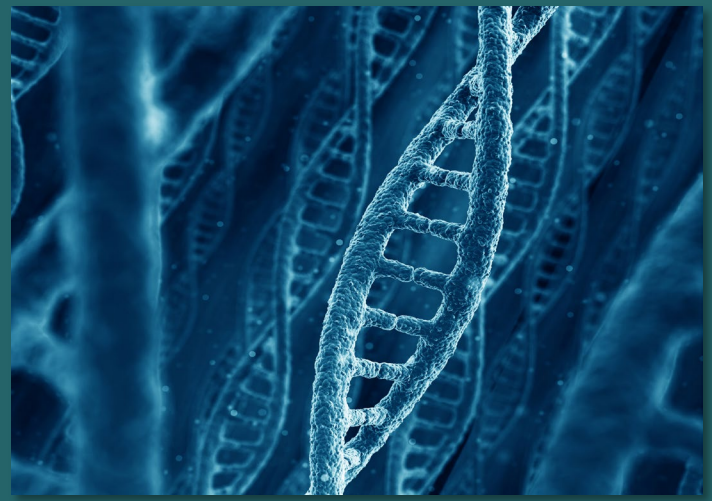
Parameterization of VOI Models Used in the Case Study

Greg Paoli MASc.
Risk Sciences International



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Information Required for VOI Analysis

Existing toxicity and exposure information

1. What is the prior uncertainty distribution for chemical toxicity?
2. What is the uncertainty distribution for the exposure to chemicals?

Toxicity testing and assessment process information

1. How much is the uncertainty in toxicity reduced?
2. How long does it take?
3. How much does it cost?

Economic valuation

1. What is the affected population size?
2. What is the time horizon?
3. What is the cost of the adverse health outcome?
4. What is the social discount rate?

BRDM-specific information

1. What is the exposure mitigation cost?

TRDM-specific information

1. What is the target risk level?
2. What is the percentage of the exposure reduction?
3. What are the quantiles used in the decision rule?

Parameters Required for VOI Analysis

- **Parameters used in baseline analysis**
  - Prior distribution of chemical toxicity
  - Exposure information
  - Toxicity testing and assessment process information
  - Economic valuation of health outcomes
  - BRDM-specific information
  - TRDM-specific information
- **Parameters used in sensitivity analyses**
  - Toxicity distribution
  - Exposure scenarios
  - Economic valuations
  - Target population size
  - Target risk level
  - Uncertainty associated with ETAP

CHARACTERIZING THE PRIOR DISTRIBUTION OF CHEMICAL TOXICITY

Prior Uncertainty Distribution for Toxic Potency

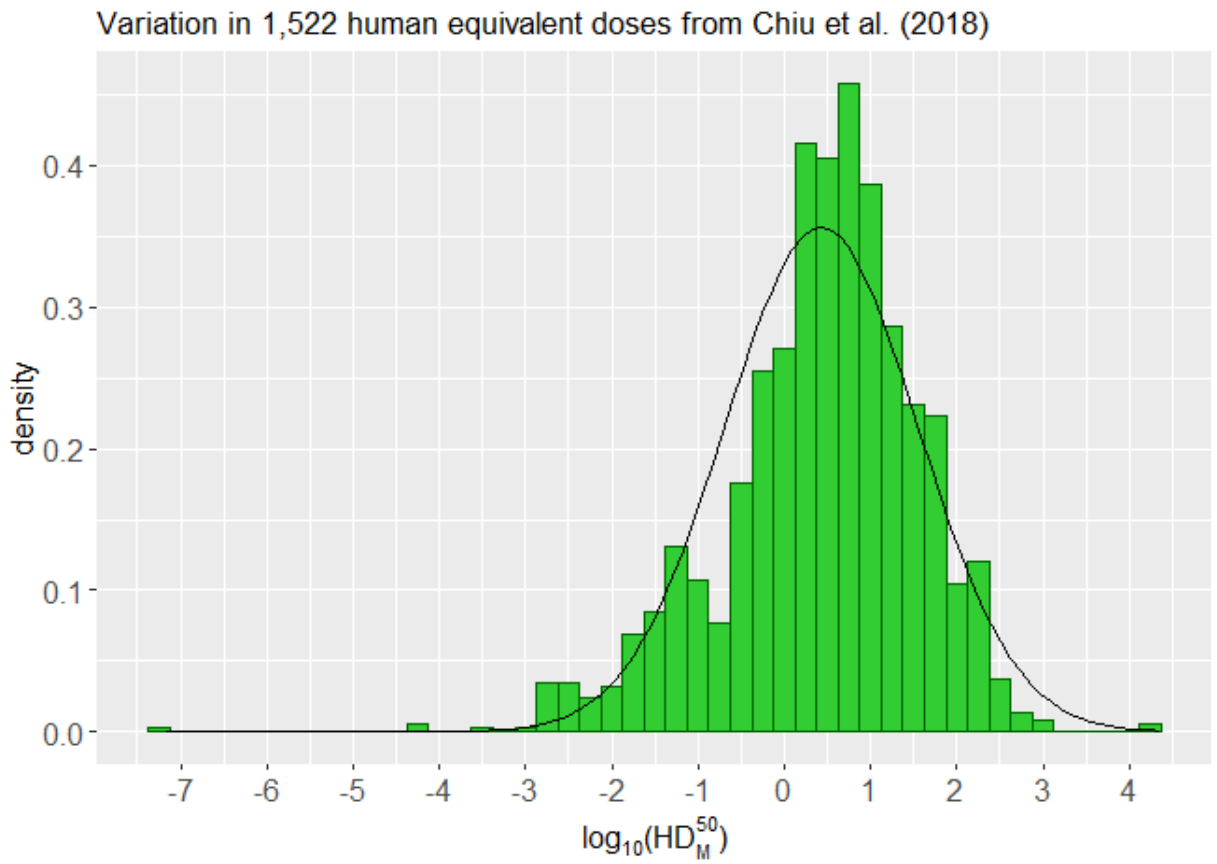
- To apply the VOI framework, it is necessary to establish a prior distribution of uncertainty in chemical toxicity in the absence of any specific knowledge about the chemical to be tested

- Chiu et al. (2018) provide toxicity data on **608 diverse chemicals** with **1,522 chemical-endpoint combinations**
  - Includes substances evaluated under EPA IRIS, EPA OPP, Superfund RSLs, CalEPA

- Median human dose associated with an effect of magnitude (severity) M and population incidence rate of 50% ($\mathrm{HD}_{\mathrm{M}}^{50}$) is **3.26mg/kg-day**
  - Average human body weight is assumed to be 80kg

HD_M: Human dose at magnitude (M) and incidence (I) | IRIS: Integrated Risk Information System| OPP: Office of Pesticide Programs| RSLs: Regional Screening Levels| CalEPA: California EPA Office of Environmental Health Hazard Assessment

Prior Uncertainty Distribution for Toxic Potency



The distribution of toxic potency spans approximately **6 OM** (excluding chemicals with extremely high potencies and chemicals tested above the limit dose of 1,000mg/kg-day)

OM: Orders of magnitude

Prior Uncertainty Distribution for Toxic Potency

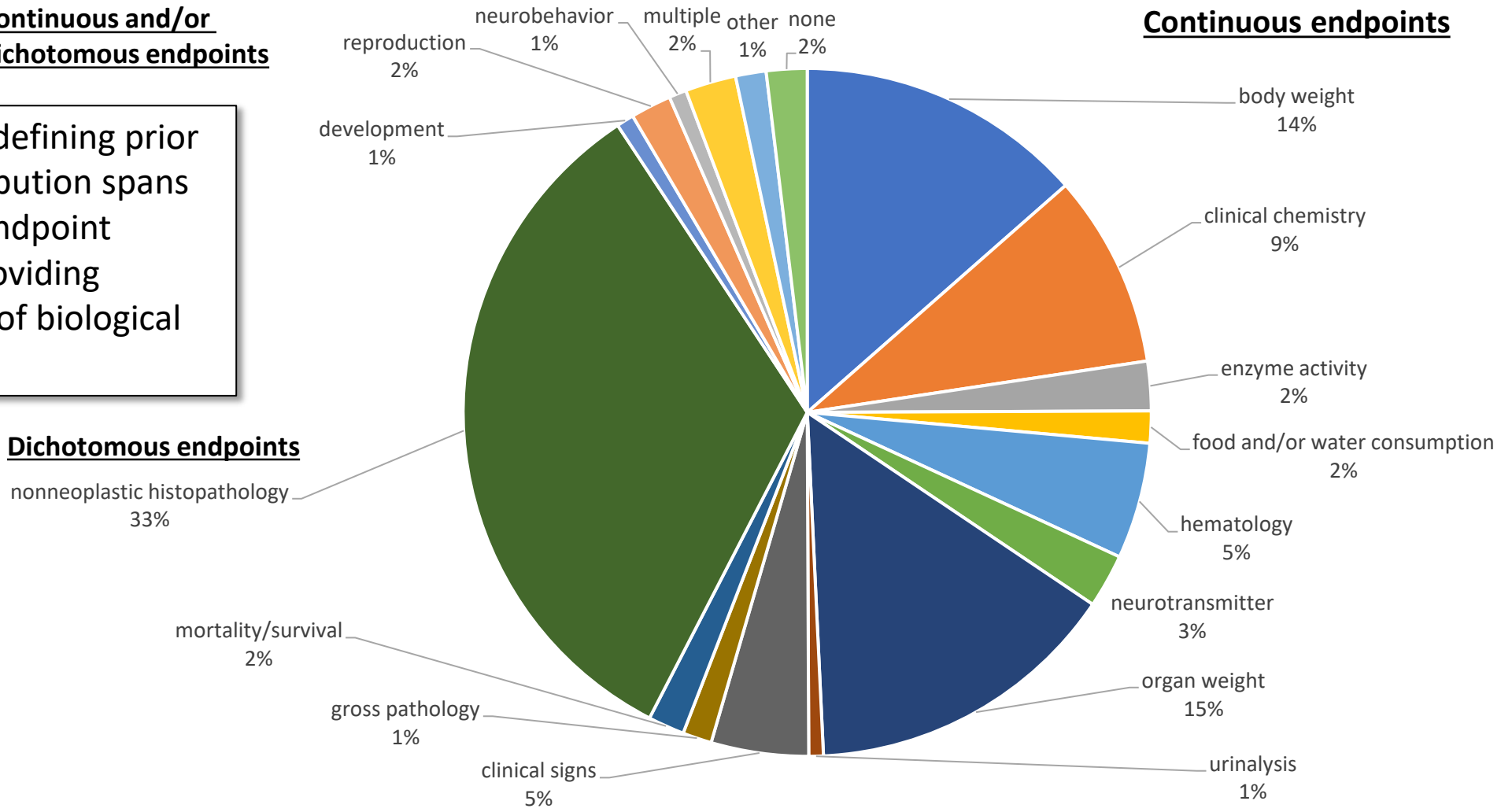
- The logarithm of the geometric standard deviation [$\log_{10}$(GSD)] of human susceptibility (σ_{tox}), is provided by the IPCS [WHO (2017), Table 4.4]
- The value of σ_{tox} is calculated to be **0.424**, using the midpoint $\mathrm{P}_{05} = 0.151$ and $P_{95} = 0.697$, and uncertainty about σ_{tox} is $u(\sigma_{\mathrm{tox}}) = 0.166$
- Since σ_{tox} cannot be negative, $u(\sigma_{\mathrm{tox}})$ is set to $\sigma_{\mathrm{tox}}/6 = \mathbf{0.0706}$ as the VOI framework integrates uncertainty distribution between $\pm 6u(\cdot)$ about σ_{tox}

