Making TSCA Work: Risk assessment concepts to reflect population responses

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Outline

1. Risk assessment practices and limitations

2. Probabilistic risk assessment approaches

3. Using the data: neurocognitive impairment associated with perchloroethylene exposure

Federal Authorities Use Risk Assessment to Regulate Chemicals

Federal Authorities Use Risk Assessment to Regulate Chemicals

President Obama signing the Frank Lautenberg Chemical Safety for the 21st Century Act

Key TSCA updates to prevent "unreasonable risk to health or to the environment"

- Requires **risk evaluations** for chemicals in commerce
- Requires consideration of risk for **vulnerable populations**
- Clearly **separates risk evaluation process from risk management**
  - Risk evaluation without consideration of costs and benefits

With these risk evaluations, EPA has the opportunity to leverage recommendations by the National Academies of Sciences to provide evidence-based risk evaluations that contextualize risk for decision-makers

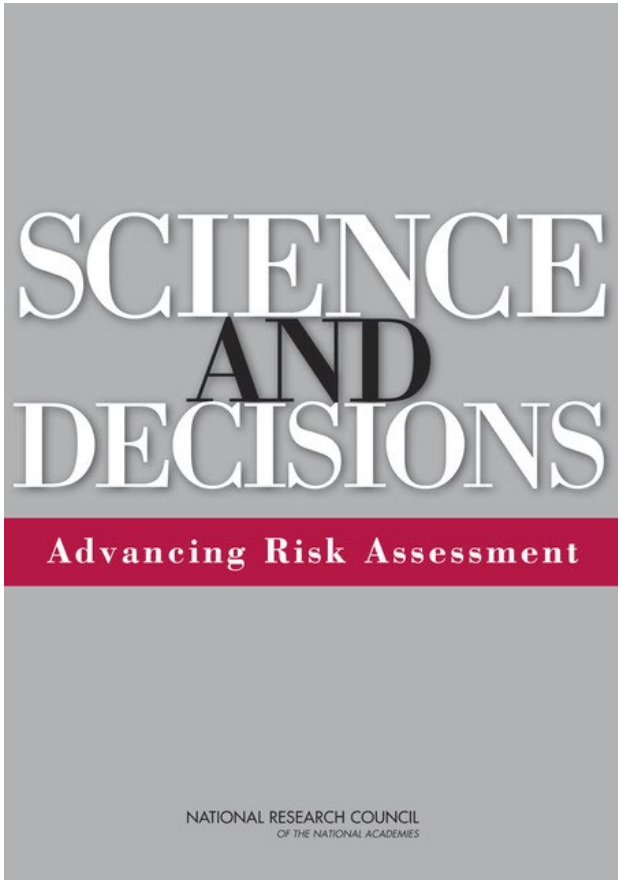
What is Risk Assessment?

- A tool to answer questions about the health risks posed by exposure to hazards

- Combines information on the amount of hazard **exposed** to and the **toxicity** of that hazard.

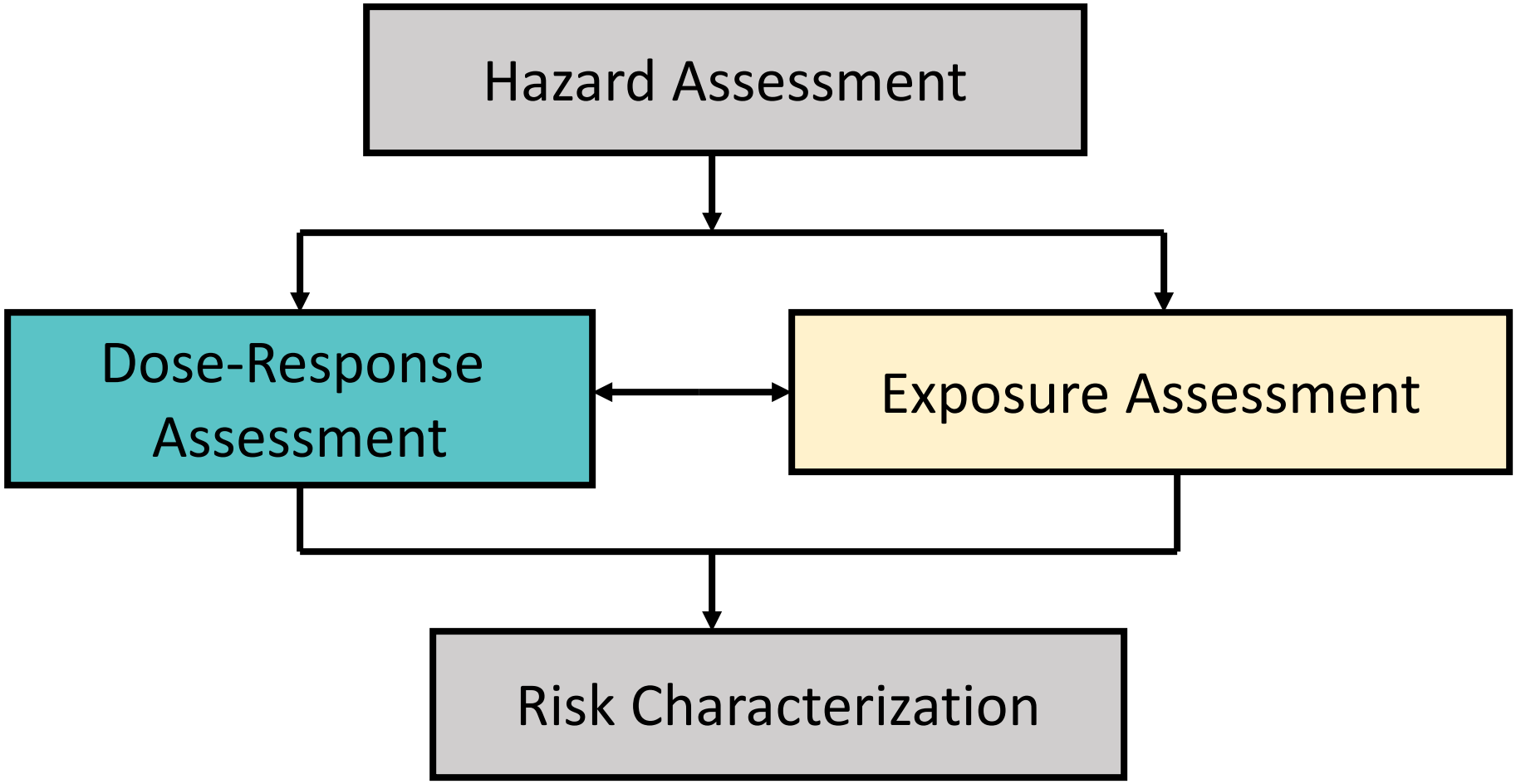
NAS Recommendations to Improve Risk Assessment

