10	≤ 10
Incomplete database			NA	NA	≤ 10
Modifying Factor	1-10	1-10	NA	NA	0 < to ≤ 10

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Chromium VI - RfC Summary

- Critical Effect: Human nasal septum atrophy
- NOAEL: none
- **LOAEL: 2E-3 mg/m^3 [7.14 E-4 mg/m^3 (HEC)]**
- Uncertainty Factor: 90
  - 3 UF for subchronic to chronic
  - 3 UF for LOAEL to NOAEL
  - 10 UF for interhuman variation
- Modifying Factor: 1
- RfC = 8E-6 mg/m^3

HEC = Human Equivalent Concentration

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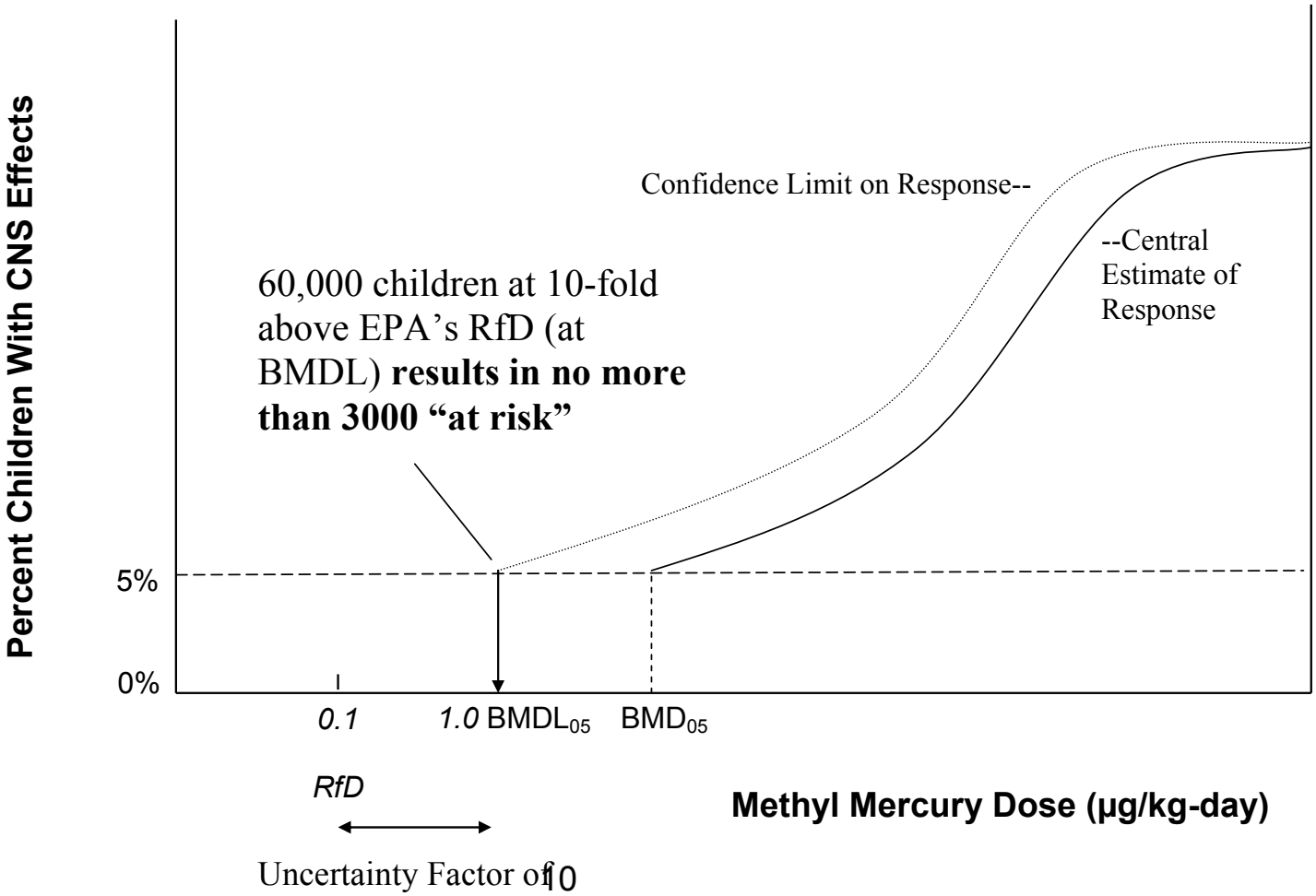
"Safe" Doses for Mercury Compared

	ICF	ATSDR	RIVM	EPA	WHO
"Safe" Dose (µg/kg-day)	**0.3 to 1**	0.3	0.1	0.1	0.23
Year	1998	1999	2000	2001	2003
Study	Seychelles	Seychelles	Seychelles	Seychelles, Faroes, New Zealand	Seychelles, Faroes
NOAEL/BMD (µg/kg-day)	0.9 to 3	1.3	1.3	0.9 to 1.5	1.5
Uncertainty Factors	3	4.5	10	10	6.4

Adapted from www.tera.org/iter

Observed Range of CNS Effects in Faroe Children



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Definition of Chemical Exposure Terminology

- The word "Exposure" has been given multiple meanings in multiple communities who have practiced exposure assessment

- Exposure has been used to mean
  - Concentration in the contact media
  - Concentration * Duration
  - Dose (mass that crosses the boundary)
  - Dose Rate (mass that crosses the boundary per unit time)