IPCS: International Programme on Chemical Safety | WHO: World Health Organization

Diversity of Biological Endpoints

Continuous and/or dichotomous endpoints

Dataset used for defining prior uncertainty distribution spans 1,522 chemical-endpoint combinations, providing diverse coverage of biological effects



TOXICITY TESTING AND HUMAN HEALTH ASSESSMENT PROCESS INFORMATION

Traditional Human Health Assessment Process (THHA)

- THHA is based on a two-year chronic toxicity test in rodents, followed by a traditional human health assessment process
- THHA is assumed to take **8 years** to complete at a cost of **$4 million**
  - The two-year rodent bioassay is assumed to take 4 years to complete, including two years for exposure and data collection and up to two years for data evaluation after testing
  - The subsequent human health assessment process is assumed to take an additional 4 years
  - The cost associated with development of the traditional human health assessment is presumed to be $0 for the purposes of the case study

Cost and time assumptions as referenced in the VOI Case Study EPA 2023 - Faustman and Omenn 2015 | NTP 1996 | Pastoor and Stevens 2005 | Krewski *et al. 2020*

Sources of Uncertainty in Toxic Potency for THHA

1. **Intra-study variation (BMD vs. BMDL)**
   - Uncertainty due to experimental error in the two-year rodent bioassay

2. **Allometric scaling**
   - Uncertainty associated with converting results in animals to humans due to differences in body sizes

3. **Animal-human TK/TD**
   - Uncertainty in differences in toxicokinetics and toxicodynamics between animals and humans

Sources of Uncertainty in Toxic Potency for THHA

1. **Intra-study variation (BMD vs. BMDL)**
   - Uncertainty due to experimental error in the two-year rodent bioassay
   - Estimated using **584 two-year rodent bioassays** considered by Sand et al. (2011)
   - The mean $\mathrm{BMD}_{10}/\mathrm{BMDL}_{10}$ ratio (i.e., P_{95}/P_{50}) is **1.803**

Sources of Uncertainty in Toxic Potency for THHA

2. Allometric scaling

- Uncertainty associated with converting results in animals to humans due to difference in body sizes
- Body size scaling done in proportion to the ratio of body weights raised to the 0.3 power
- The ratio P_{95}/P_{50} of body sizes reported by reported in Chiu et al. (2018) is **1.235**

Sources of Uncertainty in Toxic Potency for THHA

3. Animal-human TK/TD

- Uncertainty in differences in toxicokinetics (TK) and toxicodynamics (TD) between study animals and humans

- Following WHO/IPCS (2017, Table 4.3), we use an inter-species assessment factor of **3** (based on the P_{95}/P_{50} ratio for the same end-point in oral studies of TK/TD differences between animals and humans)

Combining Uncertainties for THHA

The residual uncertainty standard deviation about $\mathrm{HD}_{\mathrm{M}}^{50}$ after conducting THHA can be obtained in three steps:

1. Combine the three ratios to obtain the ratio for the HD

$$\frac{P_{95,\mathrm{HD}}}{P_{50,\mathrm{HD}}} = 10^{\left\{\sum_{i=1}^{3}\left[\log_{10}\left(\frac{P_{95,i}}{P_{50,i}}\right)\right]^2\right\}^{1/2}} = 3.541$$

2. Convert the ratio to the geometric standard deviation (GSD)

$$\mathrm{GSD}_{\mathrm{THHA}} = \left(\frac{P_{95,\mathrm{HD}}}{P_{50,\mathrm{HD}}}\right)^{1/1.645} = 2.157$$

3. Take the logarithm of the GSD to obtain the standard deviation in the log-scale

$$\sigma_{THHA} = \log_{10}(\mathrm{GSD}_{\mathrm{THHA}}) = \mathbf{0.334}$$

EPA Transcriptomic Assessment Process (ETAP)

- Five-day *in vivo* transcriptomic study, followed by EPA transcriptomic assessment process
- The entire process takes approximately **6 months** following chemical procurement, at a cost of **$200,000**
  - Estimates based on EPA ORD experience with conducting the transcriptomic studies (2022 estimates) and developing the associated ETAP documentation.

Process	Cost	Time
THHA	$4.0 million	8.0 years
ETAP	$0.2 million	0.5 years

Sources of Uncertainty in Toxic Potency for ETAP

1. **Intra-study variation (BMD vs. BMDL)**
   - Uncertainty due to experimental error within the 5-day *in vivo* transcriptomic study

2. **Allometric scaling**
   - Uncertainty associated with converting results in animals to humans due to differences in body sizes done in proportion to the ratio of body weights raised to the 0.3 power (same as THHA)

3. **Animal-human TK/TD**
   - Uncertainty in differences in toxicokinetics and toxicodynamics between animals and humans (same as THHA)

Sources of Uncertainty in Toxic Potency for ETAP

- 5-day repeat dose oral exposure in rats with transcriptomic dose response re-analysis conducted by EPA and consistent with the ETAP standard methods
- 14 chemicals with chronic apical benchmark dose (BMD) established from 2-year study; observed strong concordance between transcriptomic and apical PODs
- 8+ dose groups per chemical and matched vehicle controls, 4 replicates per group
- BMD/BMDL ratios assessed

Chemicals Tested	
Acrylamide	Hexachlorobenzene
Bromodichloroacetic acid	Methyl eugenol
Coumarin	Perfluorooctanoic acid
Pentabromodiphenyl ether mixture (DE71)	Tris(2-chloroisopropyl) phosphate
Di(2-ethylhexyl) phthalate	Pulegone
Ethinyl estradiol	3,3',4,4,'-Tetrachloroazobenzene
Furan	α,β-Thujone

Data derived from Gwinn *et al.* 2020; Scientific Studies Supporting Development of ETAP, EPA 2023

Sources of Uncertainty in Toxic Potency for ETAP

1. **Intra-study variation (BMD vs. BMDL)**
   - Uncertainty due to experimental error within the 5-day *in vivo* transcriptomic study
   - The mean $\mathrm{BMD}_{10}/\mathrm{BMDL}_{10}$ ratio for the **14 chemicals based on transcriptomic POD** and using the proposed ETAP transcriptomic dose response analysis method applied to the published data is (i.e., P_{95}/P_{50}) is **3.476**

Combining Uncertainties for ETAP

The residual uncertainty standard deviation about $\mathrm{HD}_{\mathrm{M}}^{50}$ after conducting ETAP can be obtained in three steps:

1. Combine the three ratios to obtain the ratio for the HD

$$\frac{P_{95,\mathrm{HD}}}{P_{50,\mathrm{HD}}} = 10^{\left\{\sum_{i=1}^{3}\left[\log_{10}\left(\frac{P_{95,i}}{P_{50,i}}\right)\right]^2\right\}^{1/2}} = 5.337$$

2. Convert the ratio to the geometric standard deviation (GSD)

$$\mathrm{GSD}_{\mathrm{ETAP}} = \left(\frac{P_{95,\mathrm{HD}}}{P_{50,\mathrm{HD}}}\right)^{1/1.645} = 2.768$$

3. Take the logarithm of the GSD to obtain the standard deviation in the log-scale

$$\sigma_{\mathrm{ETAP}} = \log_{10}(\mathrm{GSD}_{\mathrm{ETAP}}) = \mathbf{0.442}$$

Summary of THHA and ETAP Parameters

Process	Cost ($M)	Time (Years)	Source of Uncertainty	Uncertainty (P_{95}/P_{50})	$[\mathrm{Log}_{10}(P_{95}/P_{50})]^2$	$\frac{P_{95,\mathrm{HD}}}{P_{50,\mathrm{HD}}}$	GSD	$\sigma_{\mathrm{process}}$
THHA	4.0	8.0	Intra-study (BMD-BMDL)	1.803	0.066	3.541	2.157	**0.334**
			Allometric scaling	1.235	0.008			
			Animal-human TK/TD	3.000	0.228			
ETAP	0.2	0.5	Intra-study (BMD-BMDL)	3.476	0.293	5.337	2.768	**0.442**
			Allometric scaling	1.235	0.008			
			Animal-human TK/TD	3.000	0.228			

