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Direktionsbereich Verbraucherschutz

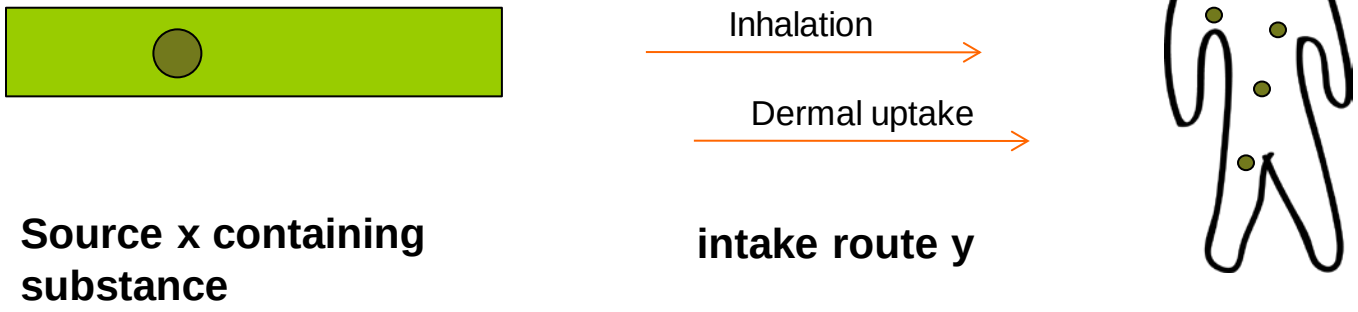
Uncertainty assessment for interdependent parameters, exemplified by PBPK modelling for risk assessment

Cecile Karrer[1] und Natalie von Goetz[1,2], [1]ETH Zurich and [2]BAG Schweiz

Interdependent parameters in “classical” statistics

- Most statistical methods require independence of parameters
- Dependence can take different forms, in many cases the definition of an additional criterion may help