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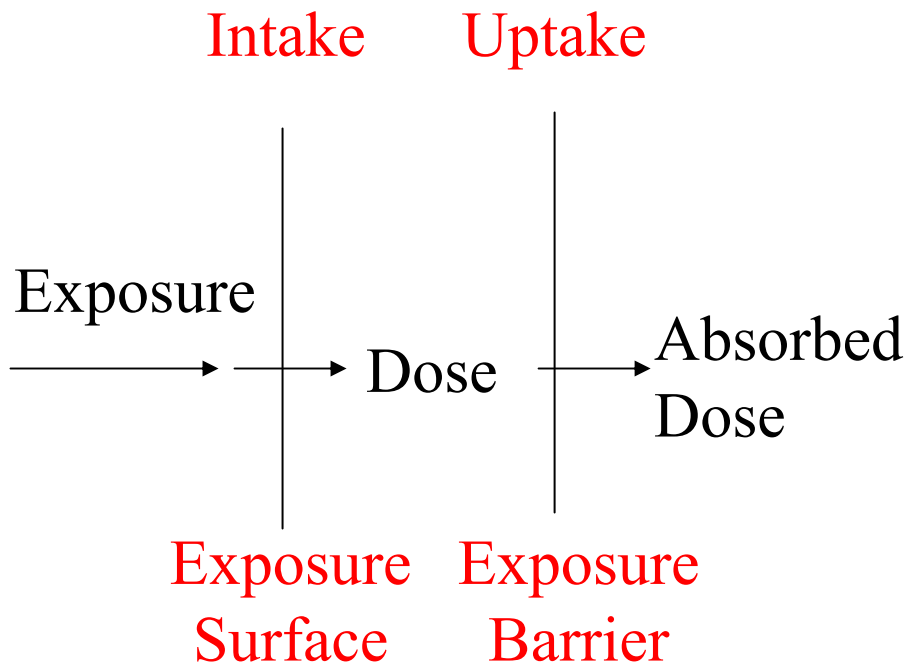
Definition of Terms

International Programme on Chemical Safety:

Harmonization of Approaches to the Assessment of Risk from Exposure to Chemicals



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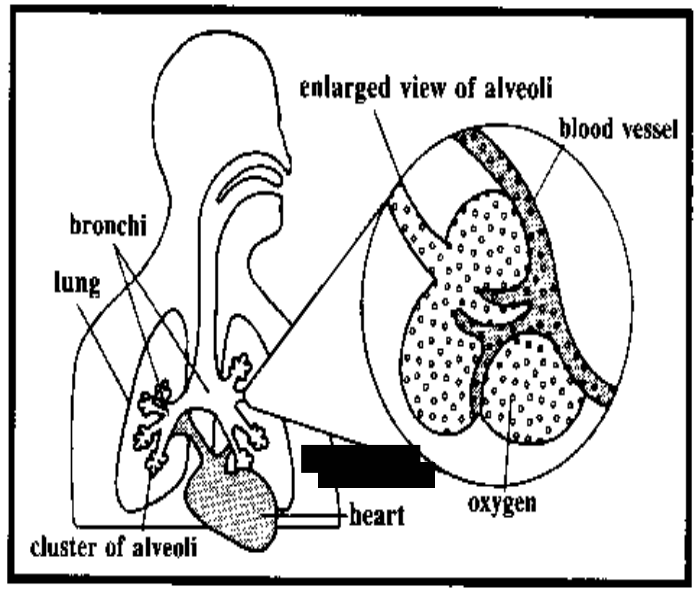
Inhalation Exposure

- Exposure surface is the mouth
- Exposure barrier is the alveoli wall
- An inhaled dose is an intake
- An absorbed dose is an uptake



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Inhalation Exposure

- Absorption take place in different places
  - Large particles and water soluble gasses-upper respiratory
  - Gasses and small particles in the alveoli
  - Mucociliary pathway (Inhalation becomes oral)
- Absorption can be complex
  - Concentration, time, breathing rate, and person specific
- Rule of thumb - 50% for lipophilic gasses and 100% hydrophilic gasses

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Tiered Analyses (Traditional)

- Complex models require expensive or unavailable data
- Simple screening models require minimal data and provide conservative answers
- Traditional solution: a tiered approach to models
  - Simple conservative screening models
  - More complex models for compounds/sources of exposures that fail the screening analysis

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Tiered Analyses (Future)

- Screening models benefit from complex analysis of factors that are not chemical or source dependent, such as:
  - Food consumption (How much fish do we eat?)
  - Activity pattern (How long do we sit on porch?)
  - Product use (How often to we gas up?)
  - Physiology of exposed individuals (Is the school near a point source?)
- Goal create a single screening/complex model that provides the best possible estimate of exposure for:
  - Chemicals with minimal data
  - But take into account additional data when it becomes available

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Air Models

- Point source releases
  - TOXST/LT
- Indoor air (Source to air)
  - CONTAM
  - IAXQ-Excellent source models
  - RISK
  - MCCEM-Muti-room
- Microenvironment Models
  - CPIEM
  - TEM-Tapwater
  - NEM/pNEM/HAPEM-MS/SHAPE/SCREAM
  - TRIM/APEX (2.0)