- Renewed focus on scoping risk assessments
- **Explicit consideration to and communication of uncertainty and variability**
- **Harmonizing approaches to cancer and non-cancer risk assessment**
- Considering cumulative risk
- Employing systematic review methods



NAS, 2009

The Risk Assessment Process



Source: NRC 1983, 1994, 2009

Dose-Response Assessment

- Commonly defined with "toxicity values"

Noncancer

Reference Dose (RfD): An estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime.

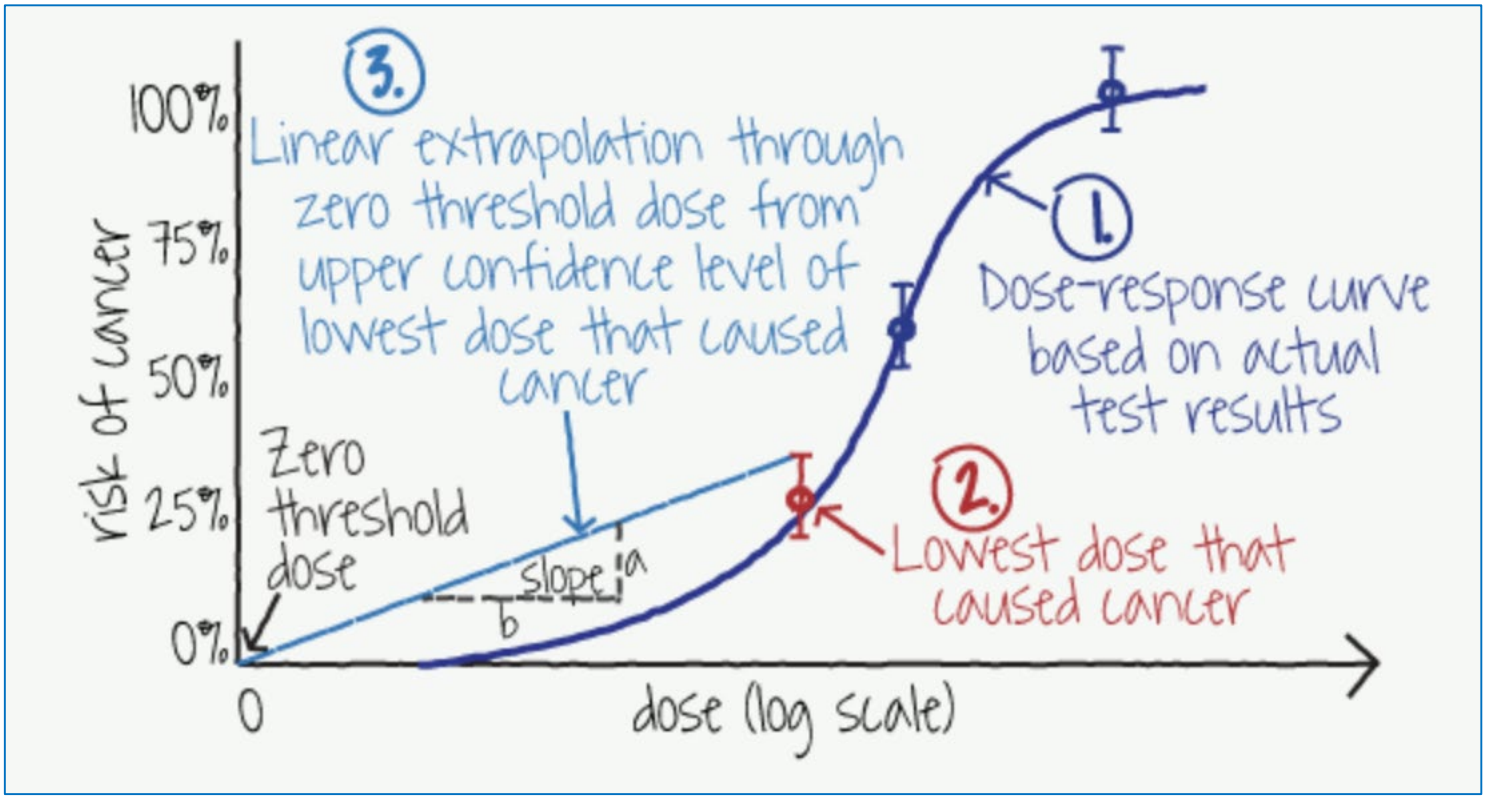
Reference Concentration (RfC): same as reference dose but an air concentration