CHEMICAL EXPOSURE INFORMATION

High-Throughput Stochastic Human Exposure and Dose Simulation Model (SHEDS-HT)

Environmental Science & Technology

Article

pubs.acs.org/est

SHEDS-HT: An Integrated Probabilistic Exposure Model for Prioritizing Exposures to Chemicals with Near-Field and Dietary Sources

Kristin K. Isaacs,*[,†] W. Graham Glen,[‡] Peter Egeghy,[†] Michael-Rock Goldsmith,[§,○] Luther Smith,[‡] Daniel Vallero,[†] Raina Brooks,[∥] Christopher M. Grulke,[⊥,○] and Halûk Özkaynak[†]

[†]U.S. Environmental Protection Agency, Office of Research and Development, National Exposure Research Laboratory, 109 T.W. Alexander Drive, Research Triangle Park, North Carolina 27709, United States

[‡]Alion Science and Technology, 1000 Park Forty Plaza Suite 200, Durham, North Carolina 27713, United States

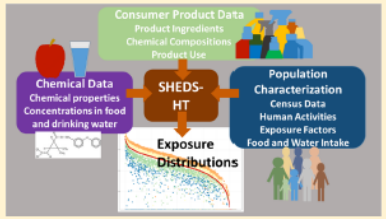
[§]Chemical Computing Group, Suite 910, 1010 Sherbrooke Street West, Montreal, QC H3A 2R7, Canada

[∥]Student Services Contractor at U.S. Environmental Protection Agency, 109 T.W. Alexander Drive, Research Triangle Park, North Carolina 27709, United States

[⊥]Lockheed Martin, 109 T.W. Alexander Drive, Research Triangle Park, North Carolina 27709, United States

Supporting Information

ABSTRACT: United States Environmental Protection Agency (USEPA) researchers are developing a strategy for high-throughput (HT) exposure-based prioritization of chemicals under the ExpoCast program. These novel modeling approaches for evaluating chemicals based on their potential for biologically relevant human exposures will inform toxicity testing and prioritization for chemical risk assessment. Based on probabilistic methods and algorithms developed for The Stochastic Human Exposure and Dose Simulation Model for Multimedia, Multi-pathway Chemicals (SHEDS-MM), a new mechanistic modeling approach has been developed to accommodate high-throughput (HT) assessment of exposure potential. In this SHEDS-HT model, the residential and dietary modules of SHEDS-MM have been operationally modified to reduce the user burden, input data demands, and run times of the higher-tier model, while maintaining critical features and inputs that influence exposure. The model has been implemented in R; the modeling framework links chemicals to consumer product categories or food groups (and thus exposure scenarios) to predict HT exposures and intake doses. Initially, SHEDS-HT has been applied to 2507 organic chemicals associated with consumer products and agricultural pesticides. These evaluations employ data from recent USEPA efforts to characterize usage (prevalence, frequency, and magnitude), chemical composition, and exposure scenarios for a wide range of consumer products. In modeling indirect exposures from near-field sources, SHEDS-HT employs a fugacity-based module to estimate concentrations in indoor environmental media. The concentration estimates, along with relevant exposure factors and human activity data, are then used by the model to rapidly generate probabilistic population distributions of near-field indirect exposures via dermal, nondietary ingestion, and inhalation pathways. Pathway-specific estimates of near-field direct exposures from consumer products are also modeled. Population dietary exposures for a variety of chemicals found in foods are combined with the corresponding chemical-specific near-field exposure predictions to produce aggregate population exposure estimates. The estimated intake dose rates (mg/kg/day) for the 2507 chemical case-study spanned 13 orders of magnitude. SHEDS-HT successfully reproduced the pathway-specific exposure results of the higher-tier SHEDS-MM for a case-study pesticide and produced median intake doses significantly correlated ($p < 0.0001$, $R^2 = 0.39$) with medians inferred using biomonitoring data for 39 chemicals from the National Health and Nutrition Examination Survey (NHANES). Based on the favorable performance of SHEDS-HT with respect to these initial evaluations, we believe this new tool will be useful for HT prediction of chemical exposure potential.

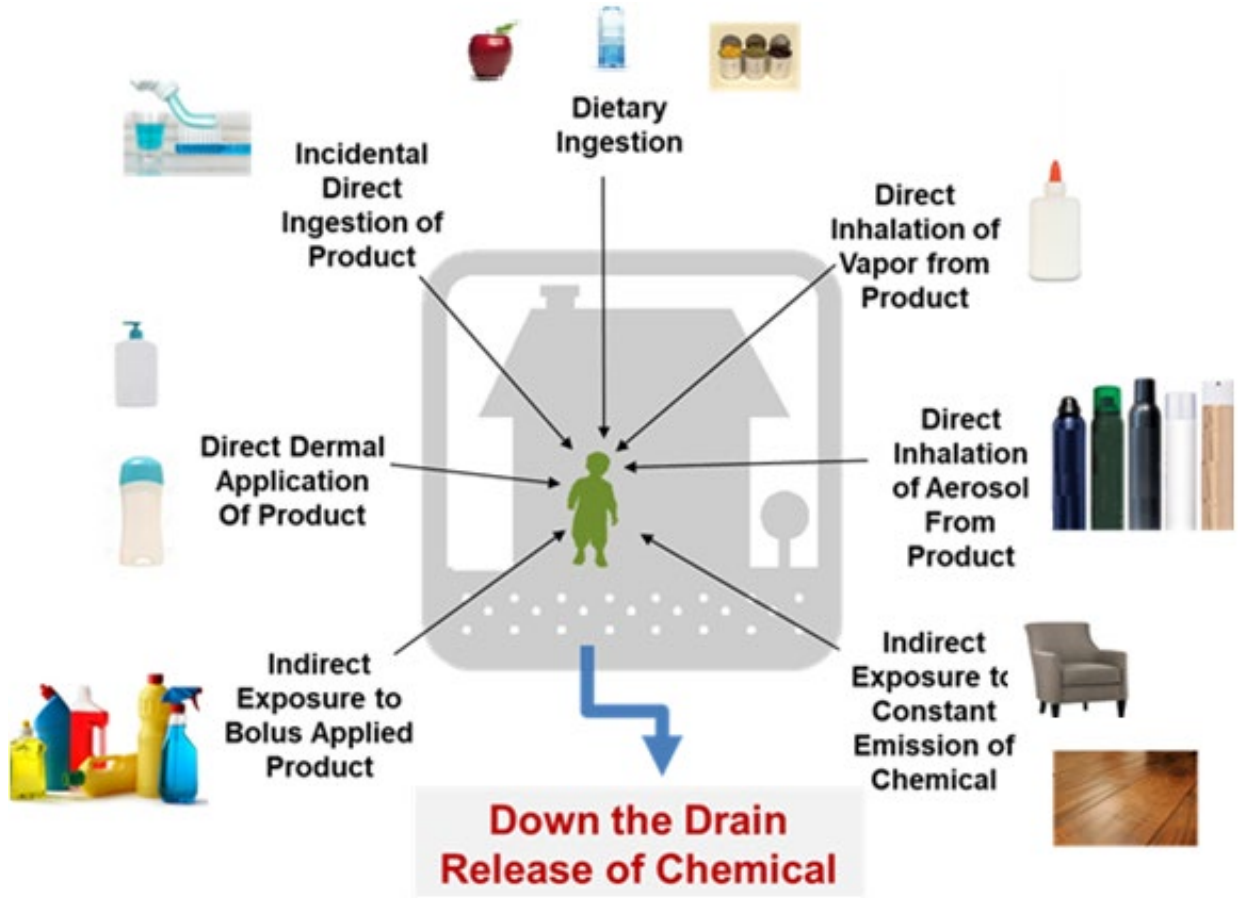


- To ensure that the case study reflects realistic chemical exposures, data derived from EPA's SHEDS-HT was used
- SHEDS-HT predicts aggregate population-based human exposures to thousands of commercial chemicals in consumer products, consumer articles, and foods via inhalation, dermal, ingestion, and dietary pathways in a high-throughput manner