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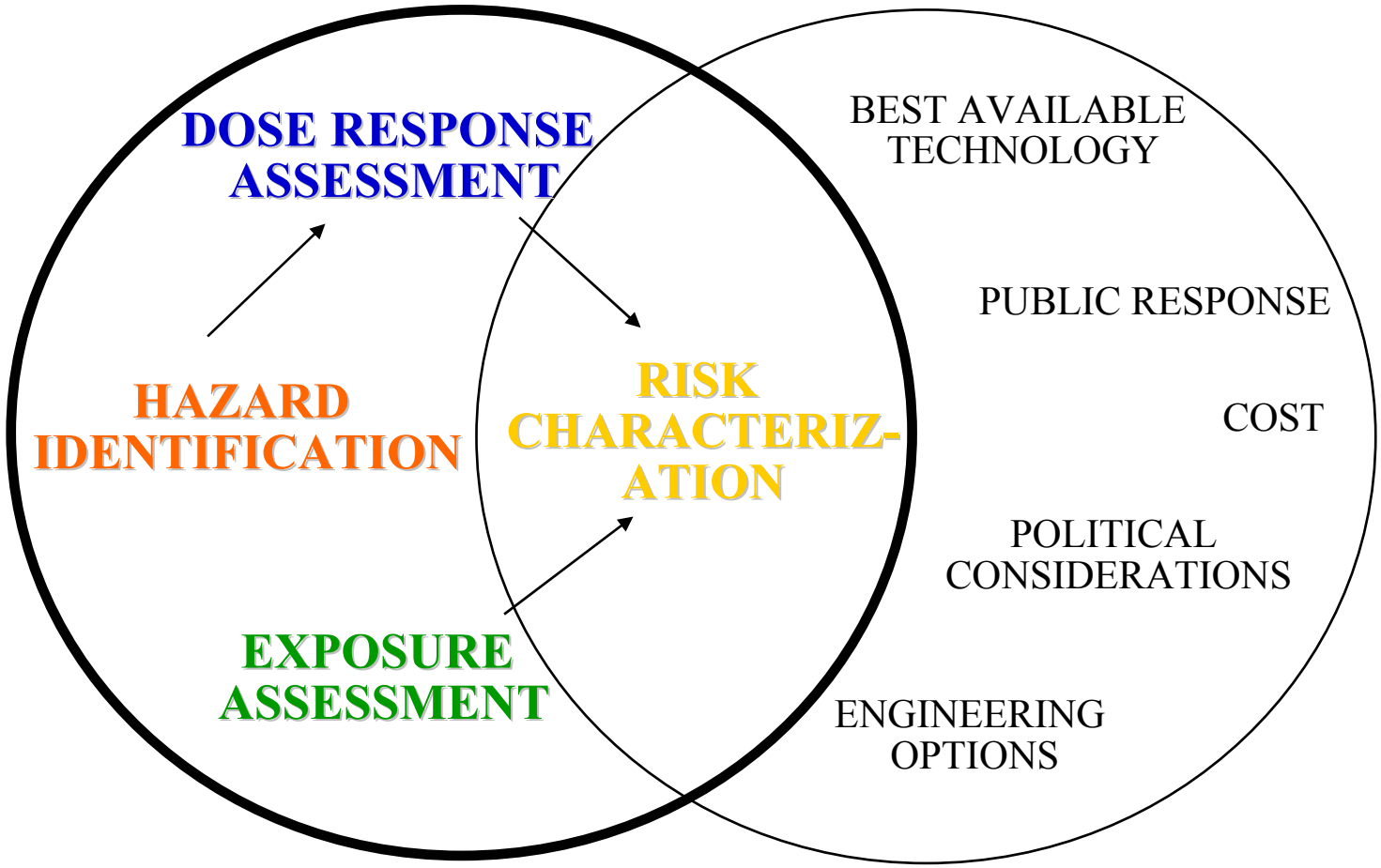

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Role of Risk Characterization in Risk Management

- You can't regulate the toxicity of chemicals, the radioactivity of isotopes or the virulence of microbes, but you can chose the population to protect, since "safe" doses will be different. "Safe" or de minimus doses are imprecise.
- You can regulate exposure. Therefore exposure assessment plays a role in the:
  - initial assessment,
  - fashioning of remedies, and
  - evaluation of the effectiveness of controls

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Questions for those pesky….risk assessors

What is the critical effect?

Should other routes of exposure be considered?

How do the risks differ for non-sensitive populations?

What uncertainties exist with the proffered safe or *de minimus* exposure level?

What are alternative judgments of risk?

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Summary

- Heath assessment determines the critical effect and uncertainties in the existing database.
- Exposure assessment determines the relationship between a source and the exposed individuals.
- Modeling is a critical part of both health and exposure assessment by providing a framework for the integration of data.
- Risk assessment scientists should be able to clearly explain the uncertainties in the resulting safe or de minimus concentrations and alternative interpretations.

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Extra Slides

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Statement of Purpose & Mission

Toxicology Excellence for Risk Assessment (*TERA*) is a non-profit, 501(c)(3) corporation organized for scientific and educational purposes.

The mission of *TERA* is to protect public health by developing and communicating risk assessment values, to improve risk assessment methods through research, and to educate the public on risk assessment issues.

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TERA: Specific Activities

- Establishing high quality risk assessment values through the Verifiable Estimates for Risk Assessment (*VERA*) program;
- Compiling and distributing peer reviewed risk values through the International Toxicity Estimates for Risk (*ITER*) database;
- Sponsoring expert peer consultation and review of risk values;
- Improving the underlying methods for risk assessment through research and publication;
- Educating diverse groups through training courses, scientific support and the State Hazard Evaluation Lending Program (State HELP);
- Facilitating improved risk assessment and management decisions through informed and neutral guidance.

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RfC Dosimetry

- NOAELs and LOAELs are converted by dosimetric adjustments to Human Equivalent Concentrations (HECs) before determination of a critical effect.

- This conversion determines the exposure concentration that would result in the same tissue dose in humans as the animals experienced.