Internal exposure to substances

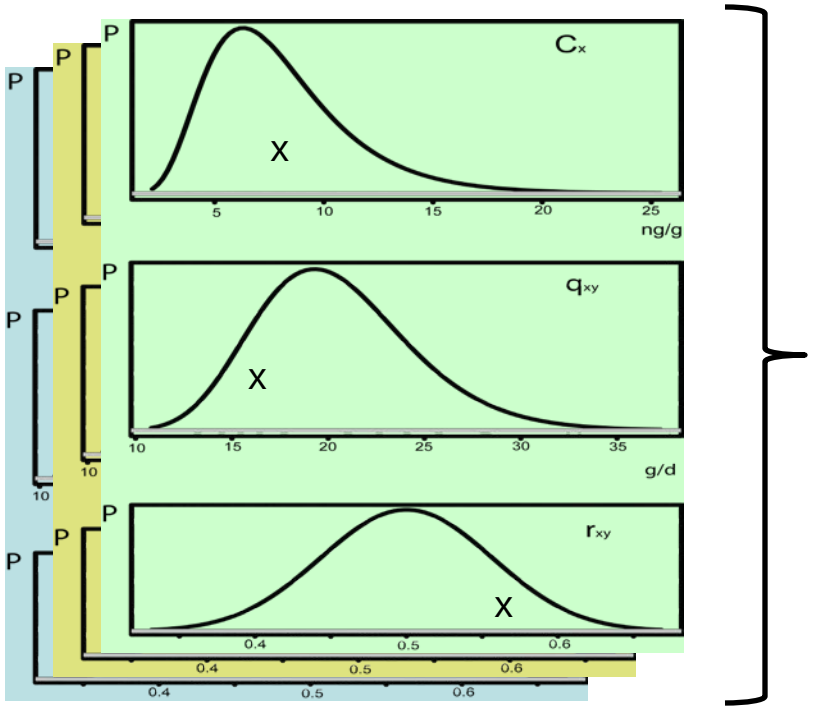


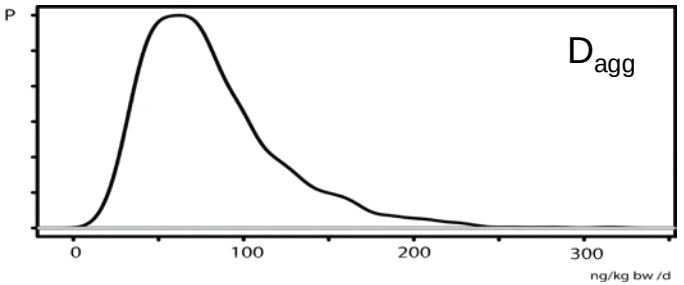
$$D_{xy} = \frac{C_x \cdot q_{xy}}{bodyweight} \cdot f_y$$

Independent parameters

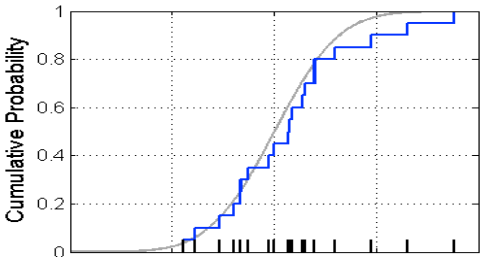
C_x: concentration in source x
q_{xy}: quantity taken up of source x via route y
f_y: uptake fraction via route y
D_{xy}: internal exposure (dose)