SHEDS-HT: Human-Chemical Exposure Prediction

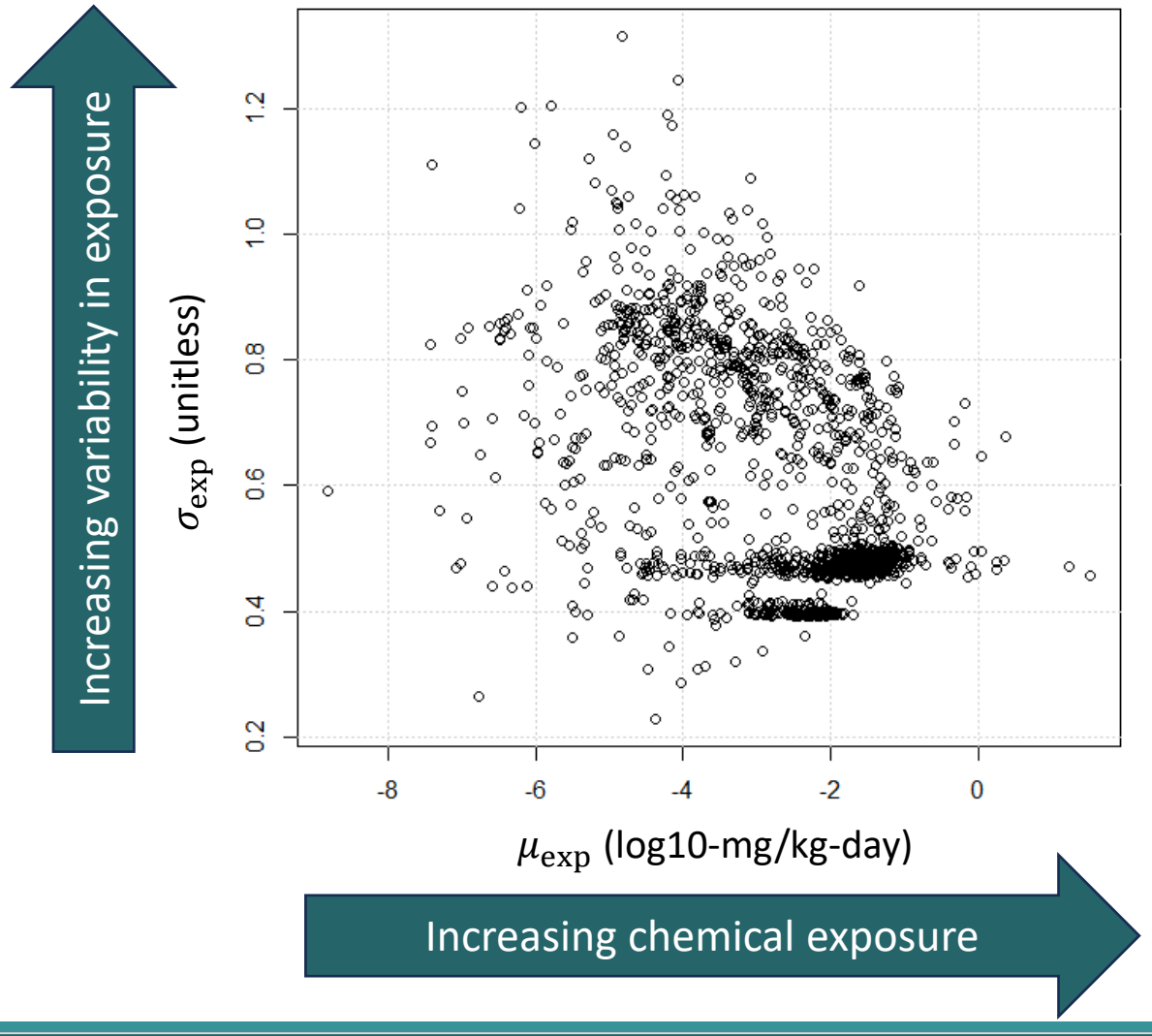
- The exposure parameters are derived based on exposure estimates for **1,578 chemicals** from the TSCA active inventory, including:
  - 665 chemicals present in consumer products
  - 625 chemicals in food contact materials
  - 288 chemicals present in both consumer products and food contact materials
- Exposure estimates based on a population of 10,000 individuals
- Assumes:
  - Prevalence of any chemical within food contact materials is 100%
  - Prevalence of any specific chemical within all products is 100% as market penetration is unknown
- May not reflect exposure from all possible sources and routes

SHEDS-HT



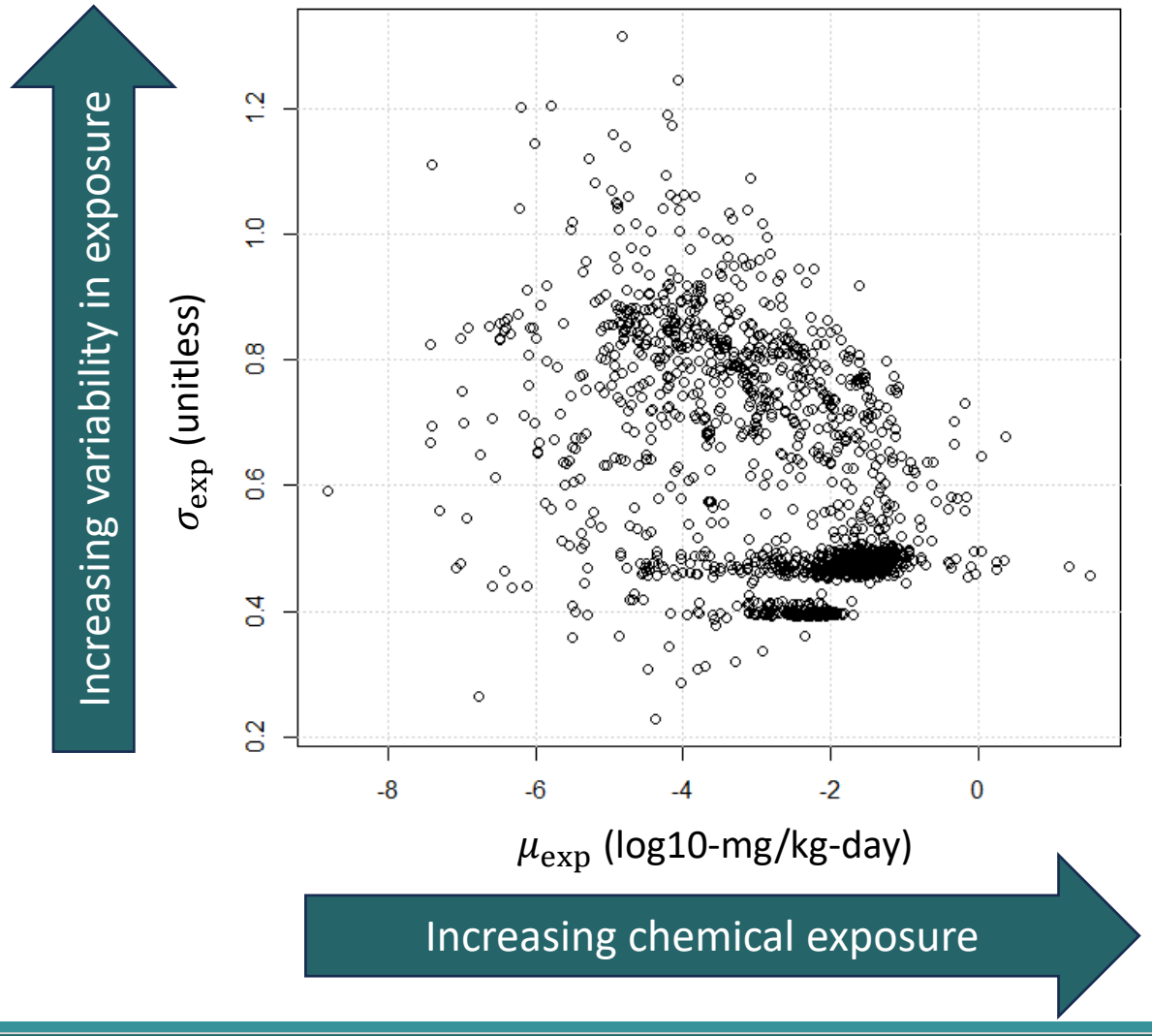
Exposure Parameterization Using SHEDS-HT

- Mean of the logarithm of the geometric means (GMs) of exposed individual is $\mu_{\exp} = -2.271$
- Uncertainty standard deviation for $\mu_{\exp}$ is $u(\mu_{\exp}) = 1.401$
- Mean of the logarithm of the geometric standard deviations (GSDs) of exposed individual is $\sigma_{\exp} = 0.493$
- Uncertainty standard deviation for $\sigma_{\exp}$ is $u(\sigma_{\exp}) = 0.183$



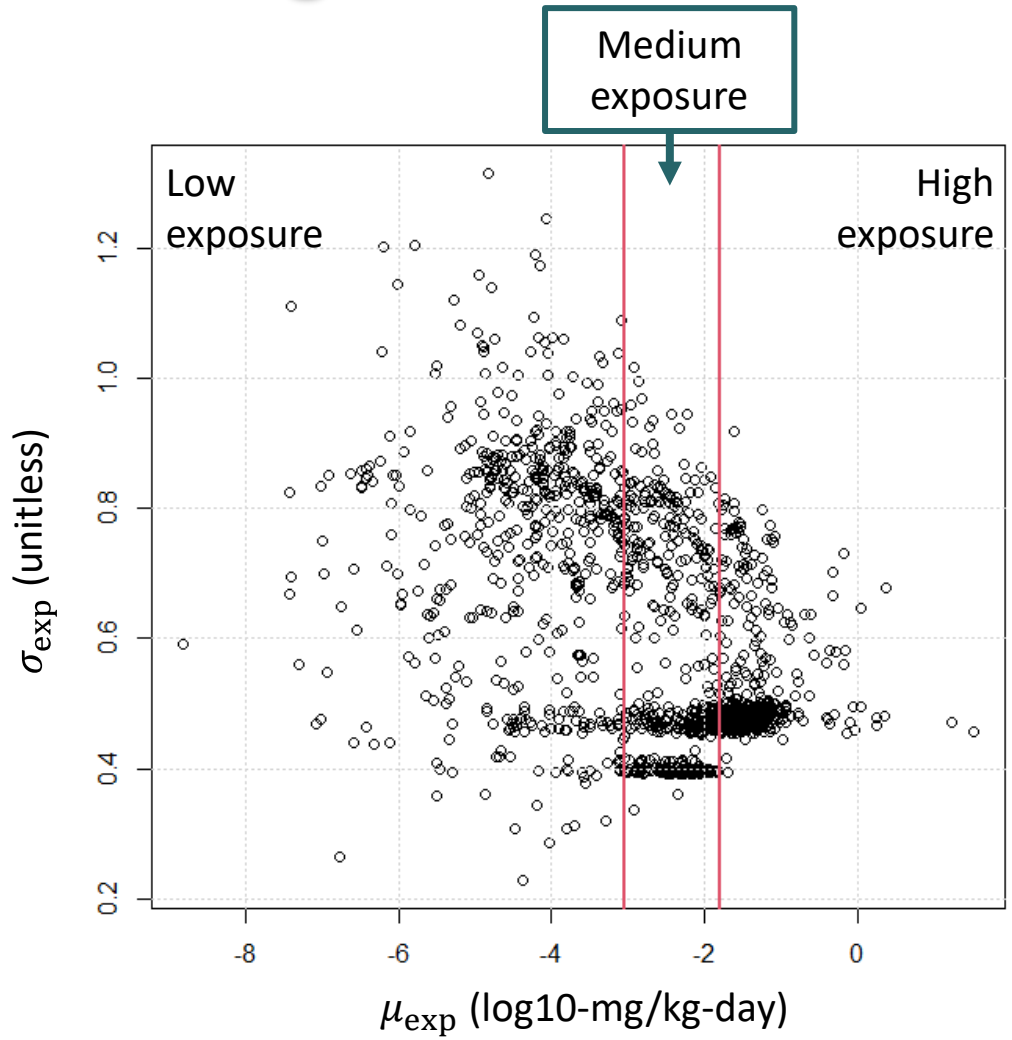
Exposure Parameterization Using SHEDS-HT