Cancer

Slope Factor: An upper bound, approximating a 95% confidence limit, on the increased cancer risk from a lifetime exposure to an agent. Usually assume a linear model.

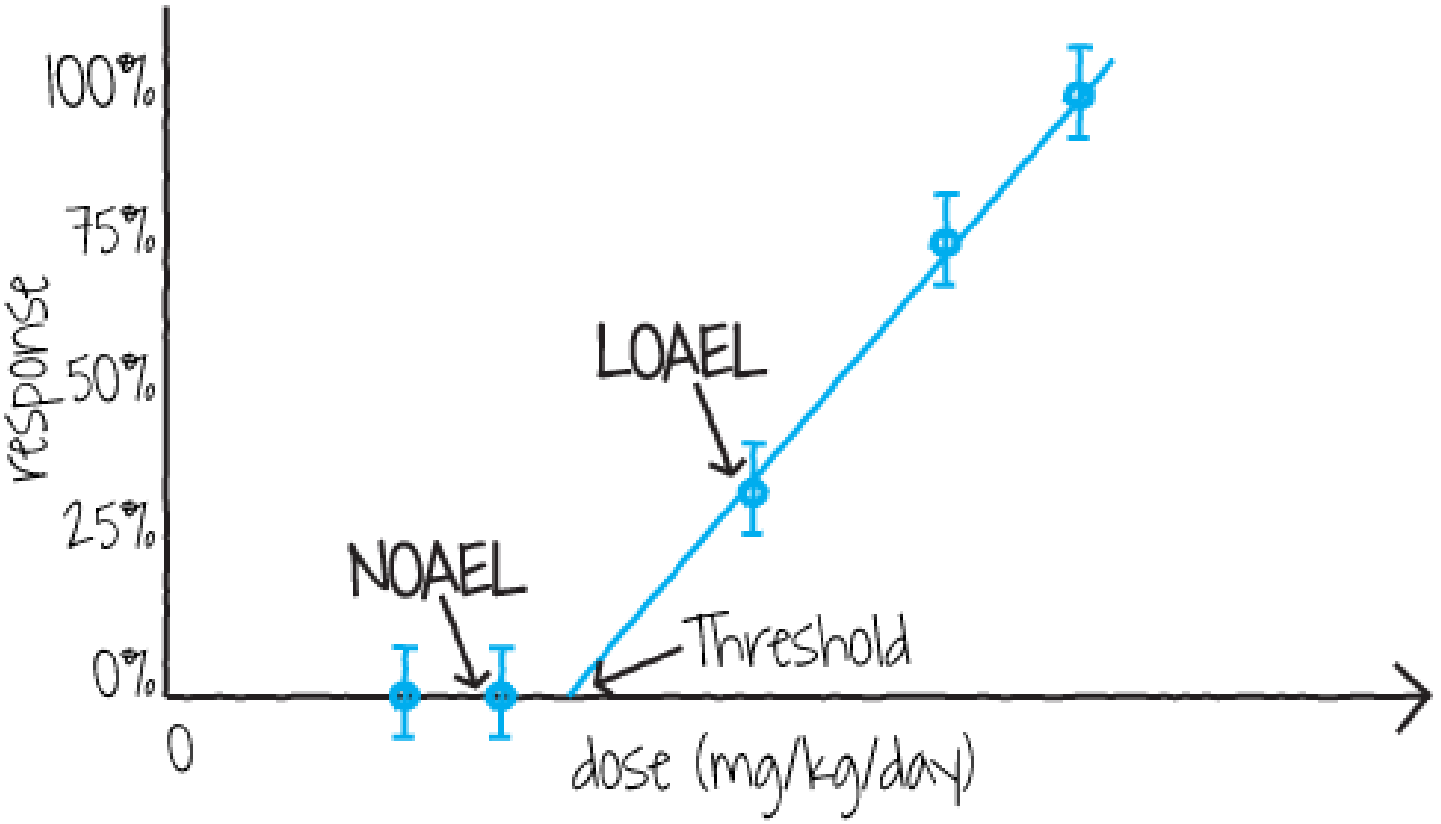
Unit Risk (UR): same as slope factor but an air concentration

