Impact of parameter distribution assumptions on distributional estimates of human equivalent doses

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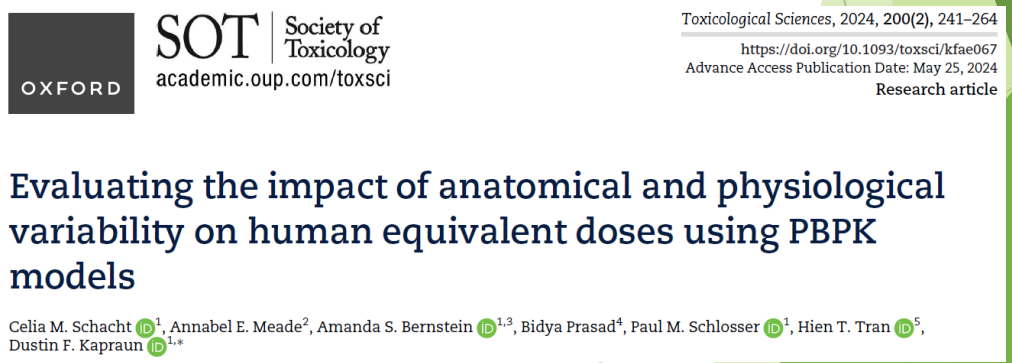
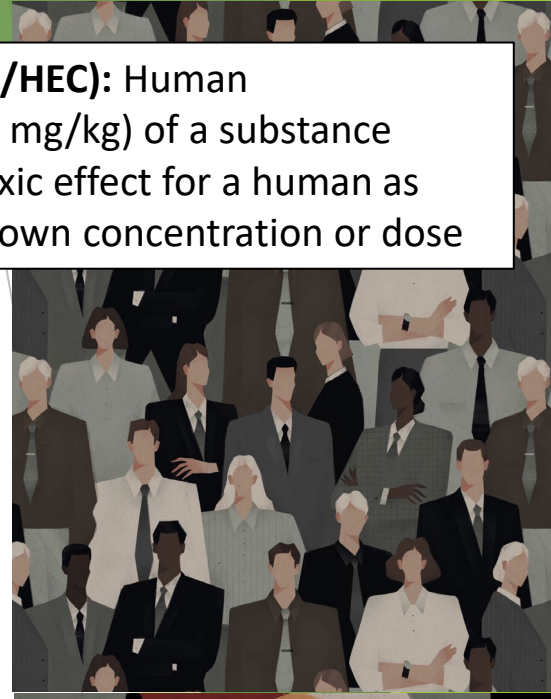
Outline

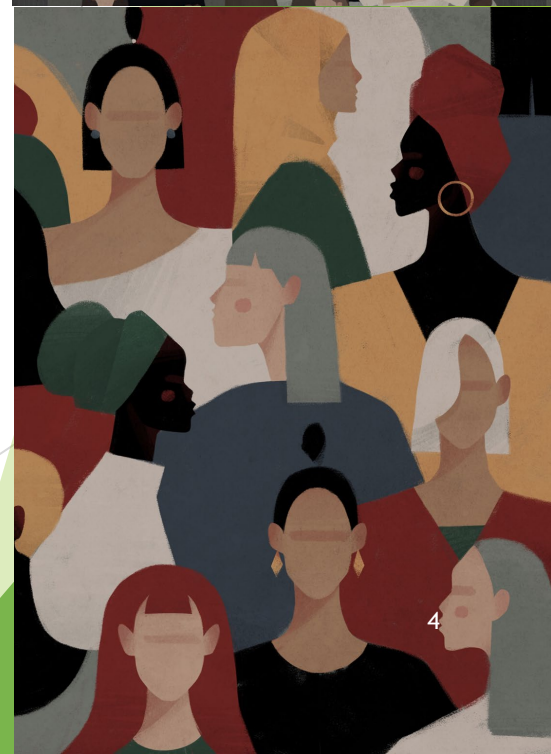
- Background and motivation - Schacht et al. 2024*
- Methods
  - Generating human equivalent doses (HEDs)/ Parameter distributions and Monte Carlo methods for Physiologically Based Pharmacokinetic (PBPK) models
  - Testing HED distributions & percentiles
  - Establishing influential parameters
- Results
- Takeaway points



Introduction/Background

Human Equivalent Dose/Concentration (HED/HEC): Human concentration (inhalation, ppm) or dose (oral, mg/kg) of a substance expected to induce the same magnitude of toxic effect for a human as that observed for lab animals exposed to a known concentration or dose





- Fixed (average) parameter values → point-estimate HEDs: ignores variability.
- Probabilistic framework proposals assume that some risk distributions are lognormally distributed (NRC, WHO IPCS-International Program on Chemical Safety).
  - Parameter distributions are also commonly described as lognormal or normal (justification for shape not supported by data, Crump et al. 2010).
- We generated HEDs using various sets of assumptions about input parameter distributions to then characterize HED distributions using two PBPK models: **DCM** (U.S. EPA IRIS Report, 2011) and **chloroform** (CF) (Sasso et al., 2013).
- How are HED distributions affected by different assumptions about underlying PBPK model parameter distributions?
  - Do model parameter distribution shapes and/or bounds significantly affect the shapes of HEDs?
- When data are limited, how can we identify the parameters most influential to the HEDs?

