Characterizing Uncertainty & Variability in Physiologically Based Pharmacokinetic (PBPK) Parameters*

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**The views expressed in this presentation are those of the author and do not necessarily reflect the views or policies of the U.S. Environmental Protection Agency.*

Outline

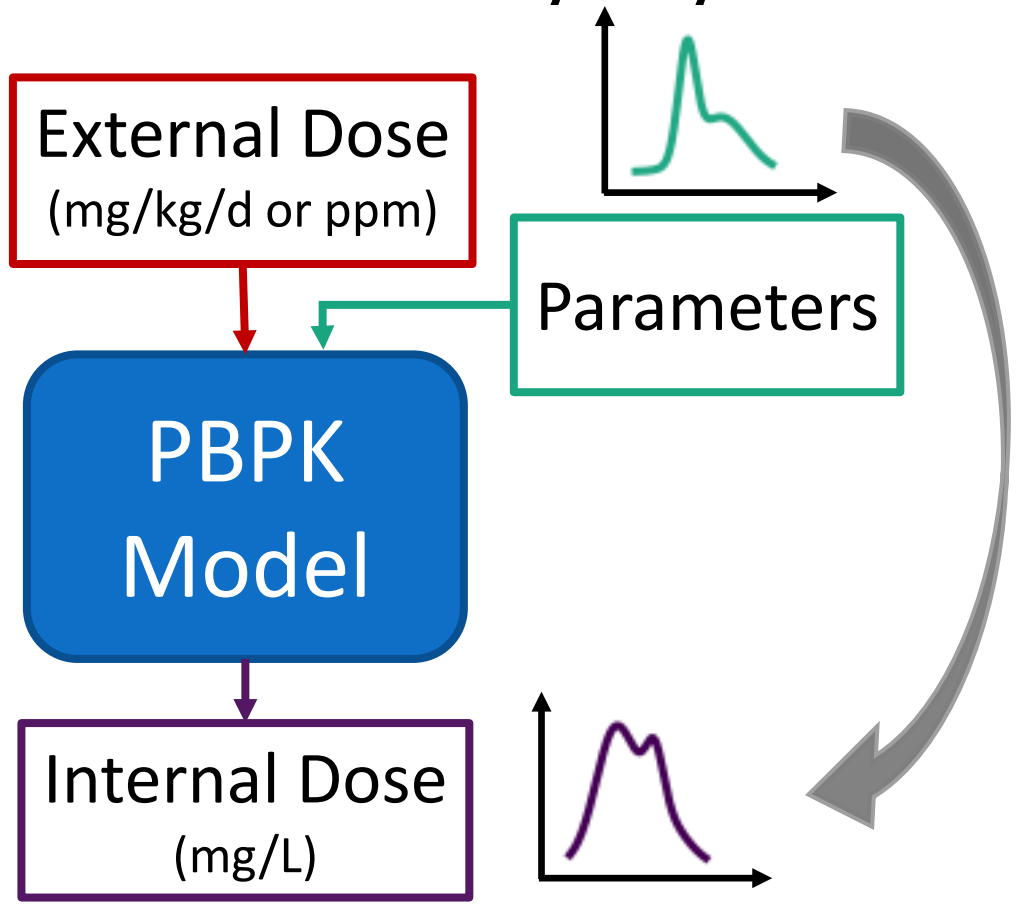
- Context: Uncertainty, variability and “Uncertainty Factors”
- How can we address uncertainty (briefly)?
- How is human parameter variability quantified?
  - Concerns with some approaches
- Why should estimates of parameter distributions (variability) be improved?
- Initial efforts to better quantify human variability
- Future directions
- Footnote: it’s not just the parameters that are uncertain

Framework for evaluating the impact of parameter uncertainty and variability*

General approach

- PBPK models predict internal dose as a function of external dose and parameter values.
- Repeating this process with large numbers of parameters sampled from distributions, representing parameter uncertainty and variability, yields predictions of internal dose distribution.