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RfC Dosimetry (2)

- Dosimetric adjustments take into account structural and physiological differences between humans and the test species. They also take into account the effect of a contaminant's chemical and physical properties on the dose-response relationship.
- Current methods are based on simplified models and are based solely on relative deposition. More complex models address clearance from lung or reaction with lung tissue.
- Physiologically based pharmacokinetic (PBPK) models can provide the greatest detail.

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RfC Dosimetric Adjustment (1)

- mg/m3 = ppm x MW / 24.25
- NOAEL[ADJ] (mg/m3-day) = E (mg/m3) x D (h/24) x W (days/7 days)

NOAEL[ADJ] = NOAEL adjusted for duration of experimental regimen;
E = experimental exposure level;
D = number of hours exposure/24 hours;
W = number of days of exposure/7 days.

Adjustment for NOAEL of 30 mg/m3 for 6 hours per day and 5 days a week: 30 mg/m3 x 6/24 x 5/7 = 5.4 mg/m3

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RfC Dosimetric Adjustment (2)

- $NOAEL_{[HEC]}$ (mg/m^3) = $NOAEL_{[ADJ]}$ (mg/m^3) x DAFr

$NOAEL_{[HEC]}$ = human equivalent NOAEL;

DAFr = dosimetric adjustment factor:

Either the regional deposited dose ratio (RDDRr) for particles or the regional gas dose ratio (RGDRr) for gases;

r = extrathoracic (ET), tracheobronchial (TB), pulmonary (PU), thoracic (TH), or total.

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Figure 5a. Cumulative Response as a function of Dose for Humans and Rats. Data are hypothetical, but approximate real situations.

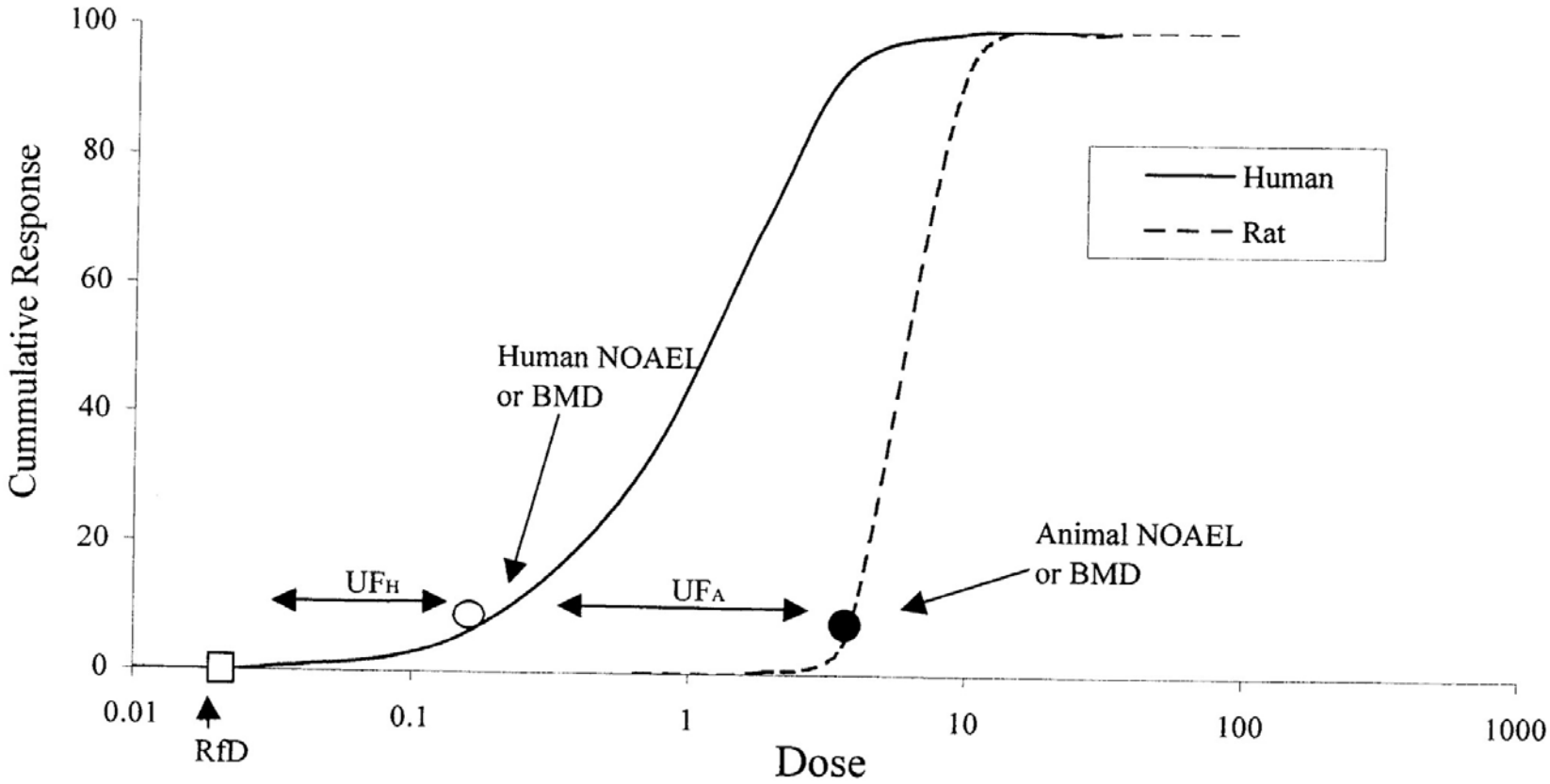


Figure 5b. Response as a function of Dose for Humans and Rats. Hypothetical data are the same as in Figure 5a.