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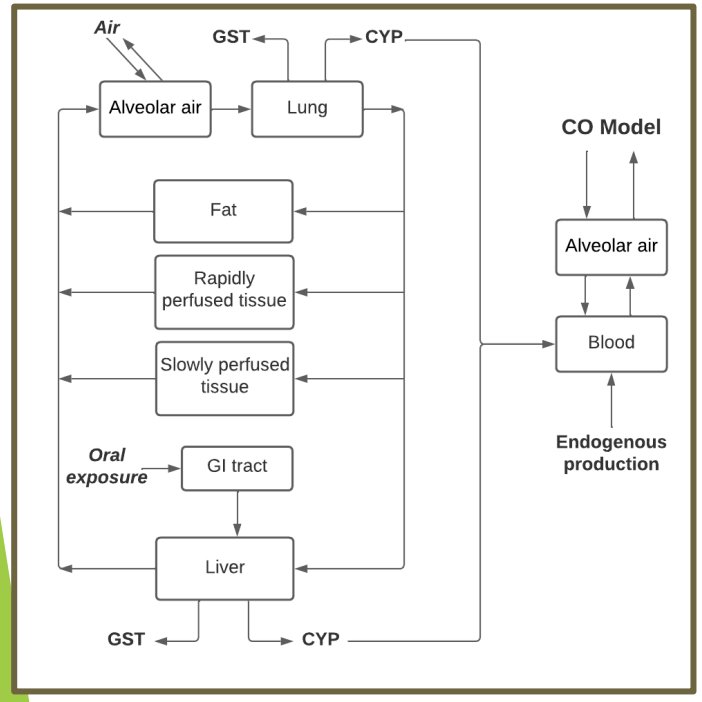
"Nearly all parameter distributions look lognormal, as long as you don't look too closely."

-Dale Hattis*

*Hattis, D. 1990. Three candidate "laws" of uncertainty analysis. Risk Analysis 10, 1, 11.

Methods: Chemicals & Dosing Patterns for Humans

DCM Model



Model: U.S. EPA (2011)

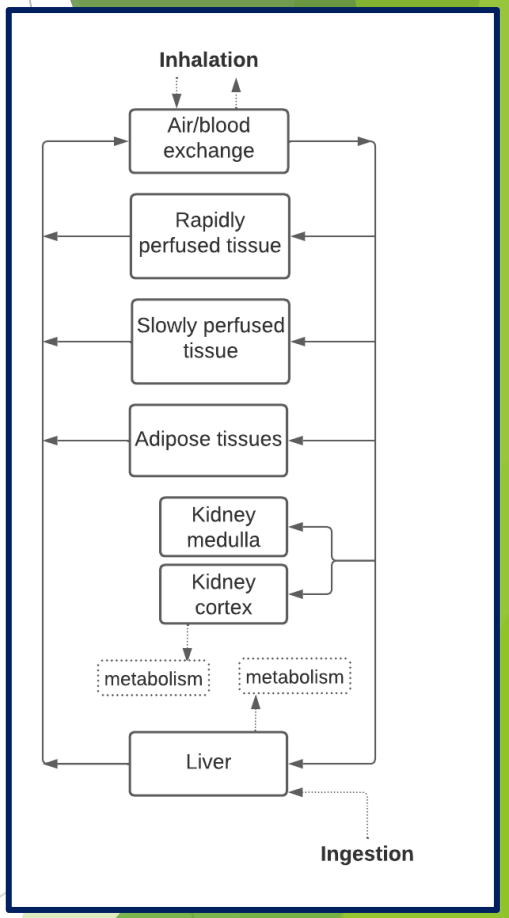
Exposure Route	Dose Structure	Amount of dose given	Exposure interval (hours dosed)
Inhalation	Constant (hours)	--	9am-3pm
Oral	Six bolus doses	25%, 10%, 25%, 10%, 25%, 5%	7am, 10am, 12pm, 3pm, 6pm, 10pm

Chemical	Exposure Dose	Duration
DCM	50 ppm (inhaled) 6 mg/kg (oral)	5 days/2 weeks 7 days/ 3 weeks
Chloroform	10 ppm (inhaled) 45 mg/kg (oral)	5 days/1 week 7 days/3 weeks