Forward dosimetry analysis

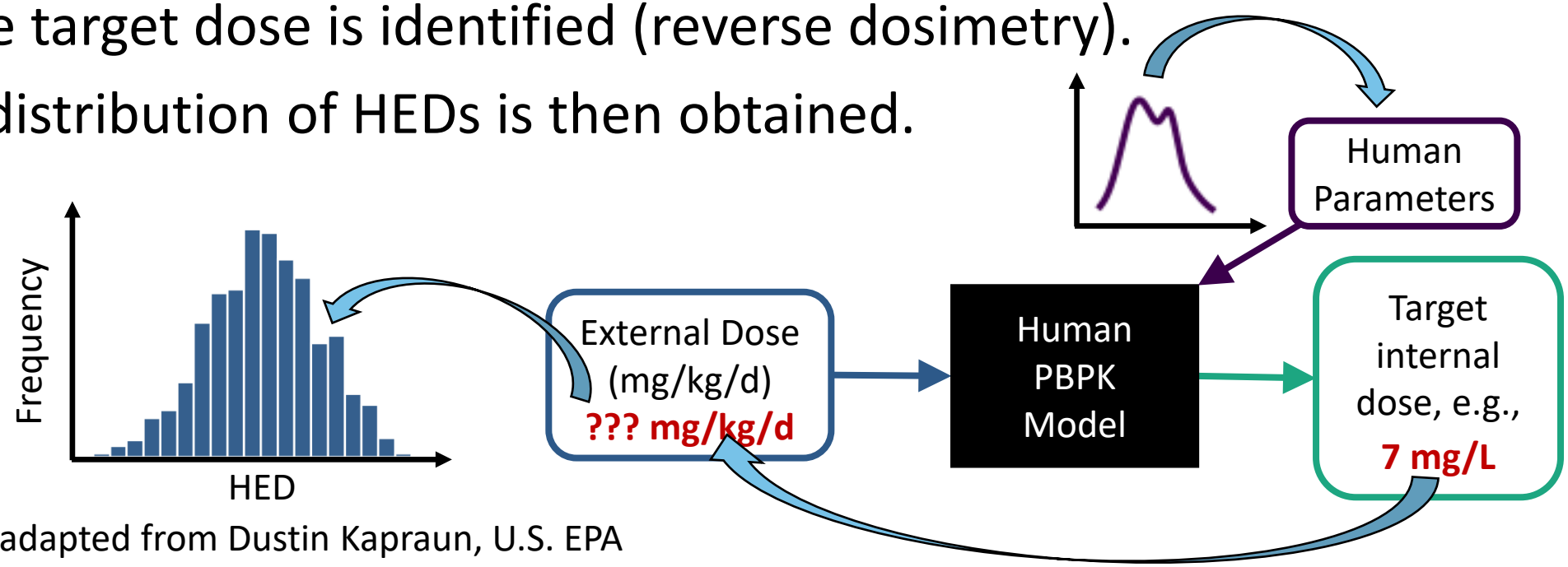


*Slide adapted from Dustin Kapraun, U.S. EPA

Framework for evaluating the impact of parameter uncertainty and variability (2)*

Evaluating human equivalent dose (HED) distributions via reverse dosimetry

- Again, human parameters are sampled from distributions to capture uncertainty and variability.
- For each parameter set the external dose (HED) that yields the target dose is identified (reverse dosimetry).
- A distribution of HEDs is then obtained.



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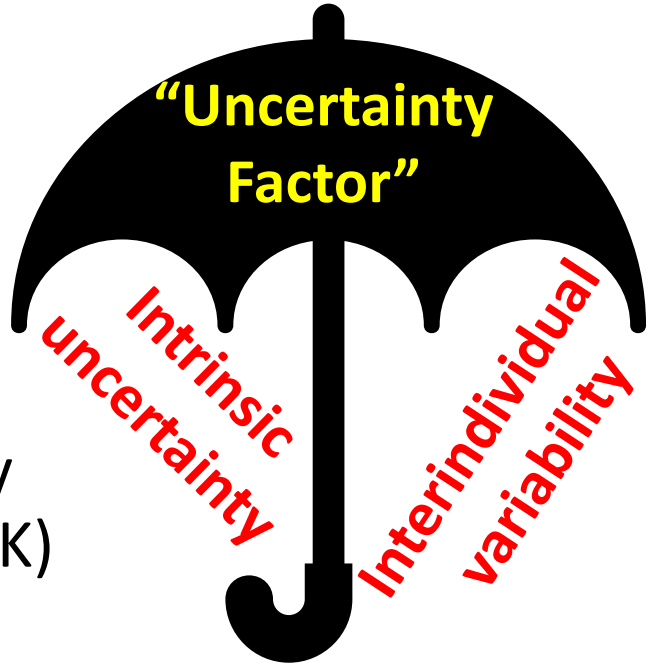
Context: "Uncertainty" and "Variability" in Pharmacokinetic Parameters