- Large variation in exposure estimates introduces substantial uncertainty into the VOI analysis that cannot be reduced by toxicity testing.
- Assuming some prior information about exposure is available for most chemicals, based on intended use and other information, the SHEDS-HT dataset is partitioned into nine (3x3) domains



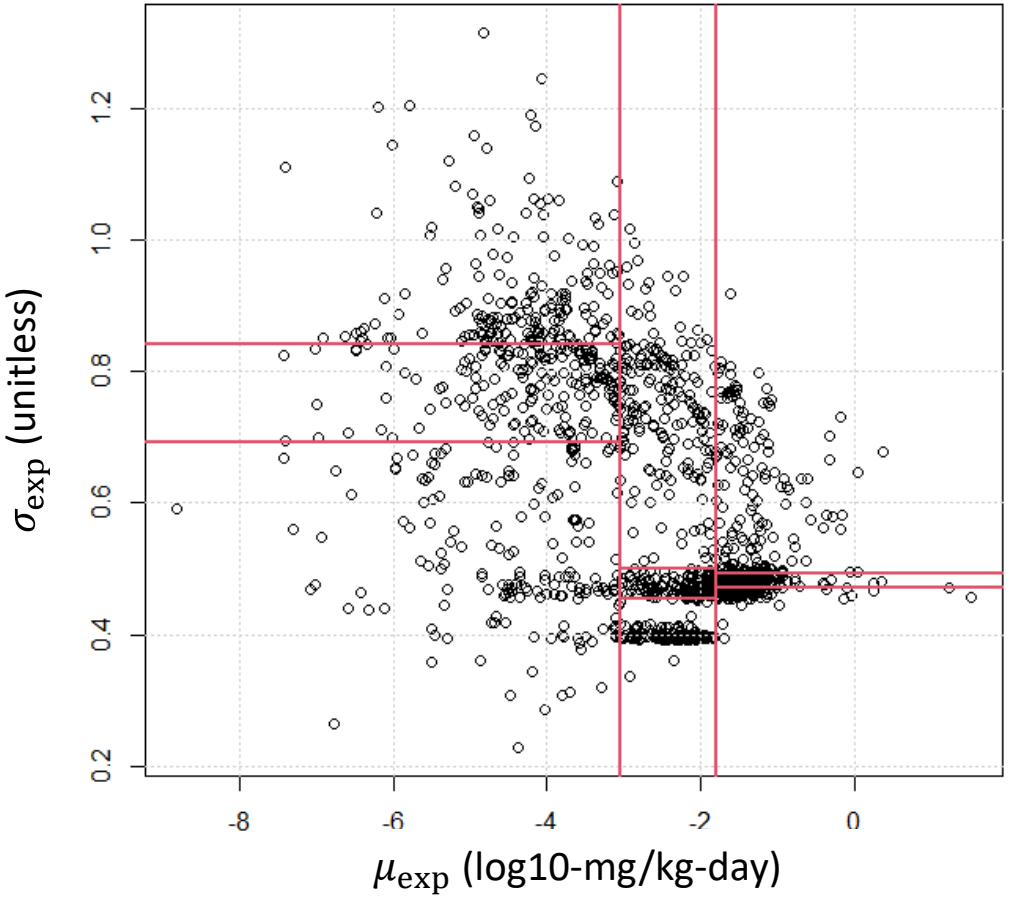
Exposure Parameterization Using SHEDS-HT

- First, chemicals are partitioned into tertiles (low/medium/high) based on their μ_{exp} values



Exposure Parameterization Using SHEDS-HT

- First, chemicals are partitioned into tertiles (low/medium/high) based on their $\mu_{\exp}$ values
- Within each tertile, chemicals are further partitioned into sub-tertiles (low/medium/high) based on their $\sigma_{\exp}$ values



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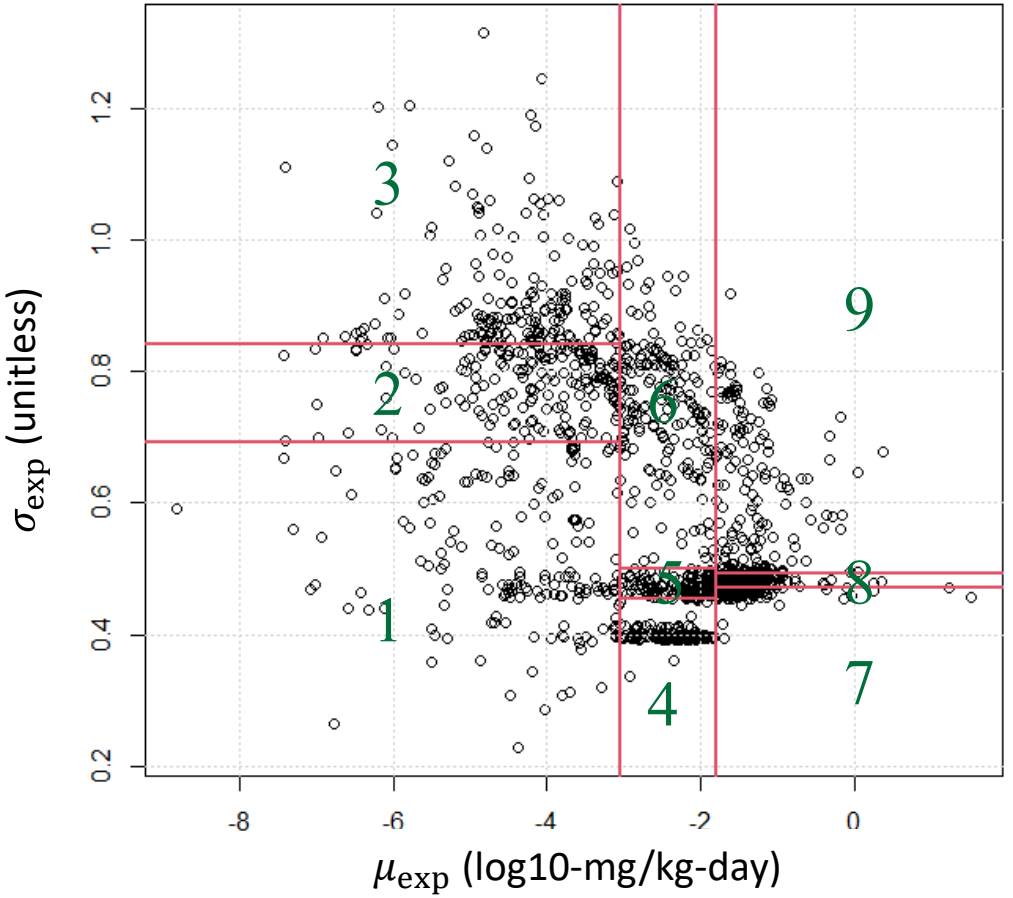

Exposure Parameterization Using SHEDS-HT

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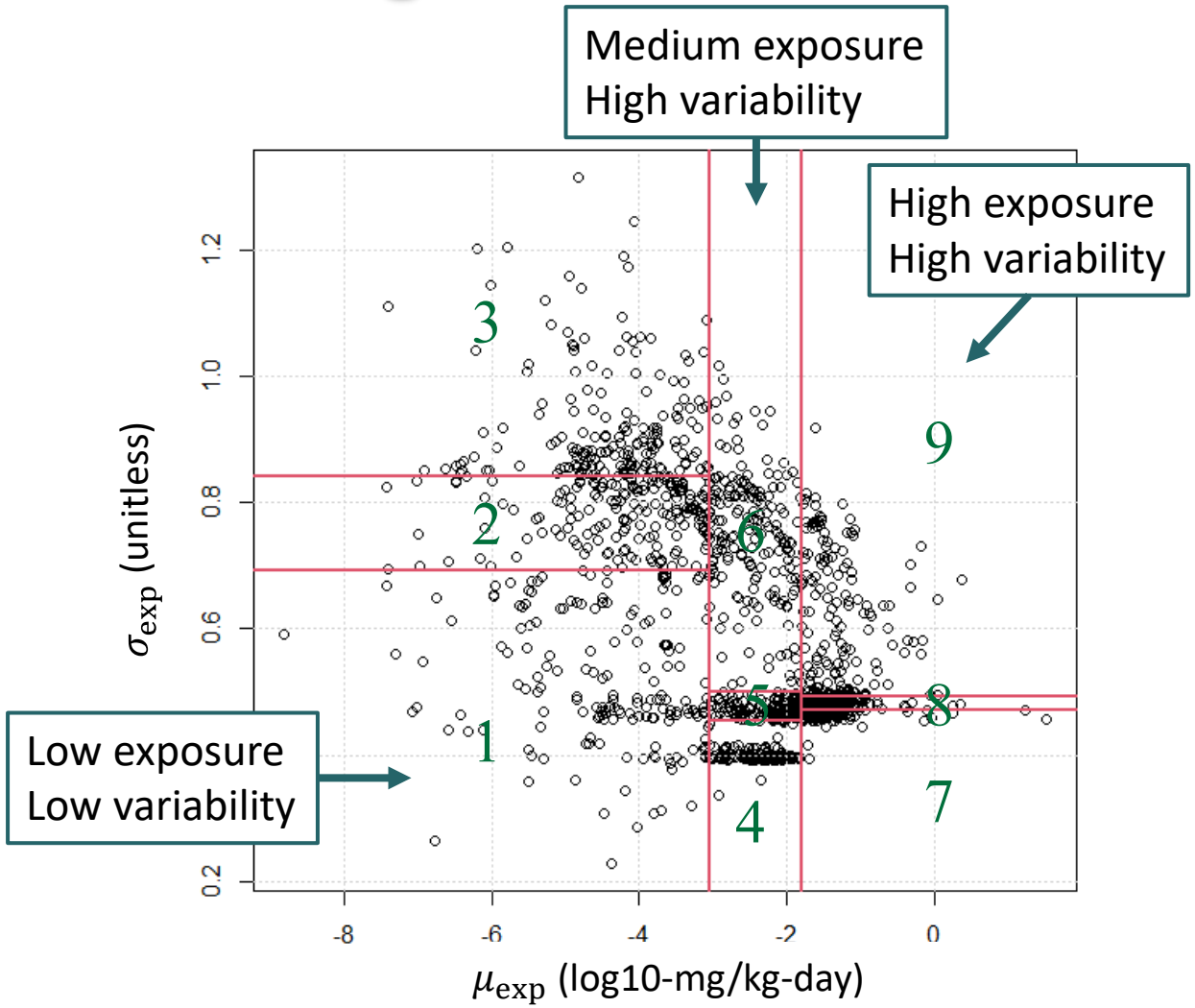
- Within each tertile, chemicals are further partitioned into sub-tertiles (low/medium/high) based on their σ_{exp} values