6 Subpopulations:

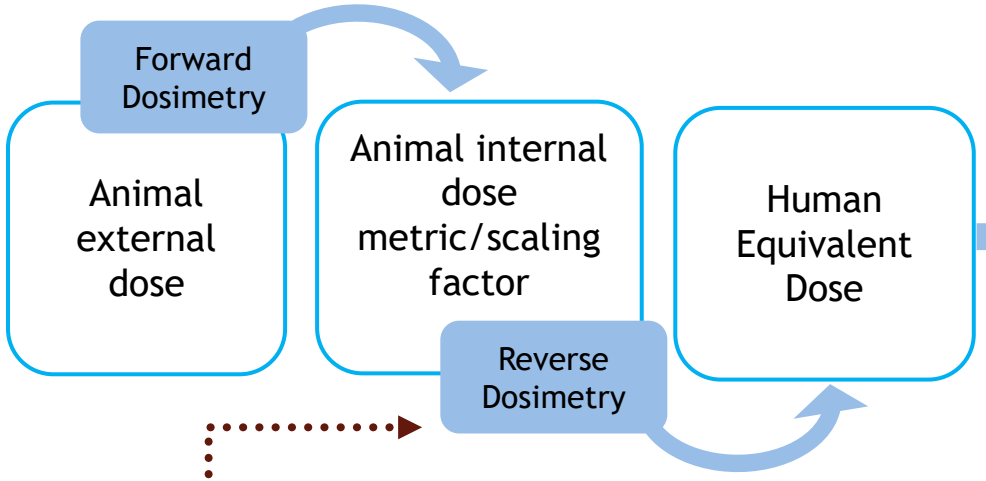
-General (ages 0.5-80, males & females)	-1 y.o. child (males & females)
-30 y.o. males	-30 y.o. females
-70 y.o. males	-70 y.o. females

Chloroform Model



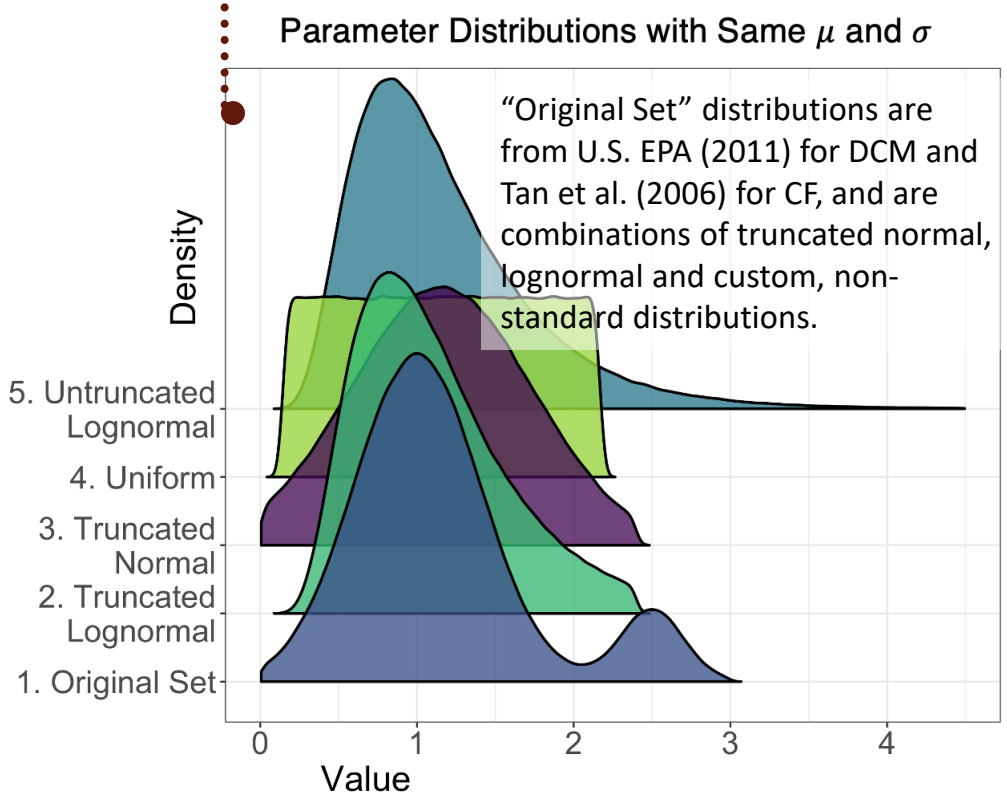
Model: Sasso et al. (2013)