Probabilistic assessment using 1D-Monte Carlo





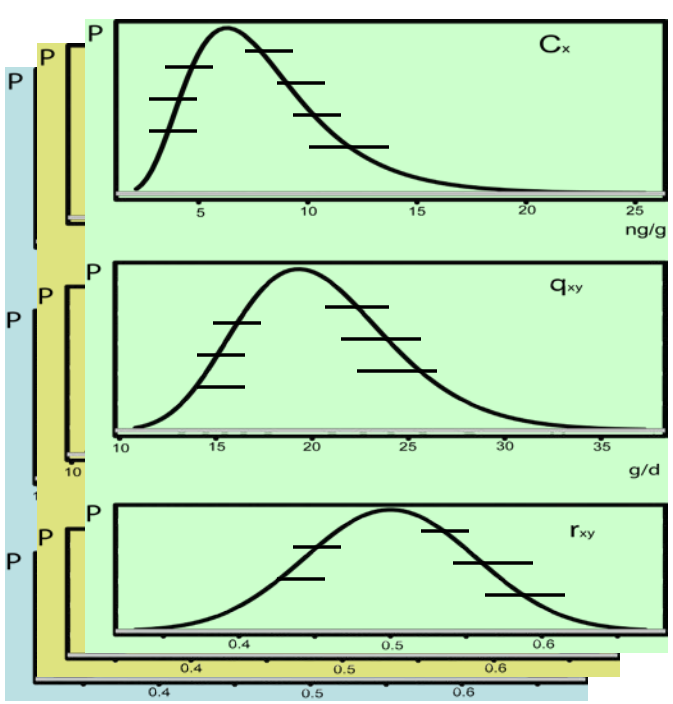
PDF: probability density function



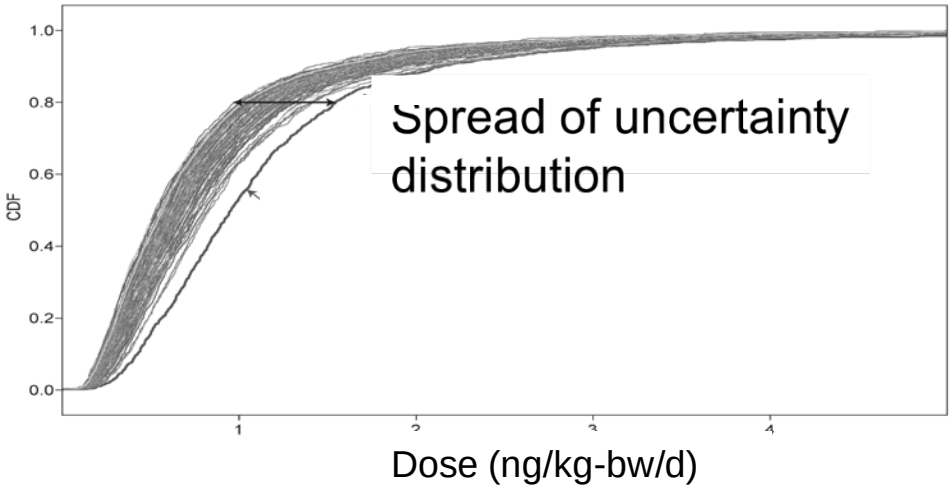
CDF: cumulative distribution function

$$D_{xy} = \frac{C_x \cdot q_{xy}}{bodyweight} \cdot f_y$$

2D-Monte Carlo method / Uncertainty for independent parameters



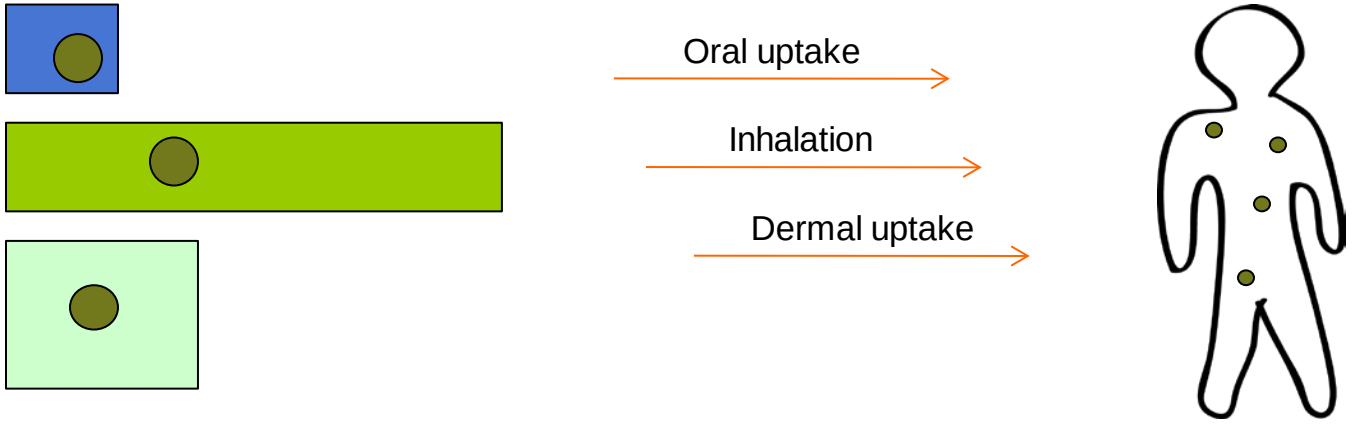
CDF: cumulative distribution function



Dose (ng/kg-bw/d)

$$D_{xy} = \frac{C_x \cdot q_{xy}}{bodyweight} \cdot f_y$$

Aggregate exposure to substances



Source x containing substance

intake route y

$$D_{xy} = \frac{C_x * q_{xy}}{bodyweight} * r_{uptake}$$

D_{xy}: dose (internal exposure)

$$D_{agg} = \sum_{x=1}^{n} \sum_{y=1}^{m} D_{xy}$$

D_{agg}: dose (internal exposure)

q_{xy}: possibly dependent parameters

Solutions for Interdependent parameters

- Use better data (individual based)
- Define boundaries (e.g. caloric intake)

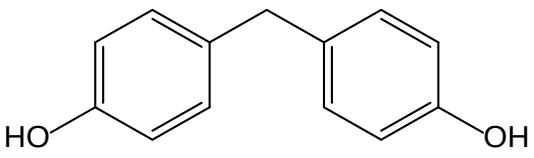
Method	RM47		EBM47-LN		RM47	
Data preparation	ROS		ROS		LN-ROS	
Gender	Female	Male	Female	Male	Female	Male
P50	0.43	0.46	0.49	0.55	0.46	0.49
P90	1.2	1.1	1	1.1	1.4	1.2
P97.5	2.2	1.7	1.7	1.7	2.5	2.1
P99	2.7	2.1	2.4	2.3	3.3	2.7

Abbreviations: EBM, energy-based method; LN, lognormal; RM, reference method; ROS, regression on order statistics.
All estimates are for ΣBDEs and given in ng/kg_{bw}/day.