ECONOMIC VALUATION

Valuation of Adverse Health Outcomes

- For fatal outcomes, EPA uses $8.8M as the value of a statistical life (VSL), corresponding to an annualized value of $110,000 over an 80-year lifetime
- Shahat and Greco (2021) conducted an international review of the economic costs associated with childhood disabilities, and highlighted the following annualized economic values for specific diseases in the U.S. ranging from $450 to $69,500
- Acute health outcomes, such as restricted airway event, have been valued at $70 per event, corresponding to an annualized value of $3,460 assuming an average of one such event per week

As more than 98% of the adverse health effects considered by Chiu et al. (2018) are non-fatal, a notional annualized valuation of $10,000 for a non-fatal adverse health outcome is used in the baseline analysis.

- Sensitivity analyses additionally considered annualized valuations of $1,000 and $110,000

Other Economic Valuation Parameters

- Time horizon: 20 years, representing a time frame commonly used in health economics
- Social discount rate: 5%, as recommended by the EPA Science Advisory Board (2004) and current economic conditions
- Affected population size: 330M, representing essentially the size of the U.S. population

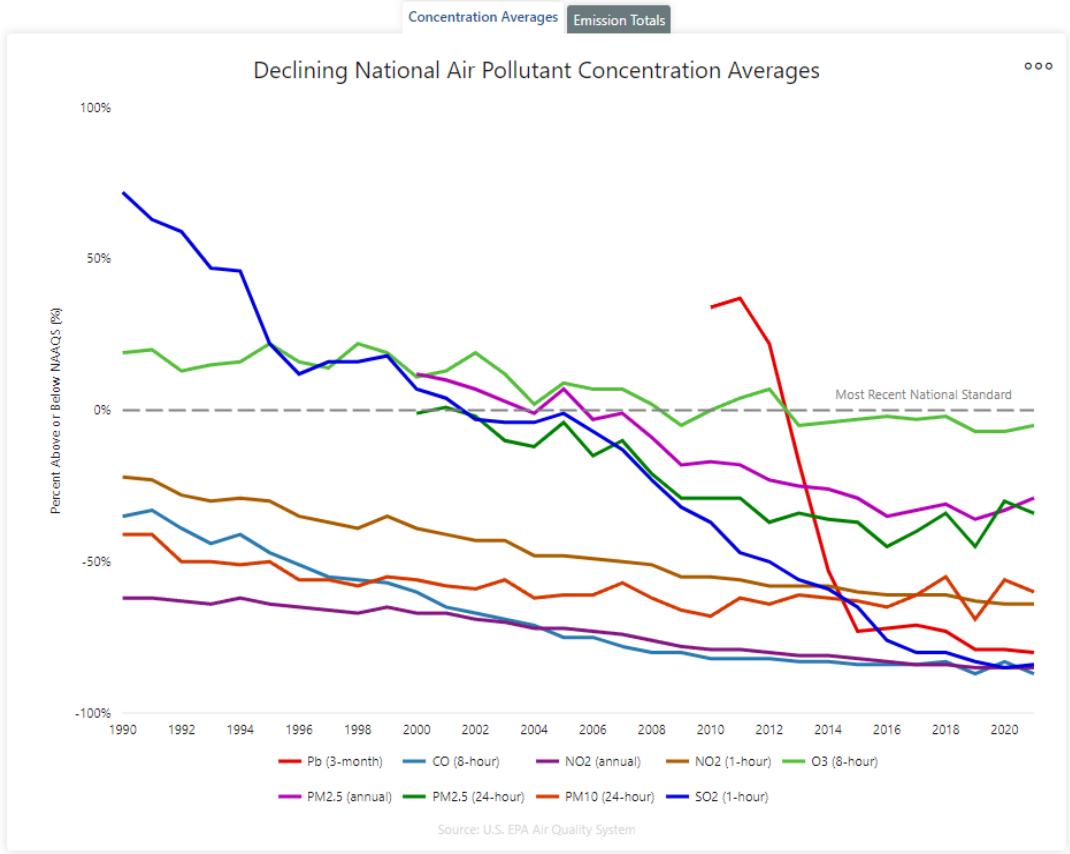
BRDM SPECIFIC INFORMATION

Benefit-Risk Decision-Maker (BRDM)

- BRDM seeks to balance population health risks and the societal costs of risk reduction

- To do this, the BRDM minimizes the expected total social cost (ETSC), which is the sum of economic value of the public health benefits of risk reduction and the cost of exposure mitigation

Cost of Exposure Mitigation Action

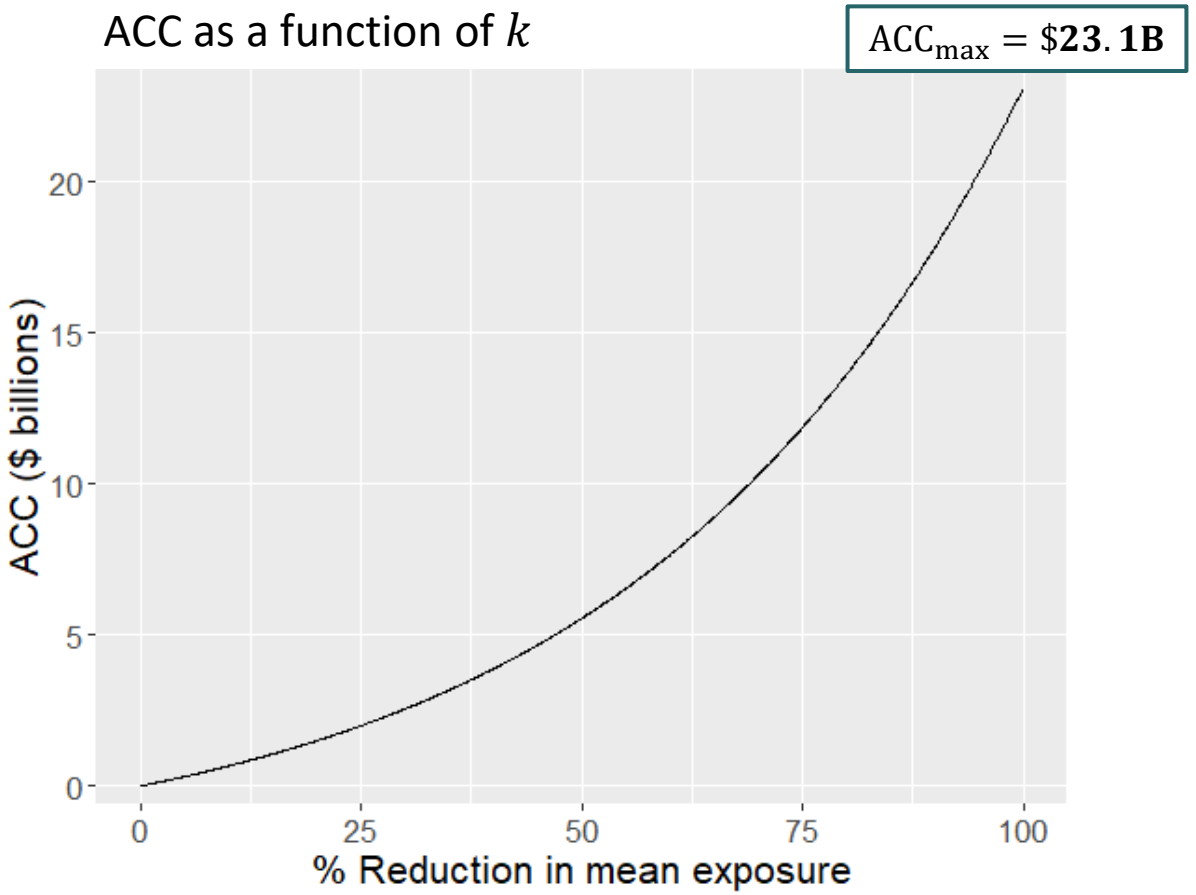


https://gispub.epa.gov/air/trendsreport/2022/#air_trends

- Estimated average annual control cost of **$2.0B** for individual criteria air pollutants (EPA, 2011)
- Trends in emission rates showed a reduction of **25%** between 1990 and 2021 across seven key air pollutants (EPA, 2022)