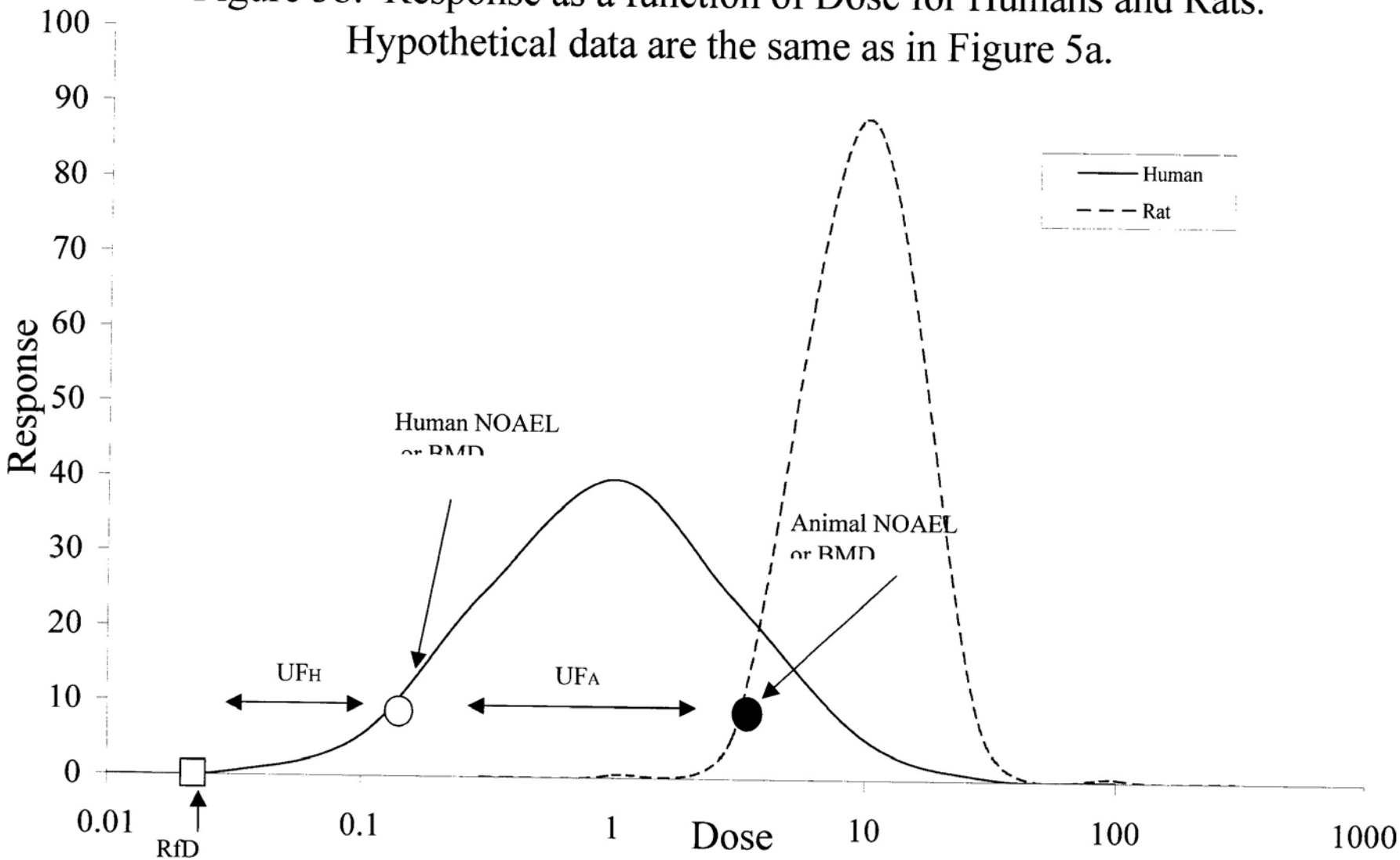


Figure 6a. Response as a function of dose for humans of different sensitivities. Hypothetical data for humans are the same as in Figure 6b.