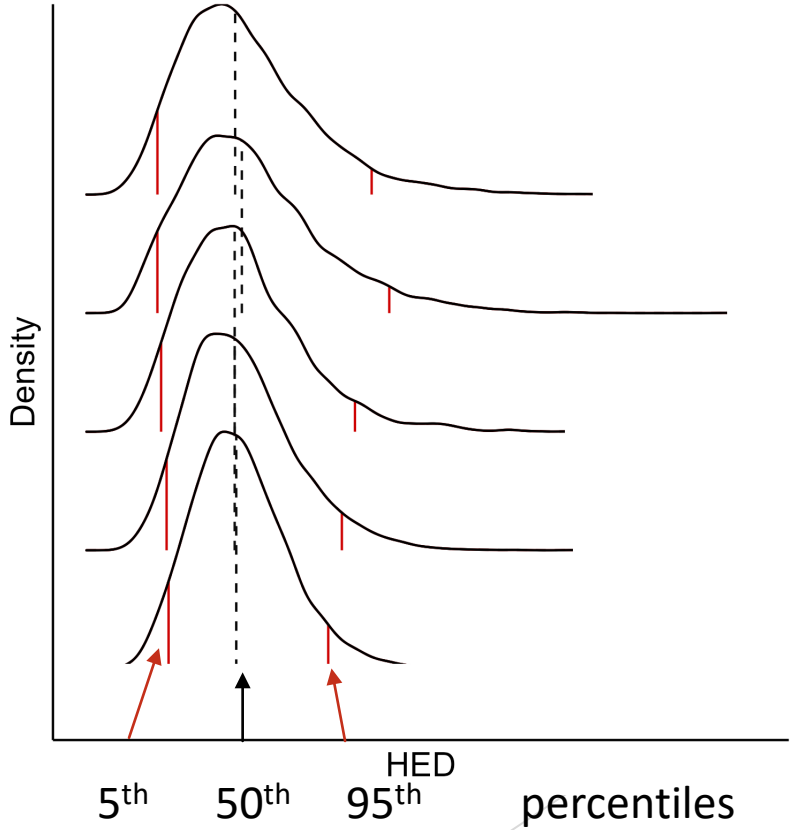
Methods: HED Calculation & Monte Carlo Methods



Compare HED distributions
-How close are the medians? How close are the extreme percentiles?
-Are they lognormal?

Internal dose metric: Measurement to describe internal kinetics of a substance following an external dose.
DCM: mg/L/d metabolized by liver-CYP.
Chloroform: mg/L/d metabolized by kidney.





Compare HED distributions
1. How close are the medians? How close are the extreme percentiles?
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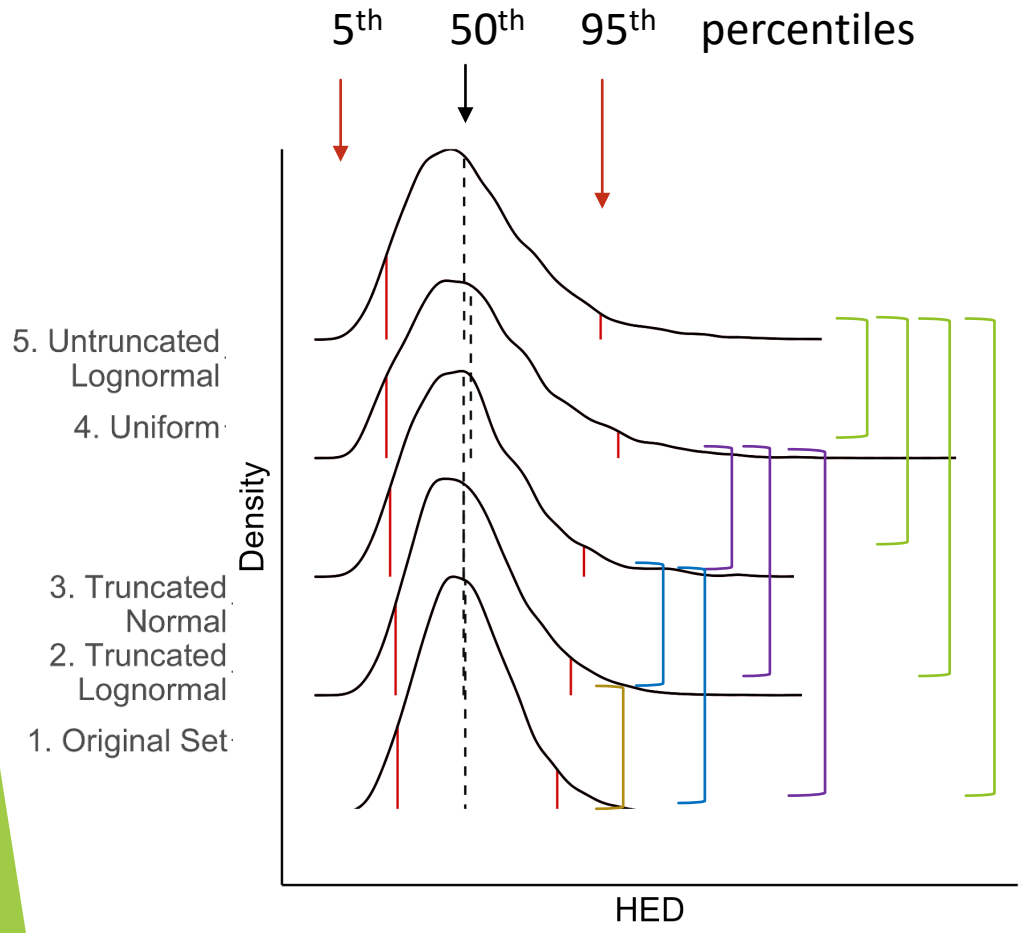
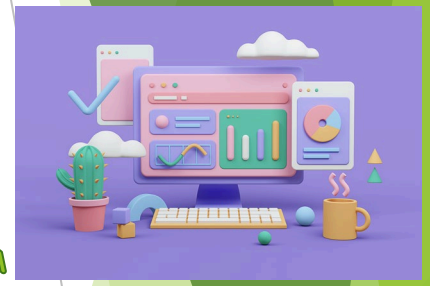
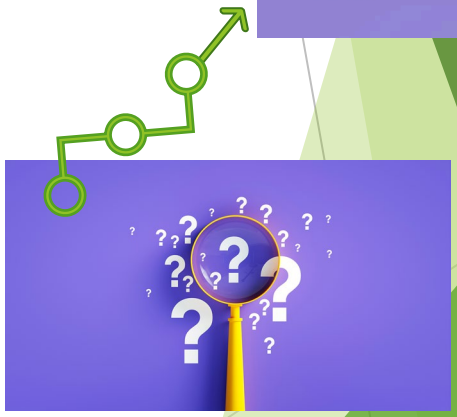