Cancer Risk Assessment: Deriving the Slope Factor



https://www.toxmsdt.com/63-dose-response-assessment.html

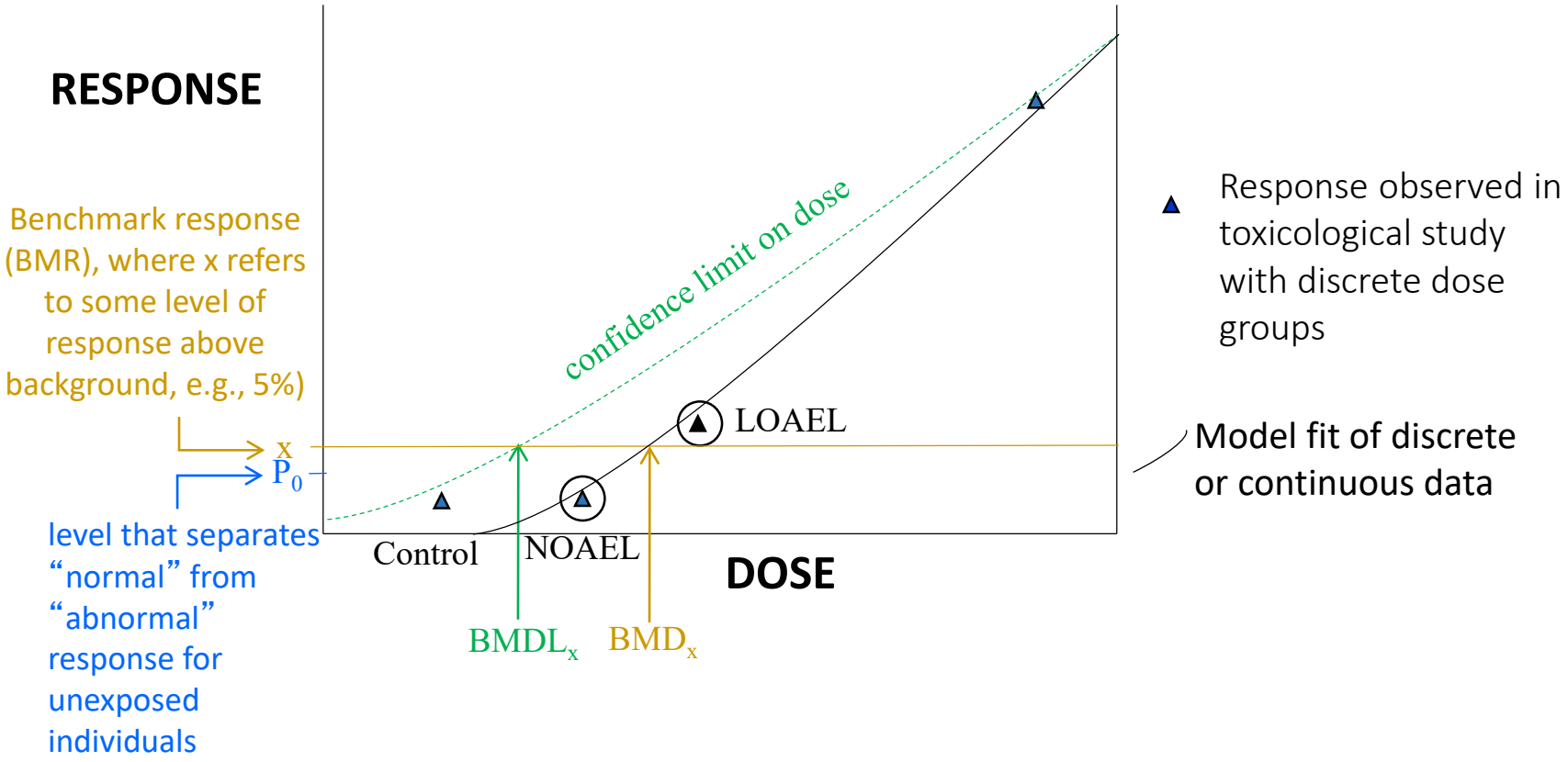
Non-Cancer Risk Assessment: Deriving the Reference Dose



https://www.toxmsdt.com/63-dose-response-assessment.html

Point of Departure (POD)

Dose where defined effects are not observed



Online Benchmark Dose training: https://www.epa.gov/bmds

Then What?
Deriving the Reference Dose (RfD)

$$RfD = \frac{POD}{UF_A \times UF_H}$$

POD = NOAEL or Benchmark Dose

inter-species extrapolation (1, 3, 10): UF_A
intra-human susceptibilities (1, 3, 10): UF_H
Timing Variables: (1, 3, 10)

RfD/RfC is "an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure for a chronic duration (up to a lifetime) to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime"

Dose-Response Assessment: Noncarcinogenic Effects (RfDs/RfCs)