Cost of Exposure Mitigation Action

% reduction (k)	ACC
25	$2.0B
90	$17.8B
99	$22.5B
100	$23.1B



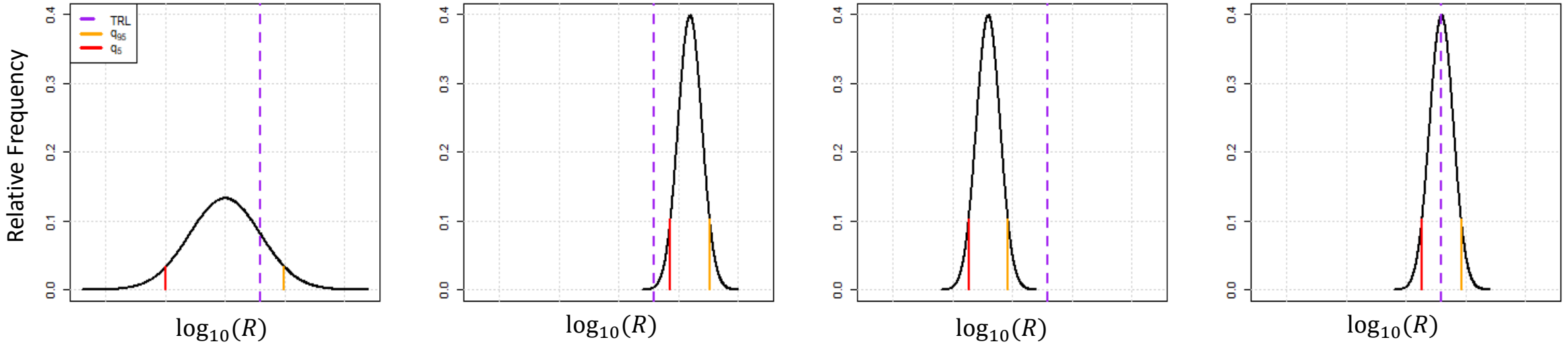
TRDM SPECIFIC INFORMATION

Target-Risk Decision-Maker (TRDM)

The objective of the target-risk decision maker (TRDM) is to control potential health risks **whenever the risk (R) is anticipated to exceed a specified target risk level (TRL) of 10^{-6}**

When regulatory action is required, the mean exposure is reduced by **90%** (assuming regulatory action is targeted towards a dominant source of exposure)

A.	B.	C.	D.
$q_{05} \leq TRL \leq q_{95}$	$TRL \leq q_{05}$	$q_{95} \leq TRL$	$q_{05} \leq TRL \leq q_{95}$
Additional information required	No regulatory action is required	Regulatory action will be taken	Additional information required

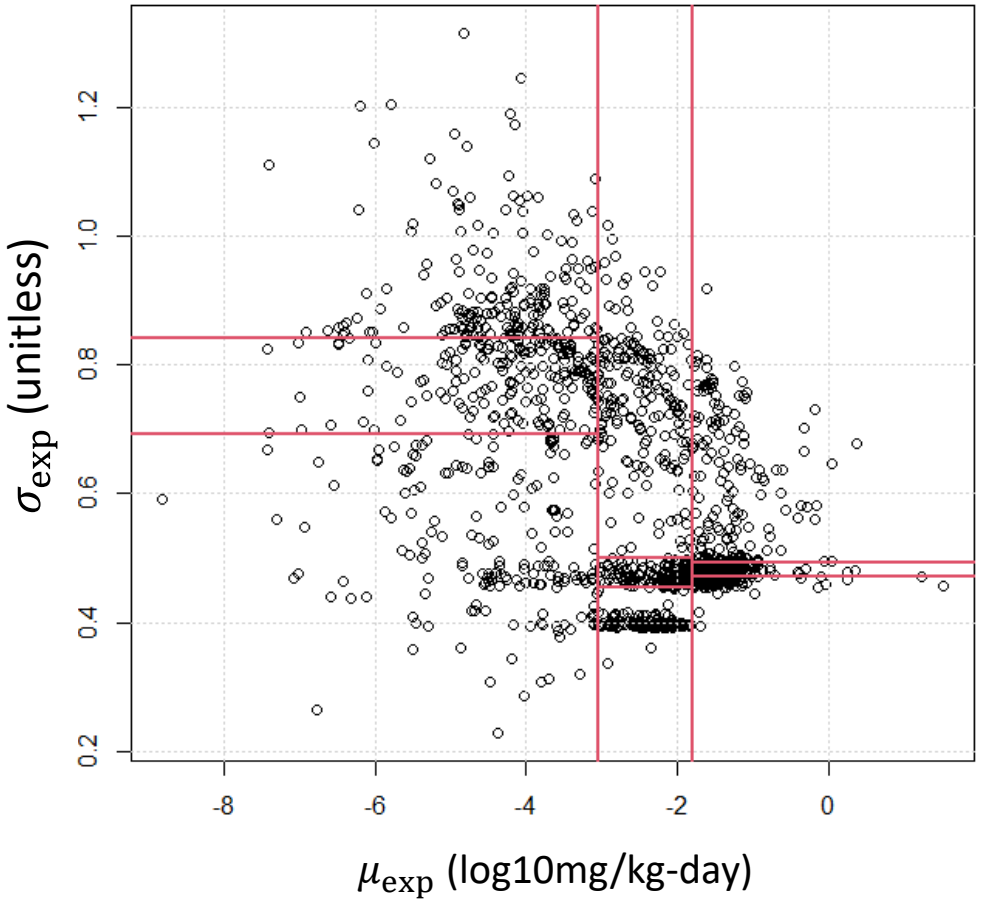


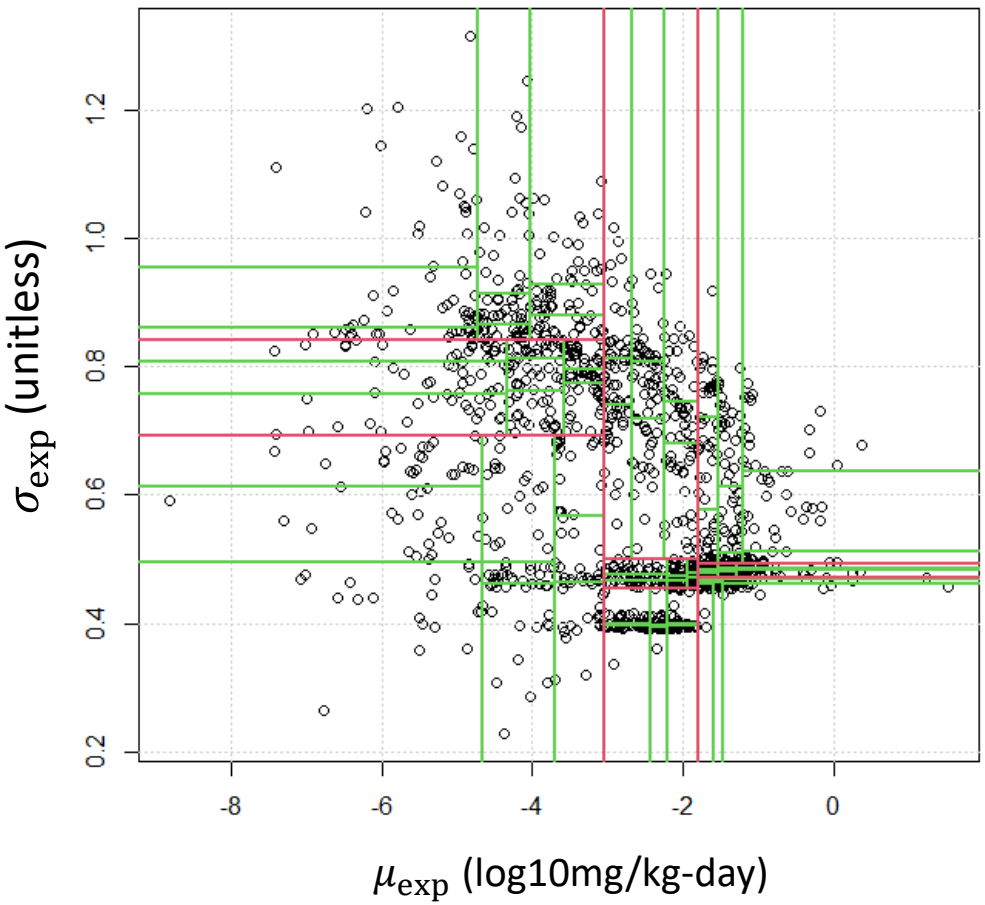
PARAMETERS USED IN SENSITIVITY ANALYSES

Parameters Used in Sensitivity Analyses

- Exposure scenarios
- Toxicity distribution
- Economic valuations
- Target population size
- Target risk level
- Uncertainty associated with ETAP