- For humans in particular there are both:
  - Intrinsic uncertainty due to limited knowledge of parameters such as the population average rate of chemical metabolism
  - Variability in parameters due to inter-individual differences
- The traditional human intraspecies "Uncertainty Factor" (UF_H) is divided into pharmacokinetic (PK) and pharmacodynamic (PD) components:

$$UF_H = UF_{H,PK} \times UF_{H,PD}$$

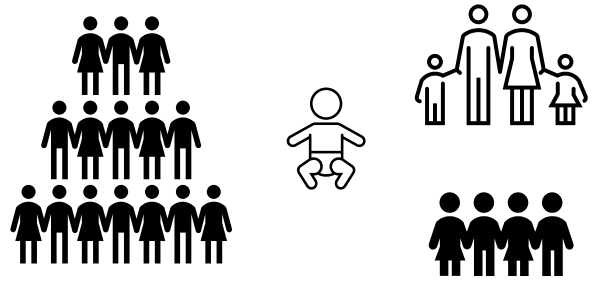
- But UF_H is intended to account for both intrinsic uncertainty and variability



How can we address uncertainty?

- Collect more data
- We are generally more uncertain about metabolic parameters and other chemical-specific values than anatomy and physiology, especially in humans for whom in-vivo PK data are limited
- While in-vitro methods can provide a lot of chemical-specific data, in-vitro to in-vivo extrapolation (IVIVE) is itself uncertain
  - Predictions often differ from in-vivo data by up to 10-fold
- However, there is significant ongoing research by EPA's CCTE, NIEHS and other research groups to improve IVIVE

How is human variability quantified? An example:



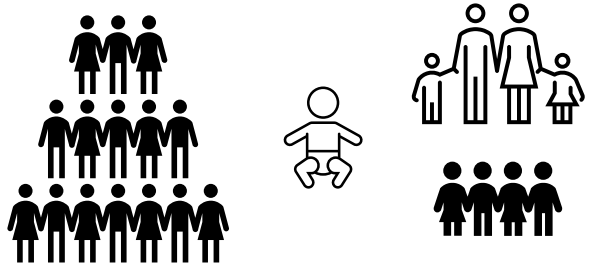
- Parameters in a PBPK model can be chosen from distributions via Monte-Carlo (MC) sampling
  - But what distributions?
  - How are they selected?
- In this example many of the SD values are simply 30% of the mean
- Vfs & Qfs were assumed normally distributed, truncated at ± 1.96·SD
- Sampled independently

Parameter	Mean	Standard deviation (SD)	Source
Tissue volume as percentage of body weight (assume unit density)[a]			
Fat	21.4	6.42	Brown et al., 1997
Liver	2.57	0.77	Brown et al., 1997
Kidney	0.44	0.13	Brown et al., 1997
Skin	5.1	1.53	Corley et al., 2000
Rapidly perfused tissue	5.39	1.62	Brown et al., 1997
Slowly perfused tissue	56.1	16.8	91%–other tissues
Flows			
Cardiac output (L/h/kg$^{0.75}$)	16.5	1.50	Clewell et al., 2000
Alveolar ventilation (L/h/kg$^{0.75}$)	24	3.8	Clewell et al., 2000
Blood flow to tissue as percentage of cardiac output[a]			
Fat	5	1.5	Brown et al., 1997
Liver	25	7.5	Brown et al., 1997
Kidney	19	5.7	Brown et al., 1997
Skin	8.6	2.6	Brown et al., 1997
Rapidly perfused tissue	25.4	7.62	100%–other tissues
Slowly perfused tissue	17	5.1	Brown et al., 1997