- EPA derives RfDs from animal (and some human) data and publishes values on Integrated Risk Information System (IRIS)

http://www.epa.gov/IRIS/

1. Examine data from animal studies, computational studies and epidemiological studies, identify critical effects
2. Graph/model dose-response data for critical endpoint/effects
3. Define point of departure (POD)- NOAEL or LOAEL or BMD
4. Apply default **uncertainty factors (UFs)**

Current Approach Falls Short of Protecting Public Health

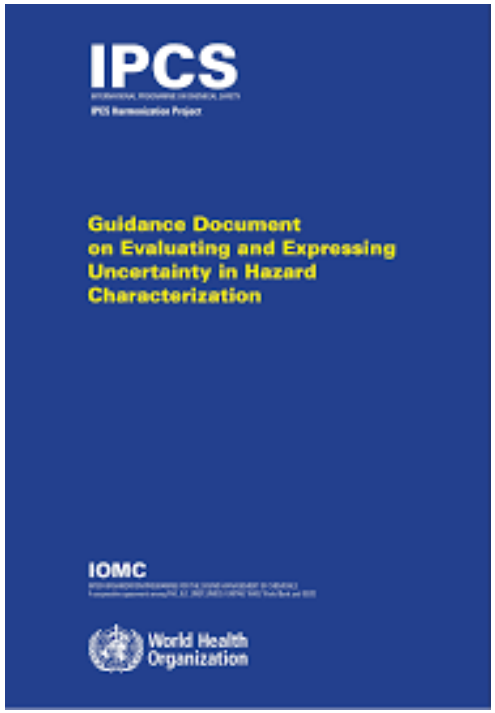
- No quantification of the **probability or severity** of risk or the proportion of population affected
  - Limits utility for economic or comparative analyses
- No distinction between **uncertainty** and **variability**
- No assessment of **uncertainty** in toxicity values
- No assessment of low dose linearity despite epidemiological studies showing a lack of threshold for non-cancer effects associated with multiple agents

We have **data** and **methods** to do this better!

Probabilistic risk approaches are **statistical methods** that incorporate uncertainty and variability into risk assessment

Probabilistic risk assessments address limitations with the RfD/RfC approach by

- Distinguishing between uncertainty and variability
- Defining the magnitude of non-cancer health effect
- Quantifying the proportion of the population expected to experience a non-cancer health effect
- Redefining RfDs/RfCs as risk-specific reference values



Three Methods That Can be Used

I. **Distributional approach**

Replace fixed uncertainty factors with distributions based on empirical data

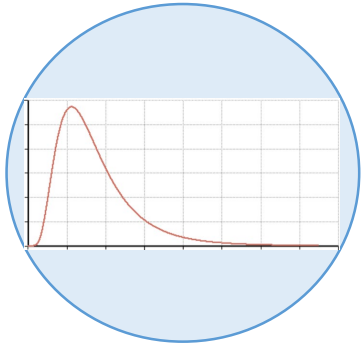
II. **Background clinical vulnerability**

Clinical Use shared biomarkers between environmental exposure and disease or aging processes to model the additional risk of health outcomes due to environmental chemical exposure

I. **Continuous risk functions**

Leverage dose-response curves from human epidemiological studies and animal toxicity studies to model risk at environmentally relevant concentrations

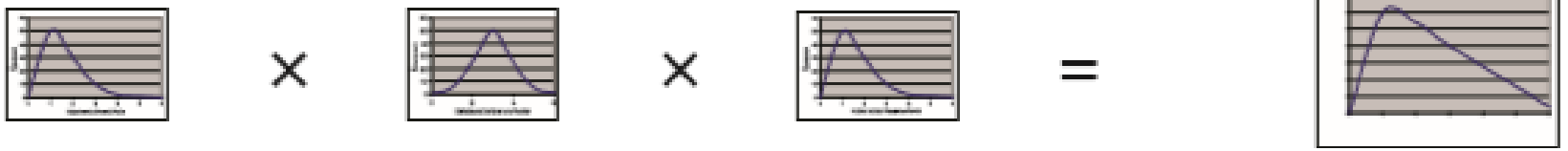
I. Distributional Approach



- Leverage existing uncertainty and variability distributions based on empirical data (i.e. Hattis et al., 2002, 2007)

- Apply uncertainty distributions to a POD using probabilistic methods (i.e. Monte Carlo) or a shorthand workflow (WHO/IPCS, 2014/Chiu et al., 2018)

Subchronic/Chronic × Animal-human × Human variability = Overall Adjustment



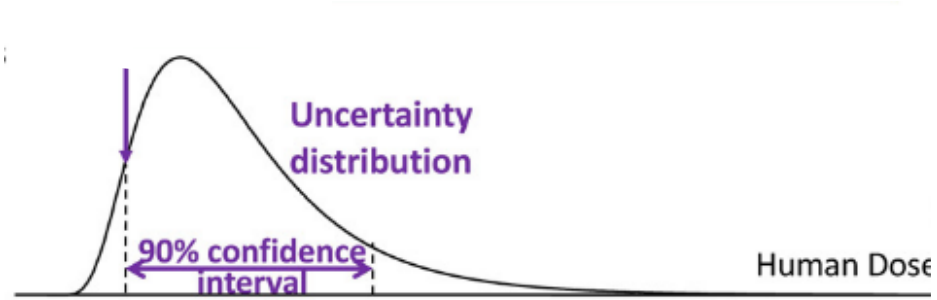
I. Distributional Approach: Opportunity to Redefine RfDs