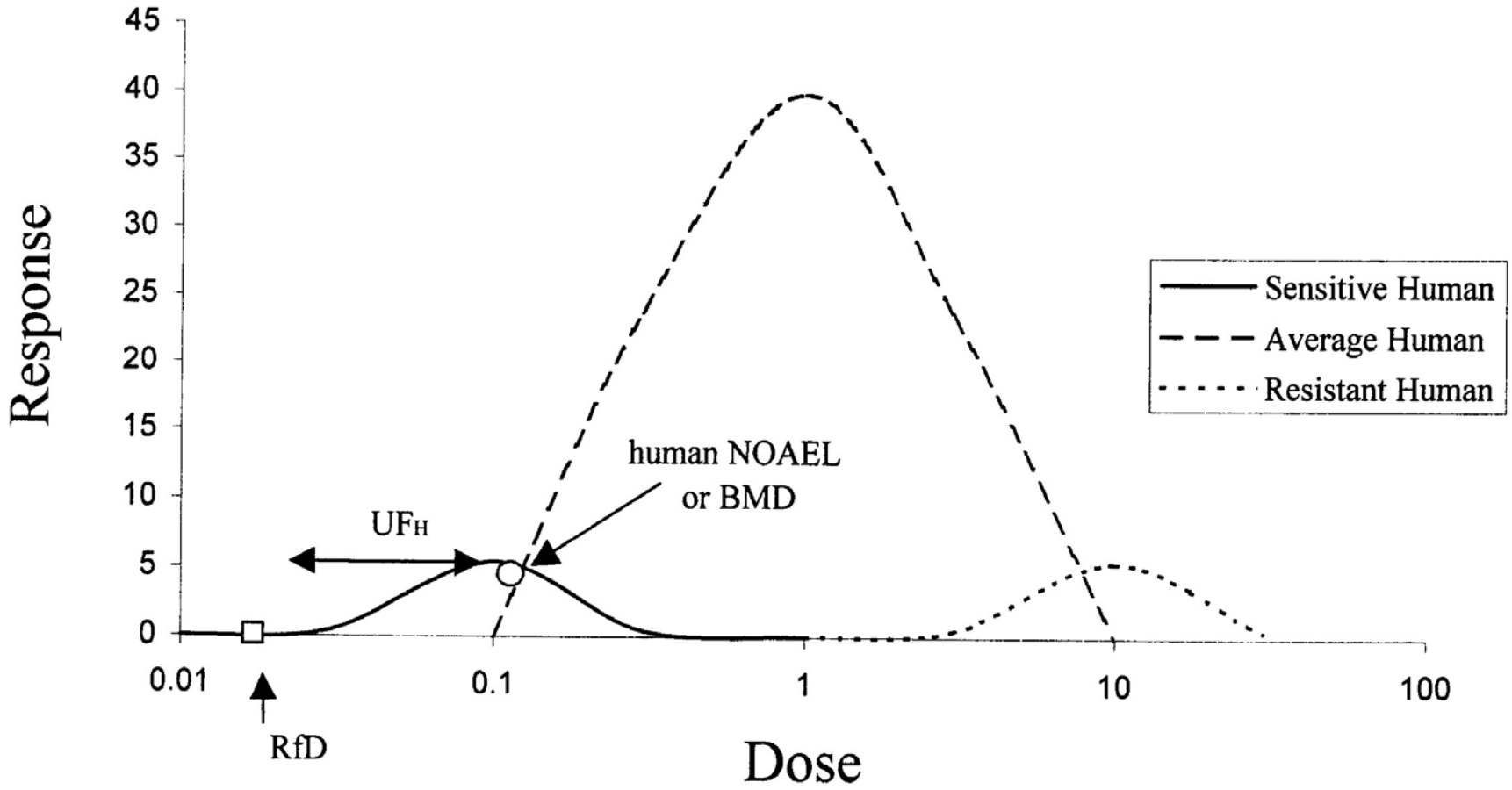
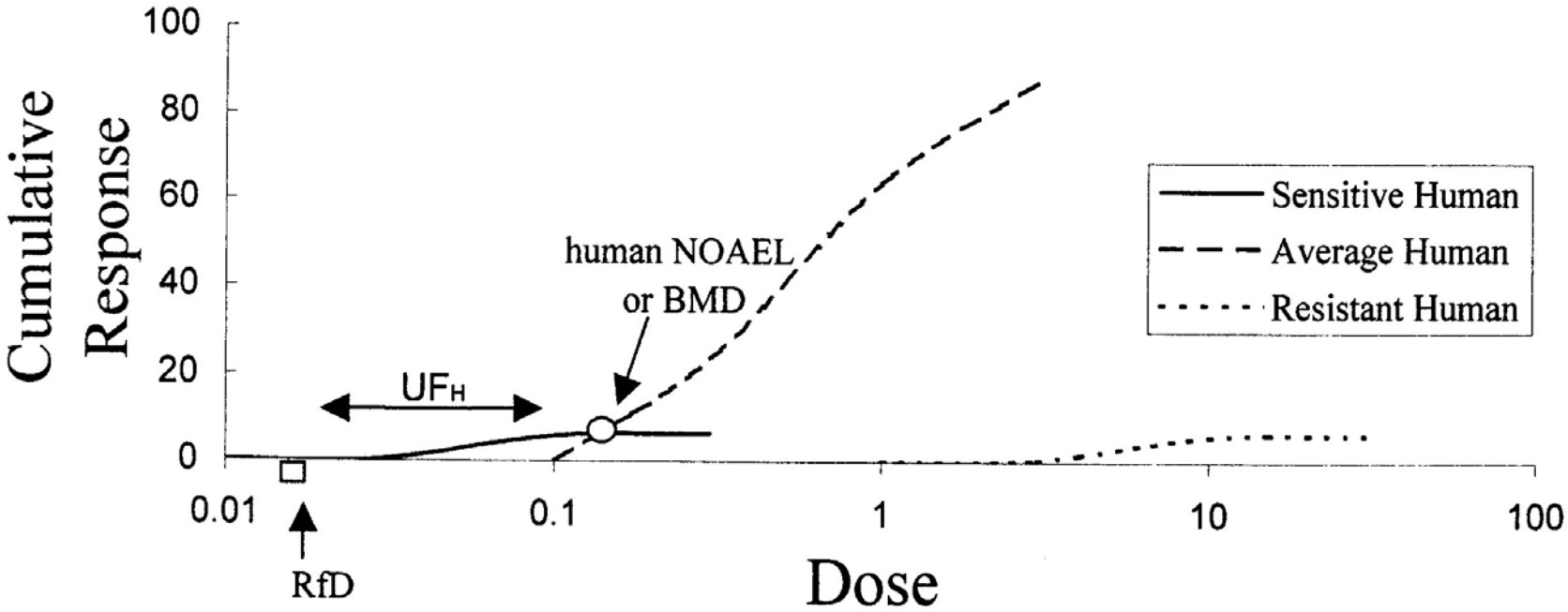
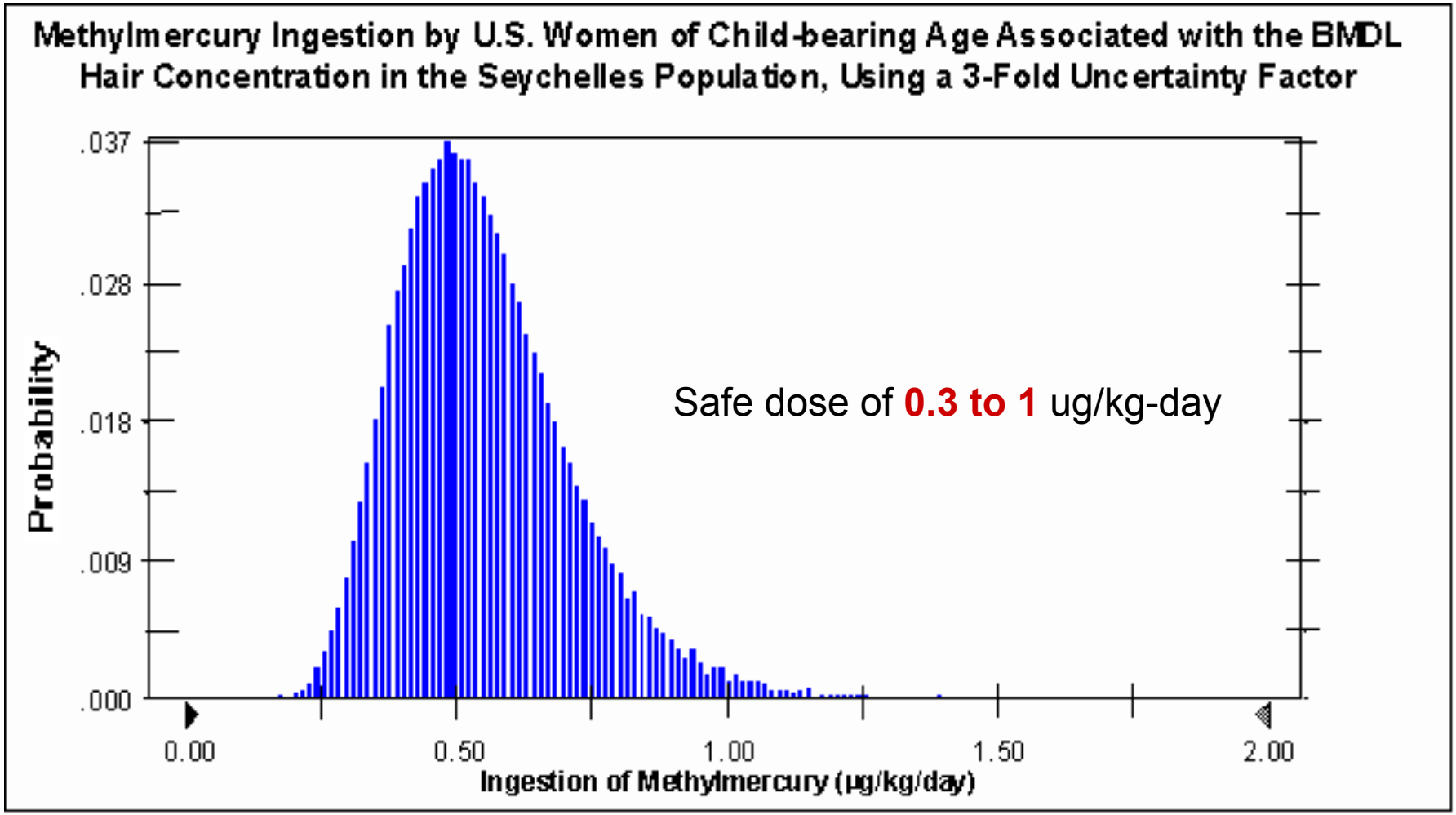