1. Compare the HED distribution percentiles across each parameter distribution type.
   - Find pairwise % difference.
     - Find maximum difference of pairwise % difference (MPPD).
2. Test HED distributions for lognormality.
   - How much do they deviate from lognormality?
   - Royston's *V'*: Turns the Shapiro-Francia test statistic $W \rightarrow$ departure index *V'*.
   - $V' \leq\approx 2 \rightarrow$ data is lognormal.

Methods: Finding the most Influential Parameters

- Sensitivity analysis: methods to determine how the uncertainty in the output of a mathematical model can be attributed to different sources of uncertainty in its inputs/parameters (Sensitivity analysis and PBPK: Evans, 2001; Hsieh, 2018; McNally, 2011).
  - Local – One-at-a-time (OAT) methods that perturb parameters around nominal values.
    - Simple to implement and inexpensive but can be misleading if there are non-negligible interactions among multiple parms or nonlinear processes.
  - Global – calculates the contribution of a parameter over the entire parameter space.
    - Examples: Morris Screening, Sobol' Indices.
    - Variance-based methods find the percentage to output variance contributed by:
      - Each parameter alone
      - Each parameter's interactions



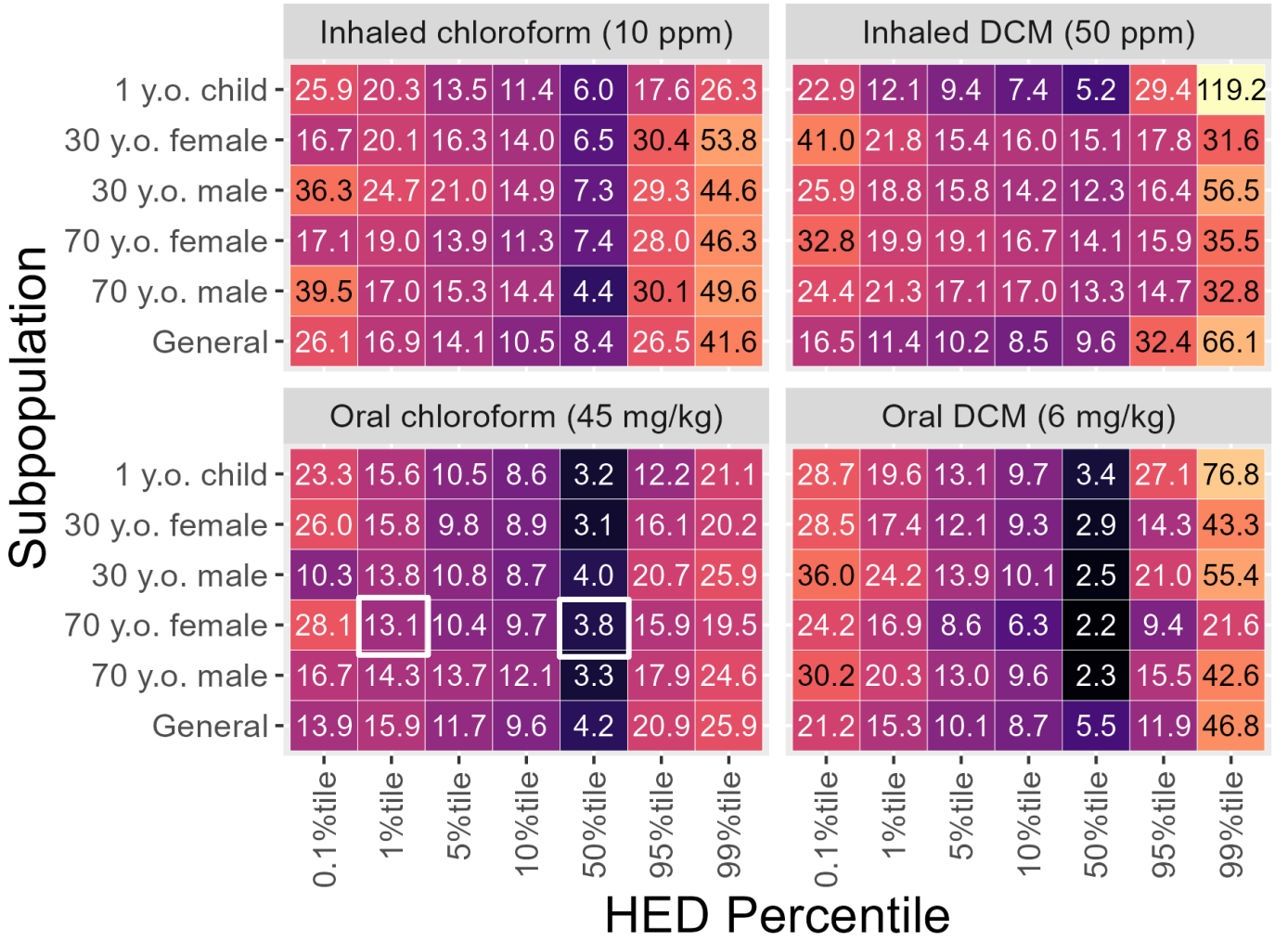


Results: MPPD values – How did HEDs Differ?

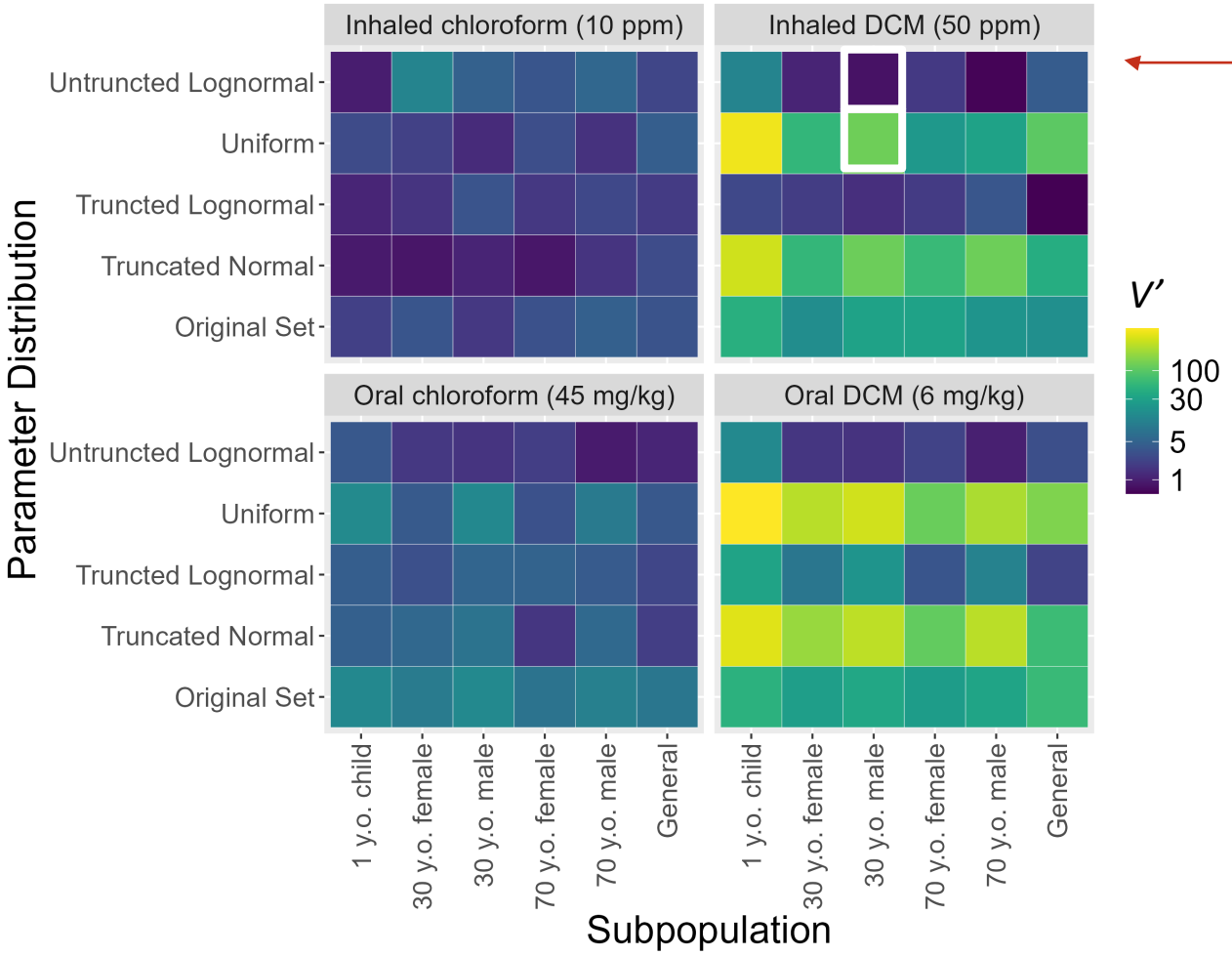
- MPPD: The maximum pairwise percent difference across parameter distributions at each HED percentile.
- For example:

  Oral chloroform HEDs/70 y.o. females HEDs:

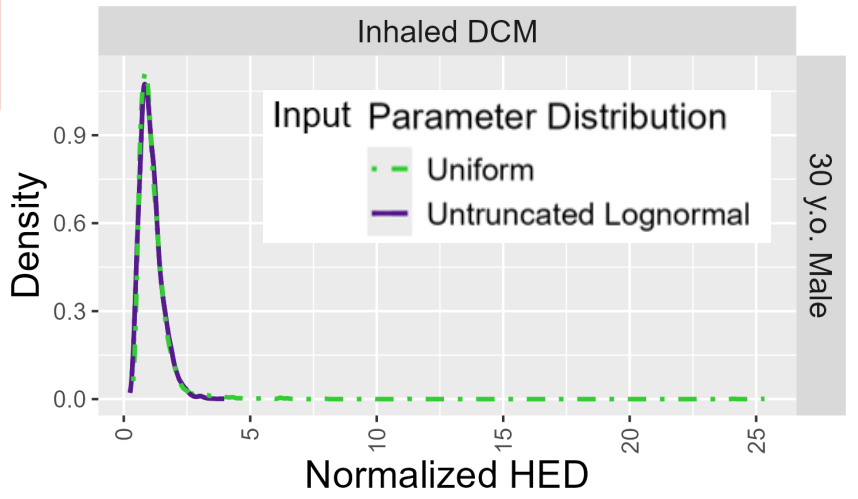
  - 50th percentile generated by 5 different parameter distribution types only differed by 3.8%, at most.
  - 1st percentile: 13.1% max difference.



Results: Departure from lognormality



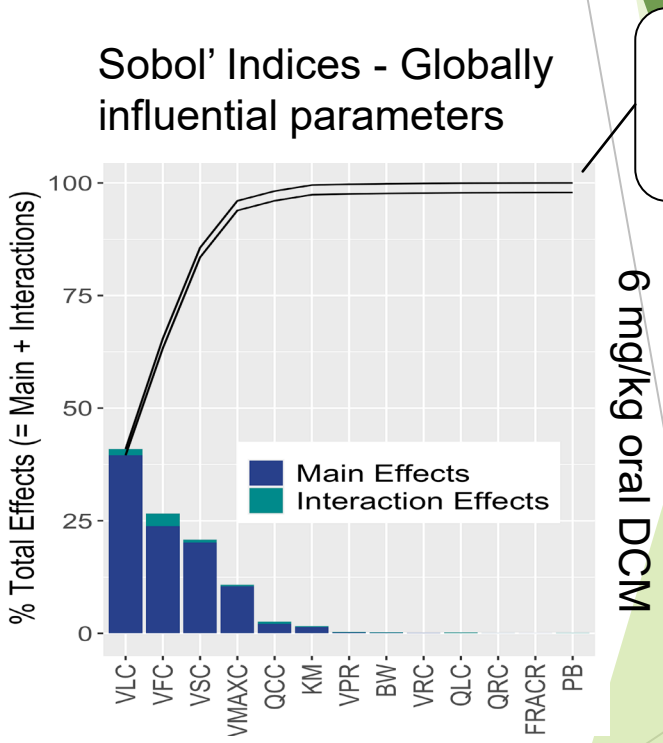
- DCM HEDs deviated more from lognormality ($V' \gg 2$).
- HEDs derived from inhaled doses conformed more to lognormality than oral doses.
- Deviations from lognormality are due to extreme percentiles/long tails.
- Long tails result from extreme values for **influential parameters**…



Results: …Which Influential Parameters?

*Influential parameters: parameters for which more accurate representations of parameter uncertainty and variability may be important.

- Global sensitivity analysis reveals the most influential parameters* for the output: amount oral DCM metabolized in the liver.
  - Total effects: % contribution to the output variation.
- Skewed/Low HEDs can result from individuals simulated with:
  - Very low liver volume.
  - Very high cardiac output.
- Skewed/high HEDs (tails) can result from:
  - Low cardiac output.
  - Low metabolism rate.
- Notice that PB (blood:air PC) and non-listed parameters have very little effect on HED distributions (in this case!).