Traditional RfD:

$$\frac{NOAEL}{UF_A \times UF_H}$$

Probabilistic RfD:

Lower 95%ile of $HD_M^I = \frac{BMD_M}{UF_{A,BW} \times UF_{A,TKTD} \times UF_{H,I}}$



HD_M^I: Human dose associated with an effect of magnitude *M*, and population incidence *I*

Chiu et al., 2018

Redefining RfDs/RfCs as Risk Specific Doses

Risk-specific reference values

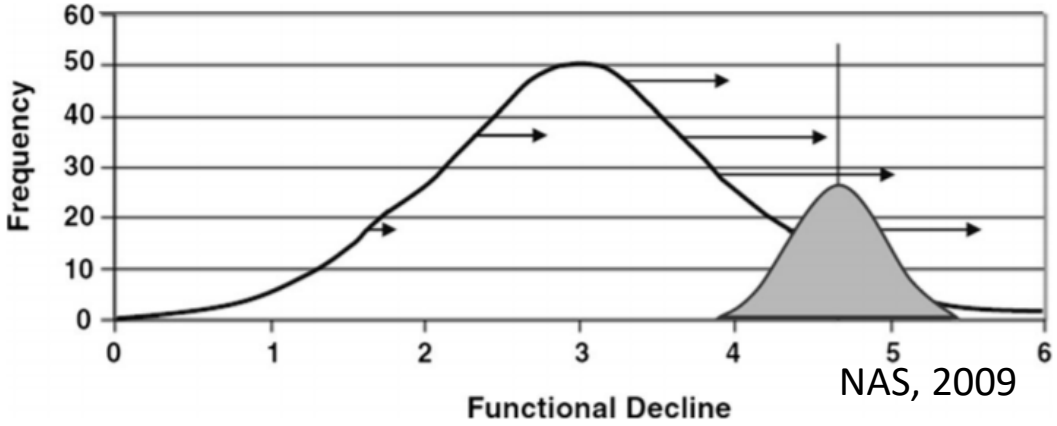
An RfD or RfC where the risk level, severity of health effect, and uncertainty are all quantified

- Consistent with cancer risk assessment
- Retain the ability to identify ‘bright line’ regulatory values
- Require risk managers to define acceptable risk level

II. Background Clinical Vulnerability Approach

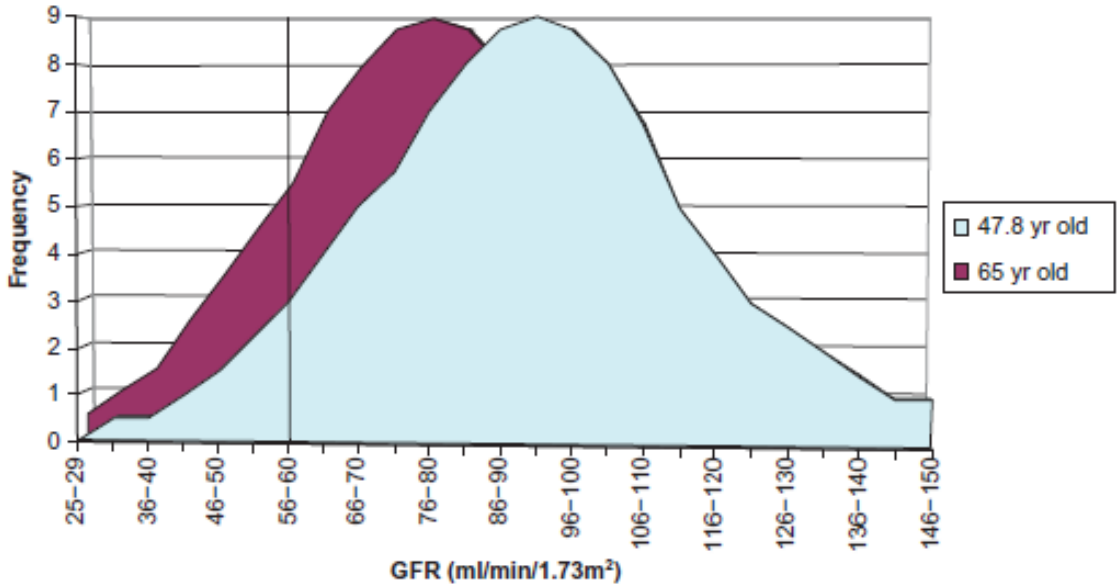
- Chemicals may interact with background aging and disease processes
- This interaction may be modeled when chemicals impact a clinical or functional biomarker of aging or disease
- This method quantifies additional risk of clinical disease due to environmental exposures