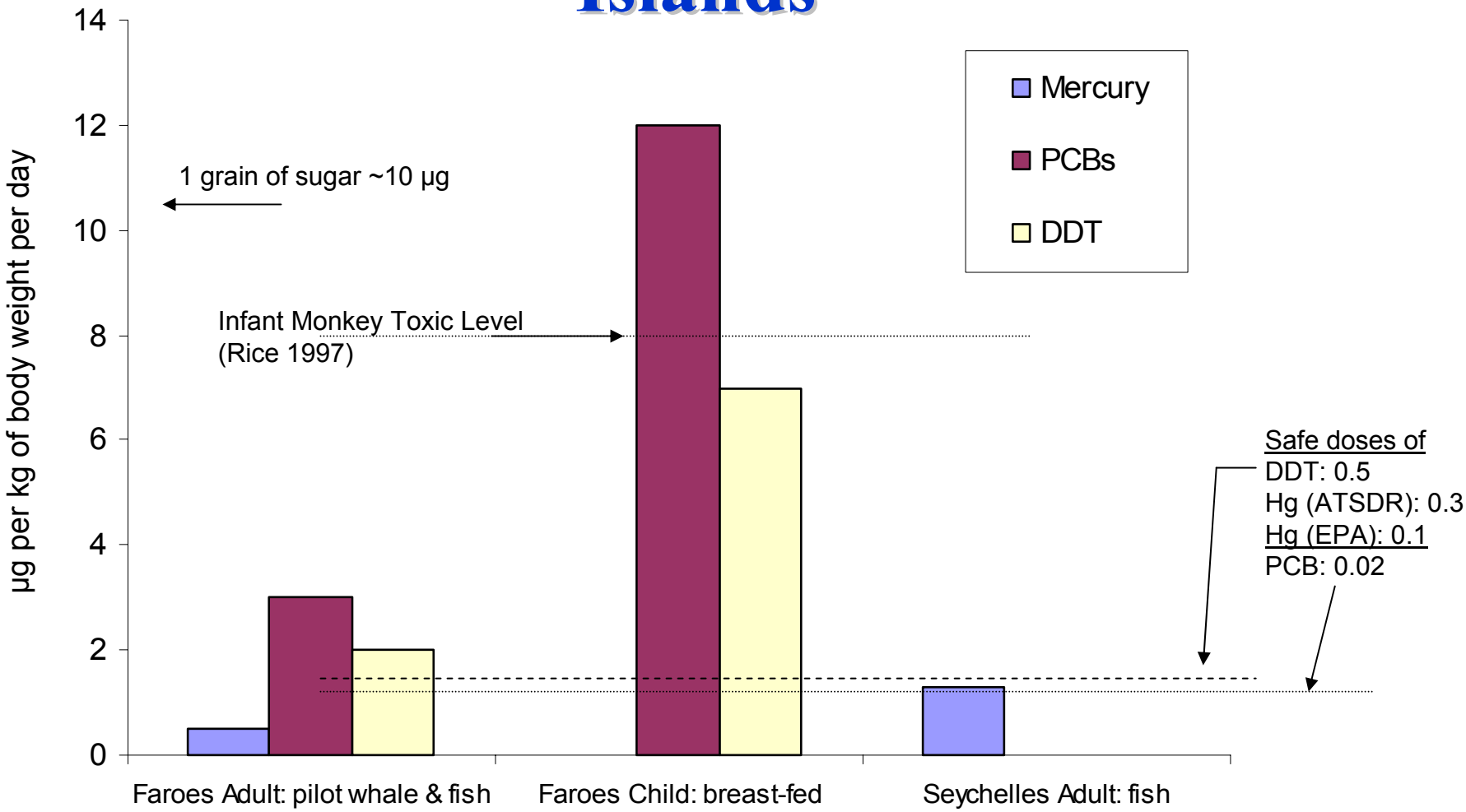
Figure 6b. Cumulative Response as a function of dose for humans of different sensitivities. Data are the same as in Figure 6a.