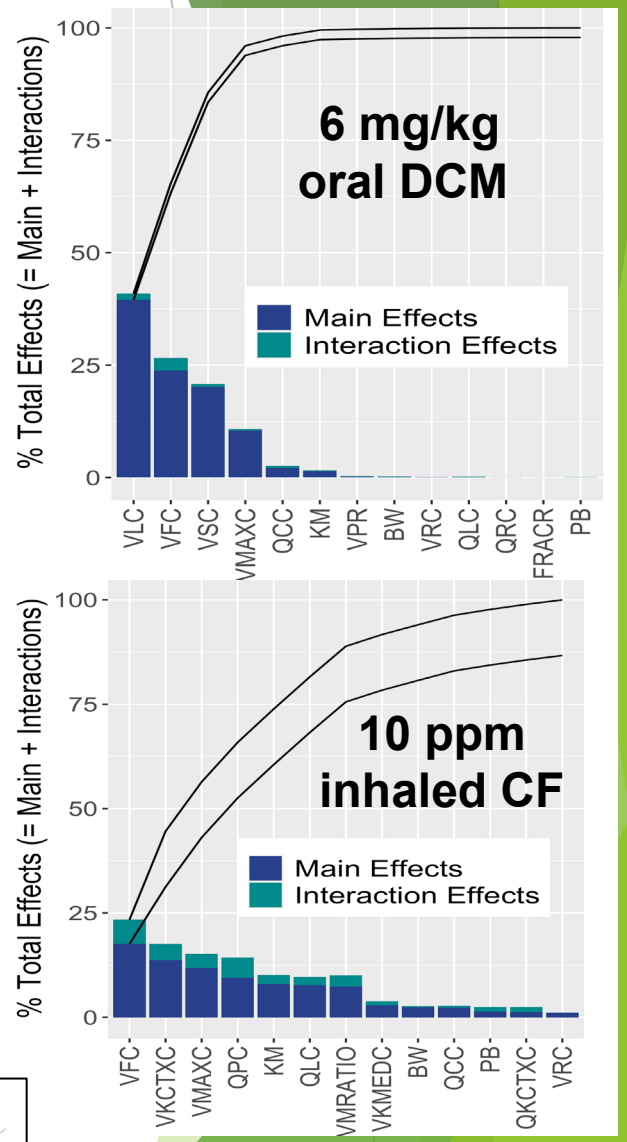


Parameters that account for ~100% of Total Effects: Fractional tissue volumes (liver, fat, slowly-perfused), maximum metabolic rate & affinity, cardiac output

	Parameter key
BW	Body mass
Fractional tissue volumes	
VFC	Fat
VLC	Liver
VKCTXC	Kidney cortex
VKMEDC	Kidney Medulla
VRC/VSC	Rapidly/Slowly-perfused
Flow rates	
QLC	Liver flow rate
QKCTXC	Cortex flow rate
QCC	Cardiac output
QPC/VPR	Respiration
Chemical-specific	
VMAXC, KM, VMRATIO	Metabolic parameters
PB	Blood:air PC

- Influence of parameters depends on the **dose metric** being tested, **route of exposure,** & **chemical/compound group.**
  - Kidney parameters influence kidney dose metrics, etc.
  - Respiration rate influences inhalation cases.
  - Some parameters may be more influential in relation to metabolically active compounds (such as VOCs) than other chemical classes.
  - Dose is also a factor (linear vs nonlinear effects).

Sobol' Indices - Globally influential parameters



Note: Schacht et al. (2024) only considered 2 PBPK models/2 dose metrics/2 routes of exposure – influential/important parameters may differ for other models/dose metrics/routes of exposure!

Discussion/Conclusion – Takeaway Messages

- The distribution types* (i.e. truncated normal & lognormal, untruncated lognormal, and uniform) used to represent uncertainty/variability in human parameter values:
  - Have little impact on the **central tendencies** of the HED distributions.
  - **Do impact extreme percentiles** of HED distributions.

*parameter distributions have the same mean and variance.

- **Tails** in HEDs are more responsive to changes in **extreme quantiles** of input parameters.
  - Thus, it is important to get accurate estimates of these parameter distribution's highest and lowest values (i.e., most sensitive populations).
  - Consider the accuracy of the distribution, not just its "family".

- Lognormality of HED distributions is scenario-dependent.
  - Chloroform/amount metabolized in kidney & inhalation routes → $\approx$ LN. ✓
  - DCM/amount metabolized in liver & oral routes → deviations. ✗

Not all parameters are created equal

- Predictions of dose metrics/HEDs (central estimates or extreme percentiles) can be greatly improved by having precise knowledge about **certain** input parameter distribution shapes & variances (but not all).
  - Some input parameters will have little/no effect on predictions of central estimates/extreme percentiles.
- Schacht et al. (2024) discussed the input parameters or situations for which it is important to allocate time and resources to collect data to develop more accurate representations of parameter uncertainty and variability.
- Some parameters exert more influence on certain outputs than others.
  - When parameter data is limited, sensitivity analysis may be used to identify the parameters for which accurate estimates are most important.

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Evaluating the impact of anatomical and physiological variability on human equivalent doses using PBPK models

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