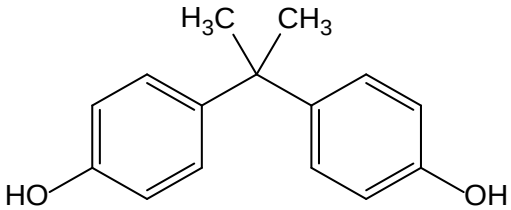
Trudel et al. 2011, JESSE, 21, 565-575

Case study: PBPK modelling for bisphenols

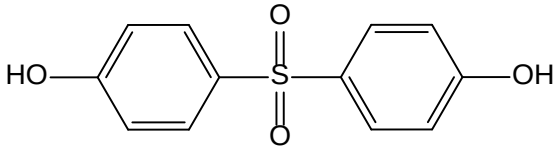
Objective: construct PBPK models for Bisphenol A (BPA) and its substitutes BPS, BPF and BPAF



BPF



BPA



BPS

Case study: Uncertainty assessment for PBPK modelling for bisphenols

Step 1: **Qualitative uncertainty** assessment of all model parameters

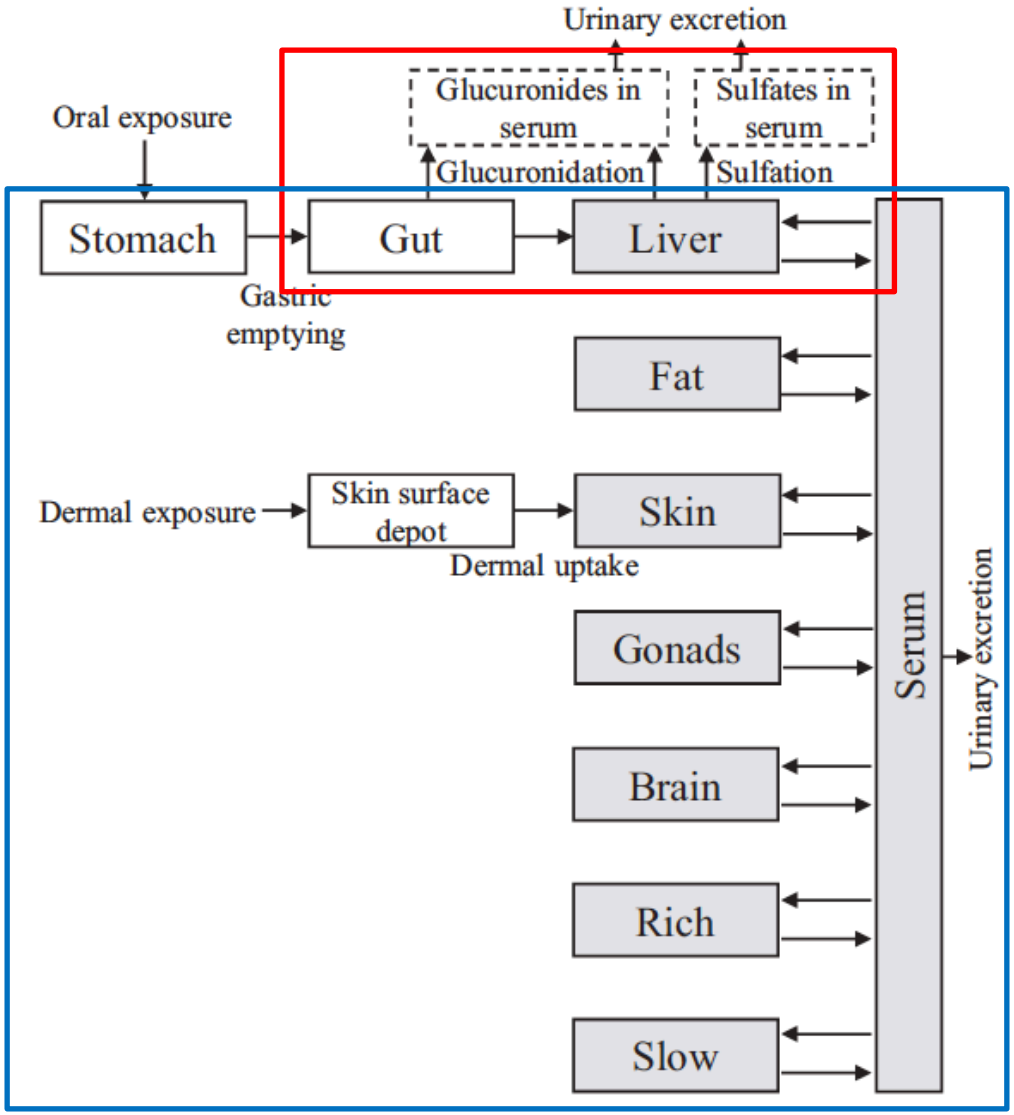
Step 2: **Quantitative assessment** with a 2D-Monte Carlo approach for the parameters with high or medium-high uncertainty (partition coefficients, metabolism parameters, uptake and excretion parameters)