Distribution of methyl mercury ingestion rates associated with 7 ppm mercury in maternal hair (ICF, 1998). The value of 7 ppm in hair is the BMDL from the Seychelles (21 ppm) divided by a factor of 3 for database uncertainties.

Contaminant Intakes in Faroe & Seychelle Islands



Faroe studies are good for understanding a mixed exposure.
Seychelle studies are good for understanding exposures to Hg.
(adapted from Dourson et al., 2001)

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What Might a Fish Advisory Look Like for Mercury?

- First, calculate the Safe Fish Intake based on:
  - the safe Hg dose
  - multiplied by a given body weight and
  - divided by the measured Hg level in fish, for example, 0.1 ppm (EPA, 1997)

- Safe Fish Intake
  - Safe Hg Dose x Body Weight ÷ Fish Level
  - 0.1 µg/kg-day (EPA, 2001) x 60 kg ÷ 0.1 µg Hg/g of fish
  - 60 grams of fish/day

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What Might a Fish Advisory Look Like for Mercury? (continued)

- Second, translate this Safe Fish Intake into meals per month or week
- 60 kg of fish/day falls into the range of 30 to 100 grams of fish per day and is consistent with three meals per week (Dourson and Clark, 1990).
- This level would be expected to be “safe” for sensitive individuals. Higher fish consumption would be appropriate for others.

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The Fish Advisories Compared

	ATSDR	EPA	ICF
"Safe" Dose (µg/kg-day)	0.3	0.1	0.3 to 1
Advisory at 0.1 ppm (meals per week)	7	3	7 to unlimited
Advisory at 1 ppm (meals per month)	4	1	4 to 12

Advisories that are inappropriately low compromise health by removing a medically recommended protein source from the food supply (e.g., Dourson et al., 2002).

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Factors that Affect Exposure

- Fate and transport
  - Determines the relationship between environmental releases and the concentrations in the media
  - A function of the chemical and the characteristic of the source
- Exposure related behaviors
  - The activities and behaviors that result in the intake of a substance
  - Independent of chemical's properties
- Barrier related effects
  - The properties of absorption/uptake
  - A function of the chemical and local media

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How Do You Describe Exposure?

- Biomarkers
  - Urine, Blood, Hair
- Point-of-contact techniques
  - Personal monitors
- Scenarios/dose-rate models

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Risk Assessment and the Workplace

- Historically, occupational risk assessment decisions relied heavily on professional judgement rather than a systematic quantitative process
- The integration of quantitative noncancer risk assessment approaches into the occupational arena is relatively new
  - OSHA's Permissible Exposure Limits (PELs)
  - NIOSH, ACGIH, and AIHA

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Occupational Approaches to Dose-Response Assessment

- Agencies that establish OELs do not have systematic guidelines for noncancer risk assessment
- Many recent occupational assessments use quantitative risk assessment principles
  - OSHA's standard for cadmium
  - OSHA's "Occupational Exposure to 2-Methoxyethanol (2-ME), 2-Ethoxyethanol (2-EE) and their Acetates" was based on NOAEL-UF approach

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