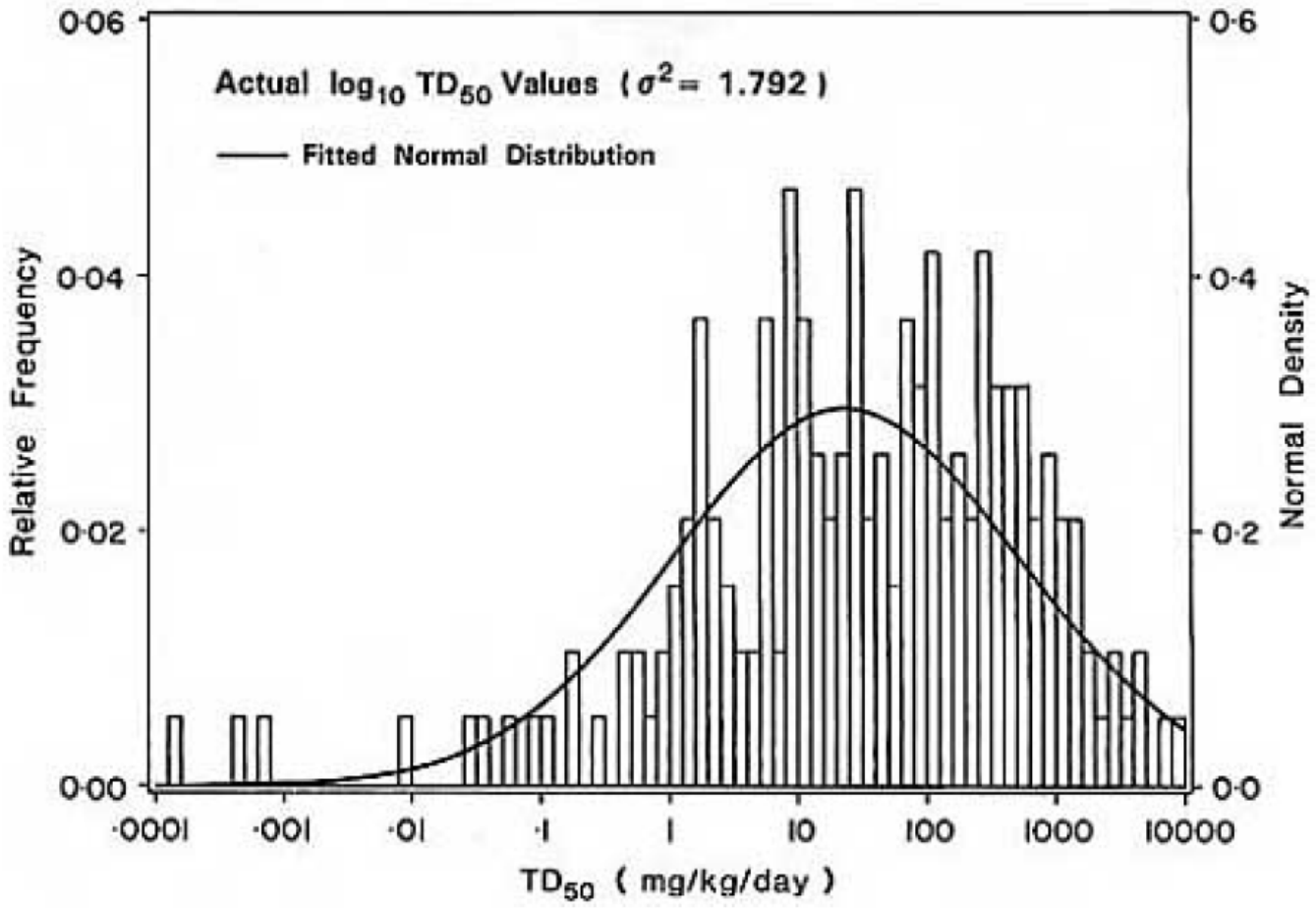
More Precise Exposure Information





Each of the 9 exposure domains are further partitioned into 3×3 sub-domains

Alternative Distribution of Toxic Potency

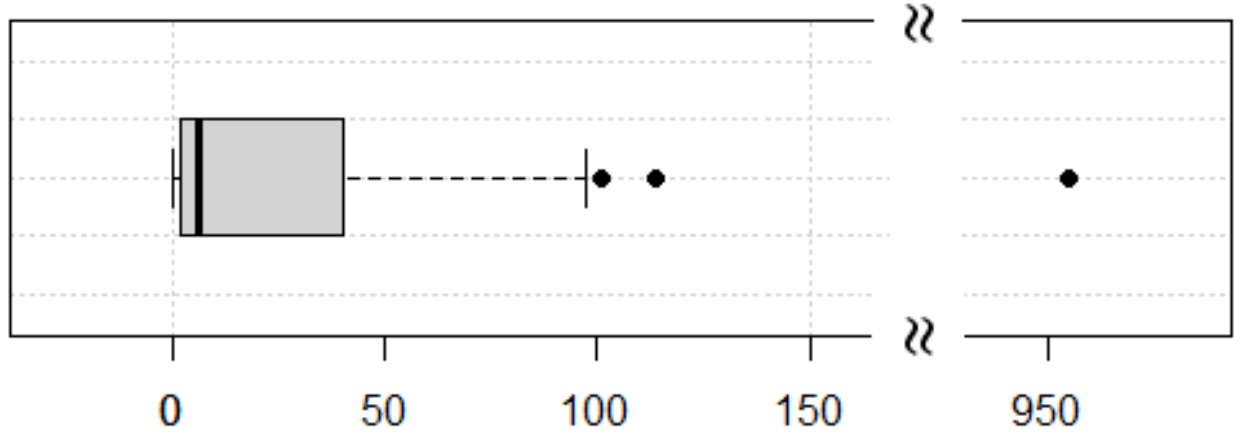


*The average HD_M^{50} across 191 carcinogens is approximately **5.0 mg/kg-day** (greater than **3.3 mg/kg-day** used in the baseline analysis)*

TD_{50}: Dose resulting in 50% tumor response

Cost of Exposure Mitigation Action

- A recent evaluation of the costs of chemical restriction proposals between January 2010 to May 2020 under REACH indicated an annualized total expenditure of €1.7B across all the proposals (ECHA 2021).
- The mean and median control cost across all chemical control programs included in this program were €53.3M and €6M, respectively, corresponding to $50.6M and $5.7M, based on average 2022 exchange rates
- $\mathrm{ACC}_{\mathrm{max}}$ is set to **$578M** (compared to $23.1B in the baseline analysis)



Boxplot of annualized control cost associated with 33 risk management programs under the REACH registration (in €M).

[Based on ECHA (2021). Costs and benefits of REACH restrictions proposed between 2016-2020. ECHA-21-R-02-EN. Helsinki, Finland: European Chemicals Agency.]

ACC: Annualized Control Cost | ECHA: European Chemicals Agency

Effect of Affected Population Size

- Baseline analysis assumed 330M people were affected, representing the situation in which essentially 100% of the U.S. population is exposed to the chemical of interest

- Sensitivity analyses were performed with **165M** (50%) and **33M** (10%) people were exposed

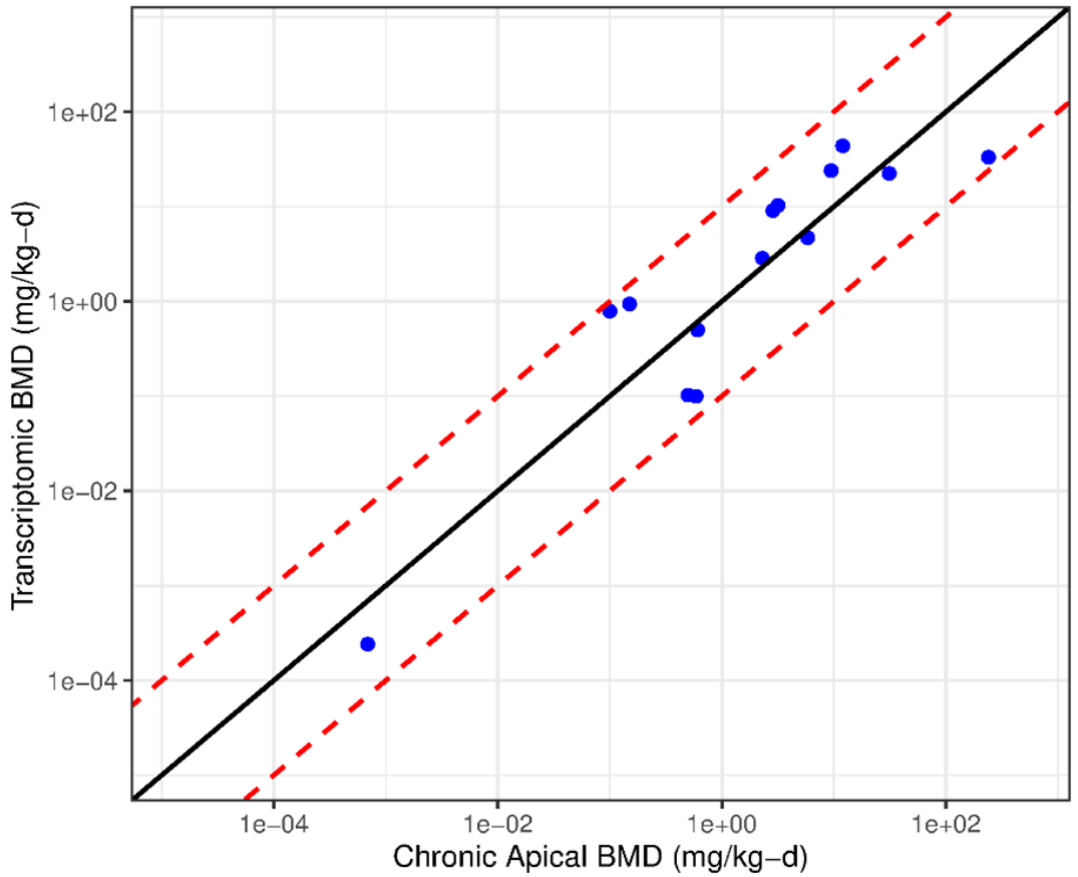
Effect of Target Risk Level

- In the baseline analysis, the TRDM is concerned about risks that exceed a TRL of $\mathbf{10^{-6}}$
- The TRL of $\mathbf{10^{-4}}$ is used in the sensitivity analysis, representing the estimated median residual risk associated with non-cancer exposure guideline values reviewed in Chiu et al. (2018)

RfD: Reference Dose

Discordance as an Additional Source of Uncertainty

- RMSD between 14 BMDs based on ETAP and traditional bioassay is 0.567
- Assigning all of this discordance as a source of uncertainty for the ETAP result leads to an increase in σ_{ETAP} to **0.741** (from 0.442)



Summary

- Parameter selections are intended to make the case-study as real-world based as possible
- There is a total of 306 scenarios considered in this case-study (18 baseline scenarios and 298 sensitivity analysis scenarios)
- These scenarios provide a range of possible outcomes for results for data-poor chemicals