Clinical Vulnerability Distribution



NAS, 2009

Case Study: Cadmium and CKD



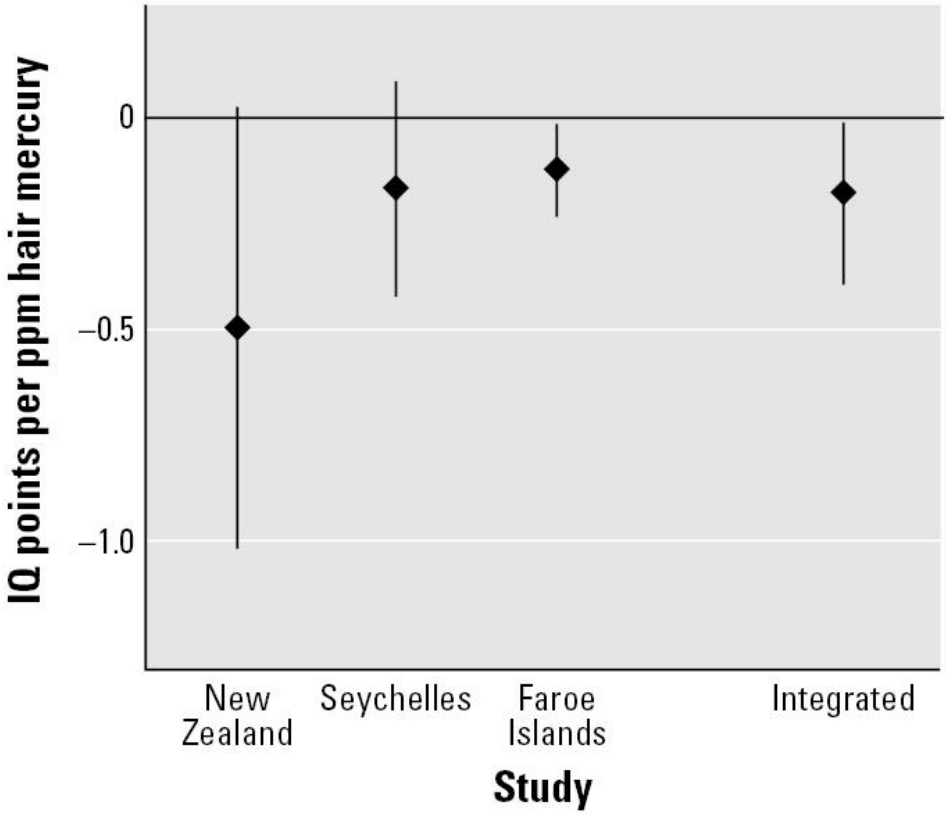
Ginsberg, 2012

Examples

- Cd/GFR/CKD
- PM/HRV/MI
- **PCE/Visual memory/aging**

III. Continuous risk functions

- Combine human data from multiple studies with similar exposure and outcome
- Extend risk function fit to human data or animal toxicity data to low doses



Axelrad et al., 2007

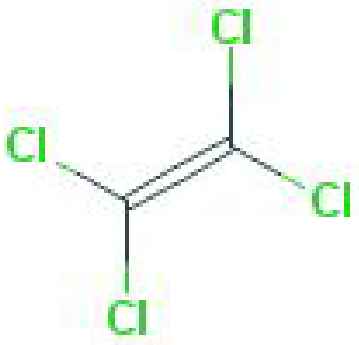
Considerations for probabilistic risk assessments and risk-specific RfDs/RfCs

- Limitations in underlying distributions
- Risk managers must choose quantified acceptable risk levels
- Some approaches are data intensive
- Non-cancer health effects may be difficult to link to clinical disease

Probabilistic and Risk-Specific RfDs/RfCs are not perfect, but they DO consider vulnerable populations (TSCA) and provide decision-making tools for risk managers

Case Study: Applying Probabilistic approaches to contextualize risk of neurocognitive impairment associated with Perchloroethylene (PCE) exposure

Perchloroethylene (PCE)



- Solvent commonly used in dry cleaning and metal degreasing and as a starting material in chemical manufacturing
- Volatile chemical that readily evaporates into air but is also mobile in soil and water
- Inhalation is the most common route of exposure though ingestion exposure can occur through contaminated water and soil as well
- PCE exposure negatively impacts neurocognitive function, liver, kidney, and reproductive function and is considered a probable carcinogen

PCE was prioritized for evaluation under TSCA

- EPA 2020 estimate of chronic exposure range 0.23 to 1.5 ppm
- EPA risk evaluation finds this exposure to be unacceptable (based on Margin of Exposure estimates)
- What is the probabilistic risk for impaired cognitive function at these workplace exposures?