Vfs: volume fractions

Qfs: blood flow fractions

How is human variability quantified? (2)

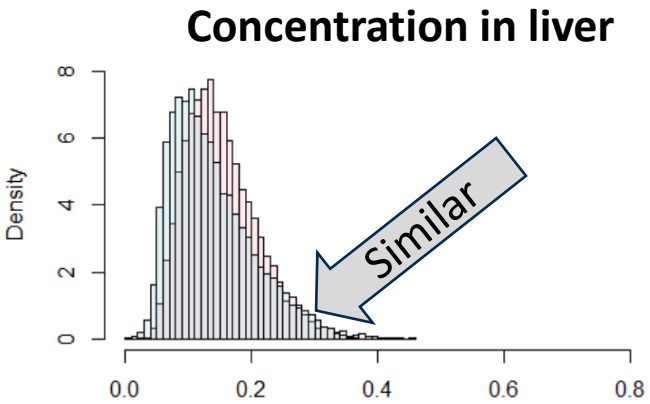


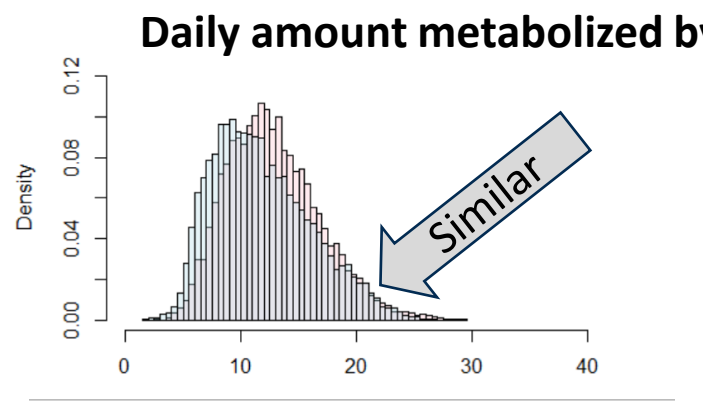
- While there may be low uncertainty in mean physiology & anatomy parameter values, variance is often only roughly characterized
- In the absence of specific information, professional judgment was used to set a degree of variation considered large enough to capture population variability … but not too large
  - Distributions are typically truncated to avoid unrealistic values
  - But range may be arbitrary; e.g., 2 standard deviations
- Despite truncation, improbable combinations can still occur
  - For example, if rapidly perfused blood flow is 100% - Σ(other tissues), this can yield negative values
- Biological distributions are probably not sharply truncated
  - I.e., if there is a finite probability that Vf_{liver} = 1.0608% (mean – 1.96*SD), it does not seem realistic to assume zero probability for Vf_{liver} = 1.0607%.
- And shouldn't Qf for a tissue be strongly correlated with Vf?

Why should estimates of parameter distributions (variability) be improved?

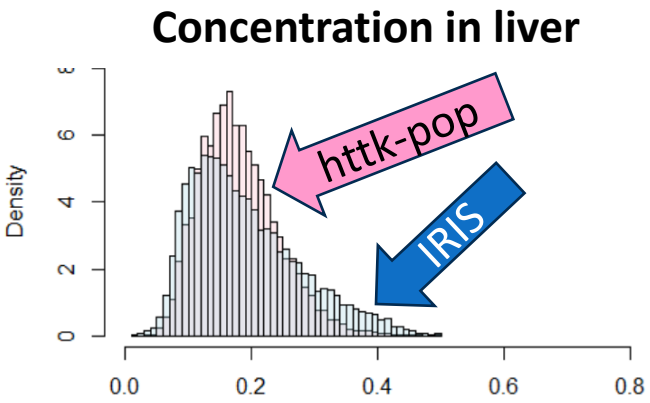
- Comparison of httk-pop parameter sampling to that used for the IRIS Toxicological Review of Dichloromethane