Setting of **boundaries for** interdependent parameters

PBPK model: Most uncertain parameters

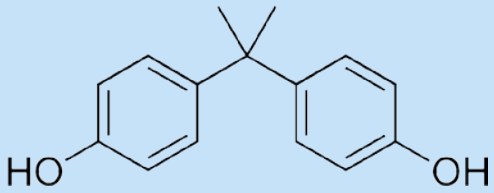
Metabolisation

Tissue-Blood Partitioning, Uptake excretion

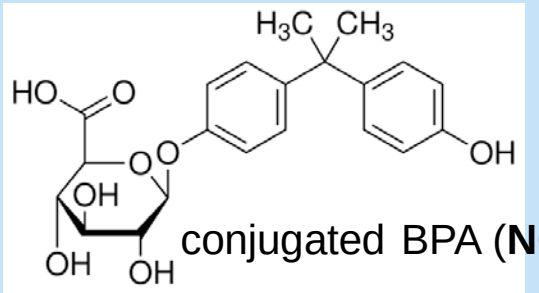


Genereic model by Edginton et al., 2006, Clin. Pharmacokinet 45(10), 1013-1034

First-path Metabolism of bisphenols

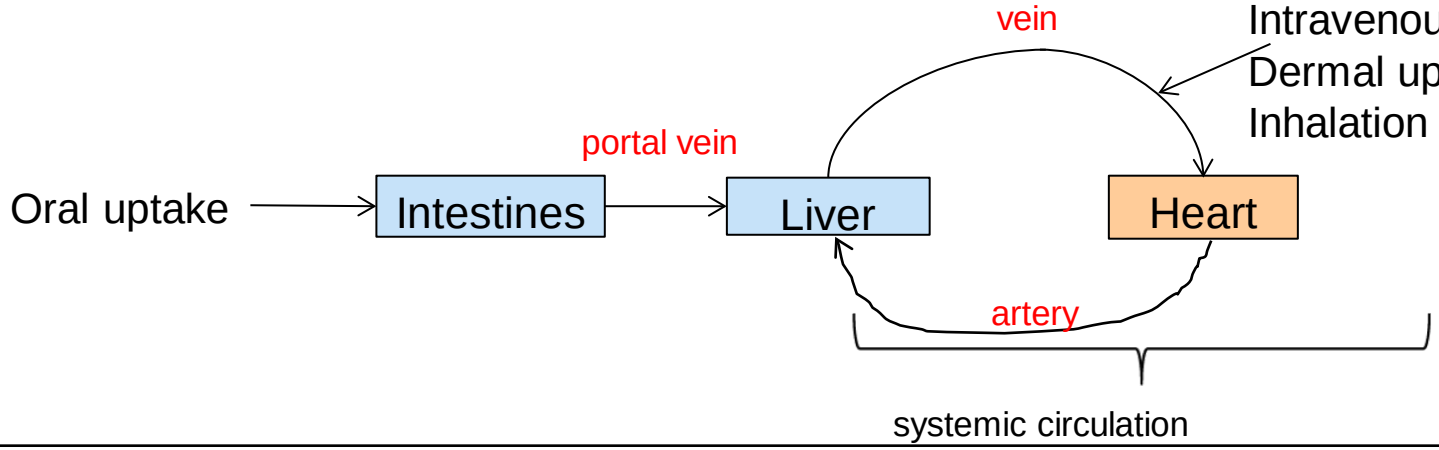


glucuronidation



Unconjugated BPA (**tox active**)

conjugated BPA (**NOT active**)

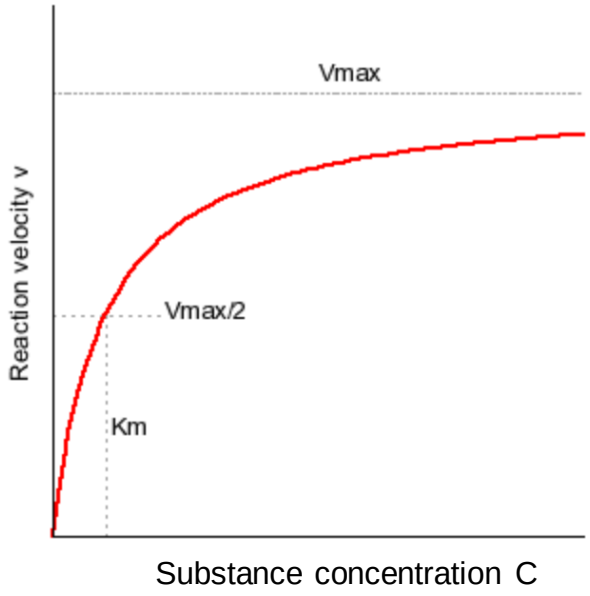


Michaelis-Menten kinetics for glucuronidation in liver and gut:

$$v = \frac{V_{max} \cdot C}{K_M + C}$$

Interdependence for V_{max} and K_M

$$v = \frac{V_{max} \cdot C}{K_M + C}$$



Reference	K_M (nM±SD)	V_{max} (nmol/h/mg protein±SD)
Hepatic glucuronidation		
Kurebayashi et al. (2010)[b]	5,300	39.8
Coughlin et al. (2012)	45,800 ± 8,900	283 ± 18
Trdan Lušin et al. (2012)	8,900 ± 800	510 ± 18
Elsby et al. (2001)[c]	71,900 ± 7,900	333 ± 21
Kuester and Sipes (2007)[c]	8,500 ± 2,500	85.2 ± 31.4
Mazur et al. (2010)[c]	4,250 ± 1,350	190 ± 16.9
Street et al. (2017)	23,000 ± 8,000	270 ± 60
Intestinal glucuronidation		
Trdan Lušin et al. (2012)	58,400 ± 7,800	84.0 ± 6.0
Mazur et al. (2010)	80,100 ± 35,900	29.2 ± 7.2

Procedure for boundary selection for metabolism parameters for BPA

- Outer loop of 2D-MC ("uncertainty"): Select V_{max} and Km independent of each other. from trapezoidal distributions based on uncertainty-related info

- Inner loop of 2D-MC ("variability"): Select Km from truncated normal distribution based on different assays

- Calculate boundaries for sampling V_{max} from truncated normal distributions on the basis of the specific Km. Boundaries are defined by the observed curves.