Case Study Goals

- Explore feasibility of different quantitative approaches to probabilistic non-cancer risk assessment
- Illustrate options with PCE RfC, neurotoxicity endpoint
- Compare risk estimates across approaches
- Estimate level of risk at various exposures
  - including the EPA RfC (0.04 mg/m^3, 0.0059 ppm)
- Compare non-cancer and cancer risk
- Identify main assumptions, uncertainties, data gaps
- Assess value-added of probabilistic approaches

Case Study Methods

- Selected one of the key studies supporting EPA's RfC for PCE to evaluate risk at and around the existing RfC (Echeverria et al., 1995)
- Assessed data availability to apply methods for probabilistic non-cancer assessment
- Conducted an approximate probabilistic analysis using the data from Echeverria et al., 1995
- Compared risk estimates across approaches and risk of cancer effects at the same dose
- Identified main assumptions, uncertainties, and data gaps
- Assessed value added of probabilistic approaches

A Behavioral Evaluation of PCE Exposure in Patients and Dry Cleaners: A Possible Relationship Between Clinical and Preclinical Effects

Diana Echeverria, PhD
Roberta F. White, PhD
Carlos Sampaio, PhD

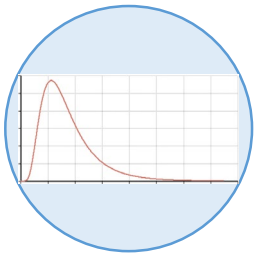
TABLE 4
Changes in Performance Presented by Lifetime PCE Exposure

	Lifetime Exposure to PCE								
	Low		Moderate		High		Differences	% Difference	Statistical Significance NS > .10*
	Mean	SD	Mean	SD	Mean	SD	[Low − High]		
Visual tests									
Visual reproductions									
Score									
Adjusted	9.45	1.21	8.89	1.24	8.08	1.24	1.36	14.4	.00
Unadjusted	9.66	2.51	8.77	2.75	7.95	2.74	1.71	17.7	.03

Participants, exposure levels, and Wechsler Memory Scale Visual Reproductions subtest (WMS-VR) performance in dry cleaning workers with varying PCE exposure

	Low Exposure	Medium Exposure	High Exposure
# of Participants	24	18	23
Breathing Zone PCE Conc.	11.2 ppm	23.2 ppm	40.8 ppm
Adjusted PCE exposure (compared to low)	NA	4.3 ppm	10.7 ppm
Mean (and 95% UCL) Reduction in WMS-VR score (compared to low)	NA	6% (11%)	14% (19%)

Calculating probabilistic, risk-specific doses for PCE using distributional approach



Factor	Median (P50)[a]	Spread (P95/P50)[a]
Human Variability [a]	I=1%: 9.7 I=0.1%: 20.42	I=1%: 4.3 I=0.1%: 6.99
$HD_{.05}^{1\%}$ (I=1%)[b]	1.9/(9.7) = 0.20 ppm	$10^{[(\log 4.3)2]1/2}$= 4.32
$HD_{.05}^{1\%}$ (I=1%)[b] (1-in-100, 95% conf)	0.20/4.32= 0.05 ppm	
$HD_{.05}^{0.1\%}$ (I=0.1%)[b]	1.9/(20.42)= 0.09 ppm	$10^{[(\log 6.99)2]1/2}$= 6.99
$HD_{.05}^{0.1\%}$ (I-0.1%)[b] (1-in-1000, 95% conf)	0.09/6.99= 0.01 ppm	

Comparing Probabilistic Estimates of PCE Neurotoxic Risk and Cancer Risk

PCE Exposure	Exposure Basis	95% CL Risk	Risk Description
0.004-0.01 ppm	Dose for 1/1000 95% LCL, IPCS/Chiu	1 per 1000	$HD_{.05}^{0.1\%}$ (see Table 3 and 4 for definition and derivation)
0.0059 ppm	USEPA 2012b RfC	0.6 to 1.5 per 1000	Probabilistic risk at RfC based upon IPCS/Chiu et al. 2018 methodology
0.0059 ppm	USEPA 2012b RfC	0.01 per 1000	Cancer risk
0.23 to 1.5 ppm	USEPA 2020 PCE workplace exposures	23 to 375 Per 1000	Neurological risk for mild impairment assoc/ workplace PCE

Case Study Key Findings

- Probabilistic methods can be easily applied to more thoroughly analyze health risk at different exposure levels

- Approx. 1 in 1000 people are predicted to experience a 5% reduction in WMS-VR performance with chronic exposure to current USEPA RfC

- The risk for this neurological impairment at the current RfC is approximately 100 fold greater than the cancer risk at a comparable exposure level

Case Study Remaining Questions

- Probabilistic expression of risk leaves open the question of its acceptability, which is ultimately a risk management decision

- Visual memory is amenable to clinical vulnerability analysis as this neurocognitive function declines with age and is associated with some neurodegenerative diseases

- These analyses rely on data in adult populations and do not consider effects for sensitive populations like children and pregnant women

Take Home Messages

Traditional RfDs/RfC approaches fail to account for population variability, distinguish between uncertainty and variability, and quantify health risk at environmentally-relevant exposures

Probabilistic methods can be easily applied to offer additional detail and capture and evaluate non-cancer health risks associated with chemical exposures

Setting reference values as risk-specific doses requires risk managers to select an acceptable level of risk for non-cancer health effects

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Questions and Discussion