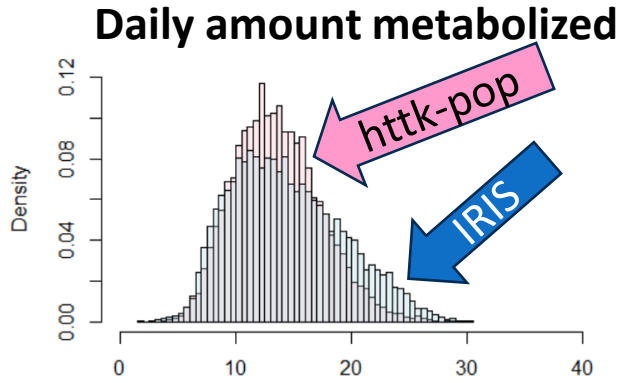
30-year-old females





30-year-old males





To be protective of the entire population we care about the 99th percentile

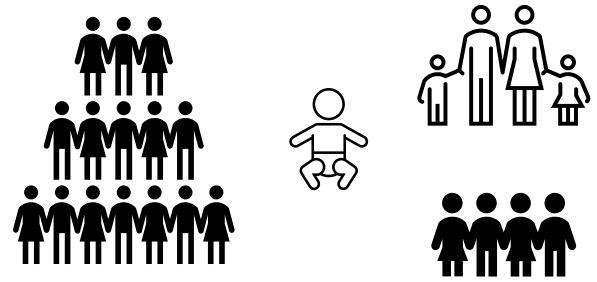
Why should estimates of parameter distributions be improved? (2)

- Why do the two samplers differ for men but not for women?
- Httk-pop used data reporting higher blood flow to muscle tissue in men than women…
  - **But** the distribution of muscle mass fraction in men and women is assumed the same and cardiac output is similar for men vs women
  - Because blood flows must add up to 100%, the blood flow to the liver in men was then lower than in women
- Assumptions about parameter distributions for a non-target tissue affected the upper tail of the target tissue distribution
- Celia Schacht's talk (next) further evaluates the impact of assumed distribution type

Why should estimates of parameter distributions be improved? (3)

- Confidence in PBPK models derives from the extent to which they accurately describe biology, chemistry and physics
- Over-predicting variation may generally lead to wider estimates of dose variability, which could be health-protective
  - For example, ignoring correlations between tissue masses and blood flows may result in wider dose distributions
- But dose distribution tails are more sensitive to some parameters than others (Celia's talk)
- The interaction among parameters required by conservation of mass and blood flow can have unintended consequences for key parameters

Initial efforts to better quantify human variability



- Like uncertainty, the optimal approach to better characterizing variability is to “Collect more data”
- But measurements of human physiological and anatomical parameters (and how they may be correlated) are difficult
- We began to mine the scientific literature, including tracing back supporting references from those used in classical sources of PBPK parameters
- But in many cases the underlying data needed to characterize the parameters of interest, such as the correlation between body mass and adipose mass, seemed to be unavailable
- Further, large samples are needed to determine 99th percentiles

Future Directions

- Other data may be found
  - E.g., variation in vascular density in tissues
  - May require more than broad, automated searches, checking older references.
- Even so, it seems unlikely that sufficient data will be identified to characterize distribution shapes for volume fractions, etc., with high certainty, especially for the distribution tails.
- But we can say some things based on reasoning!
  - For example, tissue volume fractions must be bounded: total ≤ 100%
- And if it is unlikely that these distributions are sharply truncated, other distribution types can be used that smoothly go to zero.

Future Directions (2)

- Ultimately, how to best describe variability will likely require some use of expert judgment
- But the judgment should come from groups of scientists working through the questions and options
- Choices should be consistent with, bounded by available data
- Refinement can be limited to the degree of accuracy desired for risk assessment

Footnote: it’s not just the parameters that are uncertain

- There is uncertainty in any model structure and accuracy of the assumptions behind that model, for example:
  - Tissue distribution may be diffusion-limited when assumed not
  - IVIVE of metabolism involves implicit models relating results observed in vitro to rates in vivo
- We have a framework to address PBPK parameter uncertainty and variability, but can we systematically address structural uncertainty for PBPK models? How?

THANKS FOR YOUR ATTENTION!