Identification of “basic model”

- Identify most probable PBPK model by choosing the parameter set with largest resemblance to biomonitoring for BPA, using

$$MRD = 10^{\sqrt{\frac{\sum_{i=1}^{n}\left(\log_{10}(predicted) - \log_{10}(observed)\right)^2}{n}}}$$

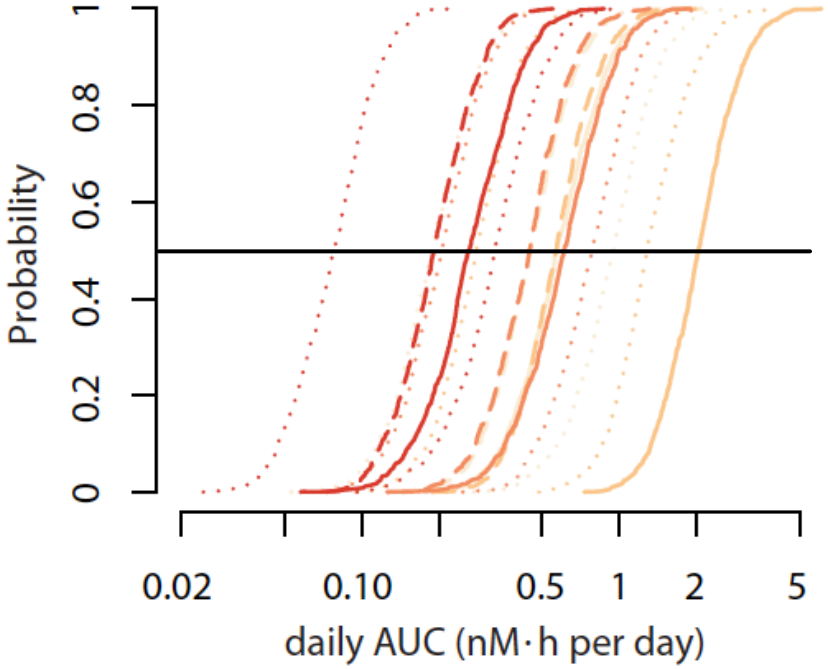
$$AFE = 10^{\left|\frac{\sum_{i=1}^{n}\left(\log_{10}(predicted) - \log_{10}(observed)\right)}{n}\right|}$$

Precision: Mean relative deviation (MRD)
Bias: Average fold error (AFE)

Predicted: PBPK Model
Observed: Biomonitoring*, averaged over all persons
n: number of observation time points

* Thayer et al. 2015, Environ Int 83, 107-115

Serum concentration of adult women: Variability/uncertainty of daily AUC (2D-MC)



Uncertainty	Mean	Uncertainty	Mean
BPA		BPF	
basic model	0.622	basic model	0.651
5%	0.201	5%	0.216
50%	0.481	50%	0.469
95%	0.998	95%	0.825
BPS		BPAF	
basic model	2.15	basic model	0.285
5%	0.295	5%	0.0822
50%	0.602	50%	0.203
95%	1.39	95%	0.352

BPA BPS BPF BPAF (unconjugated)

— Variability of basic model -- P50 uncertainty ···· P5 & P95 uncertainty

Conclusions

- Qualititative assessment of uncertainties at least as important as quantitative assessment
  → "**problem formulation**" also needed for uncertainty assessment

- Quantitative assessment of uncertainty helps to identify **data gaps** to allow a better consideration of uncertainty (e.g. to identify missing data for defining uncertainty distributions)

- Bayesian statistics may be more accurate (e.g. Bois et al., 1996), our approach approximation

Bois et al. 1996, Archives of Toxicology, 70:347-355

EuroMix consortium

further info:
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Based on:
Karrer et al., 2018 “Physiologically based pharmacokinetic (PBPK) modelling of the Bisphenols BPA, BPS, BPF and BPAF with new experimental metabolic parameters: Comparing the Pharmacokinetic Behavior of BPA with Its Substitutes, **Env Health Persp 126 (7), 1-17**