UF College of Public Health and Health Professions
Department of Environmental and Global Health
UNIVERSITY of FLORIDA

--- National Institute of Environmental Health Sciences (NIEHS) Workshop in Oct. 26-27, 2022
--- Part of the workshop entitled: “Using New Approach Methodologies to Address Variability and Susceptibility Across Populations”

Integrating Bayesian approaches with PBPK modeling in a Human Health Risk Assessment: A Case Study with Perfluorooctane Sulfonate (PFOS)

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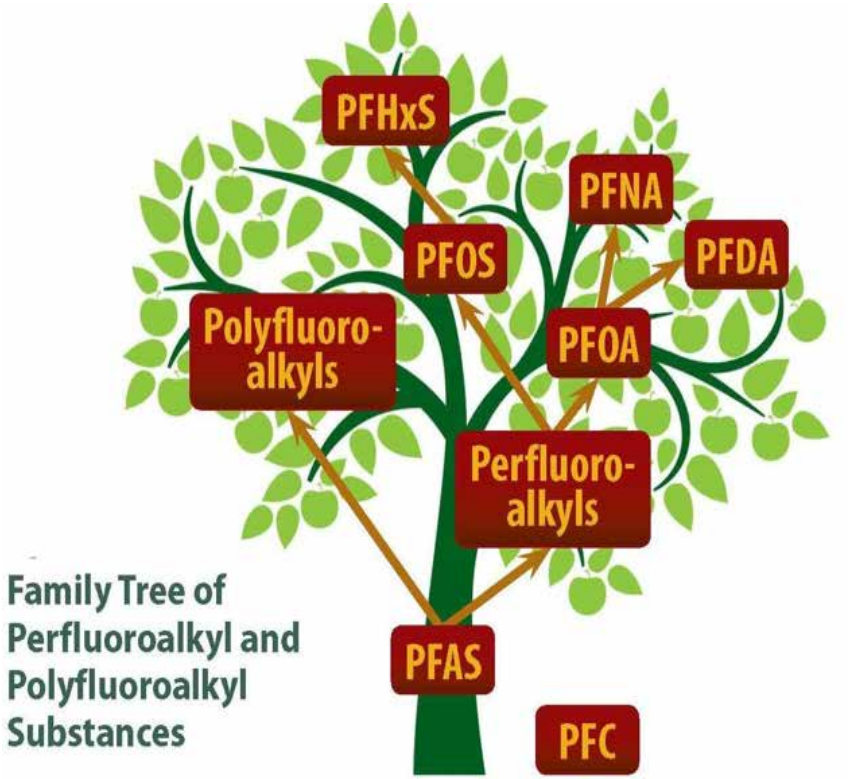
Importance of assessing PFAS exposure in human

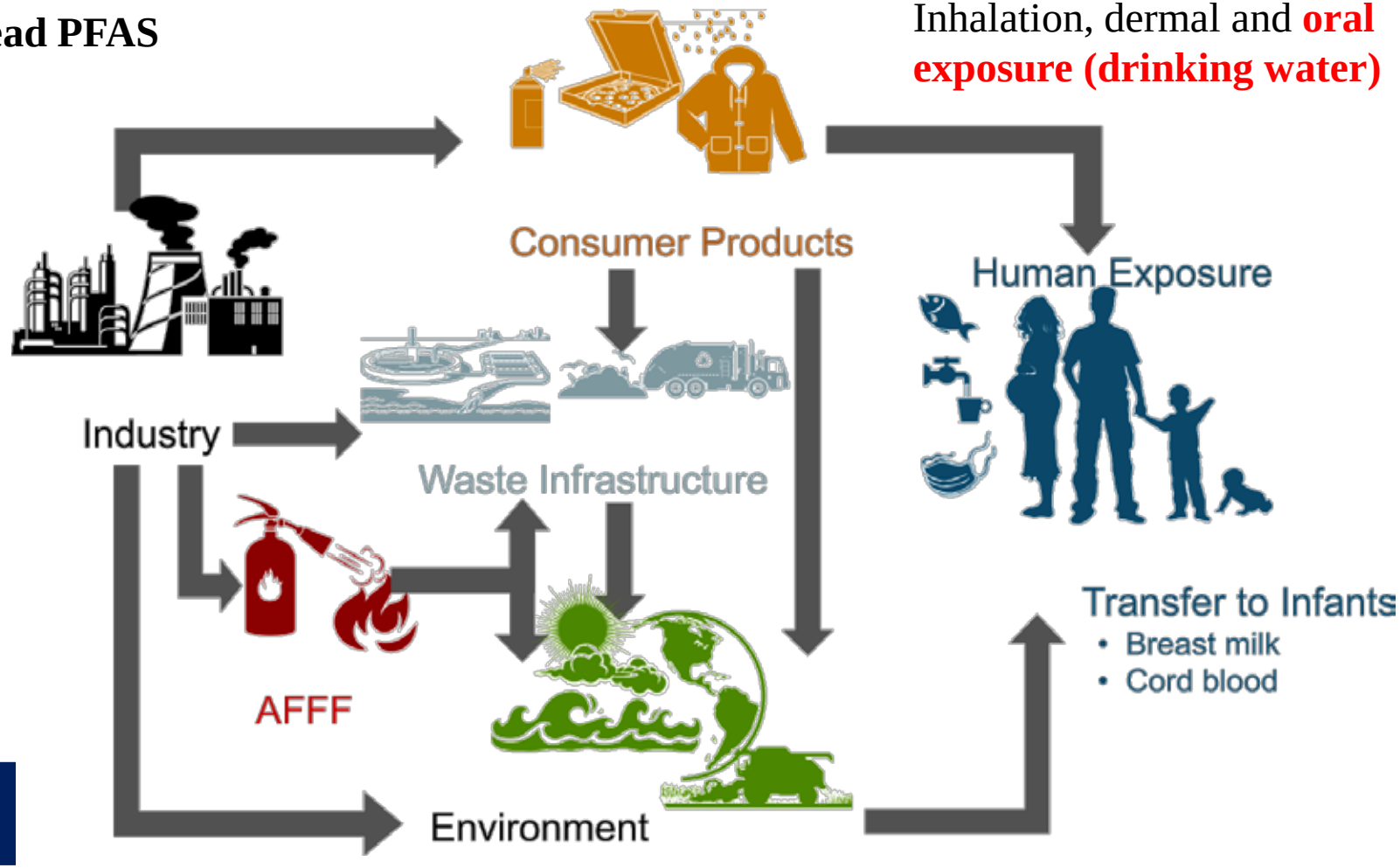
Human Can Be Exposed to PFAS in a Variety of Ways

PFOA and PFOS are two of most widespread PFAS



PFAS were invented by 3M company in 1930s; ; has been widely used since 1950s

Inhalation, dermal and **oral exposure (drinking water)**



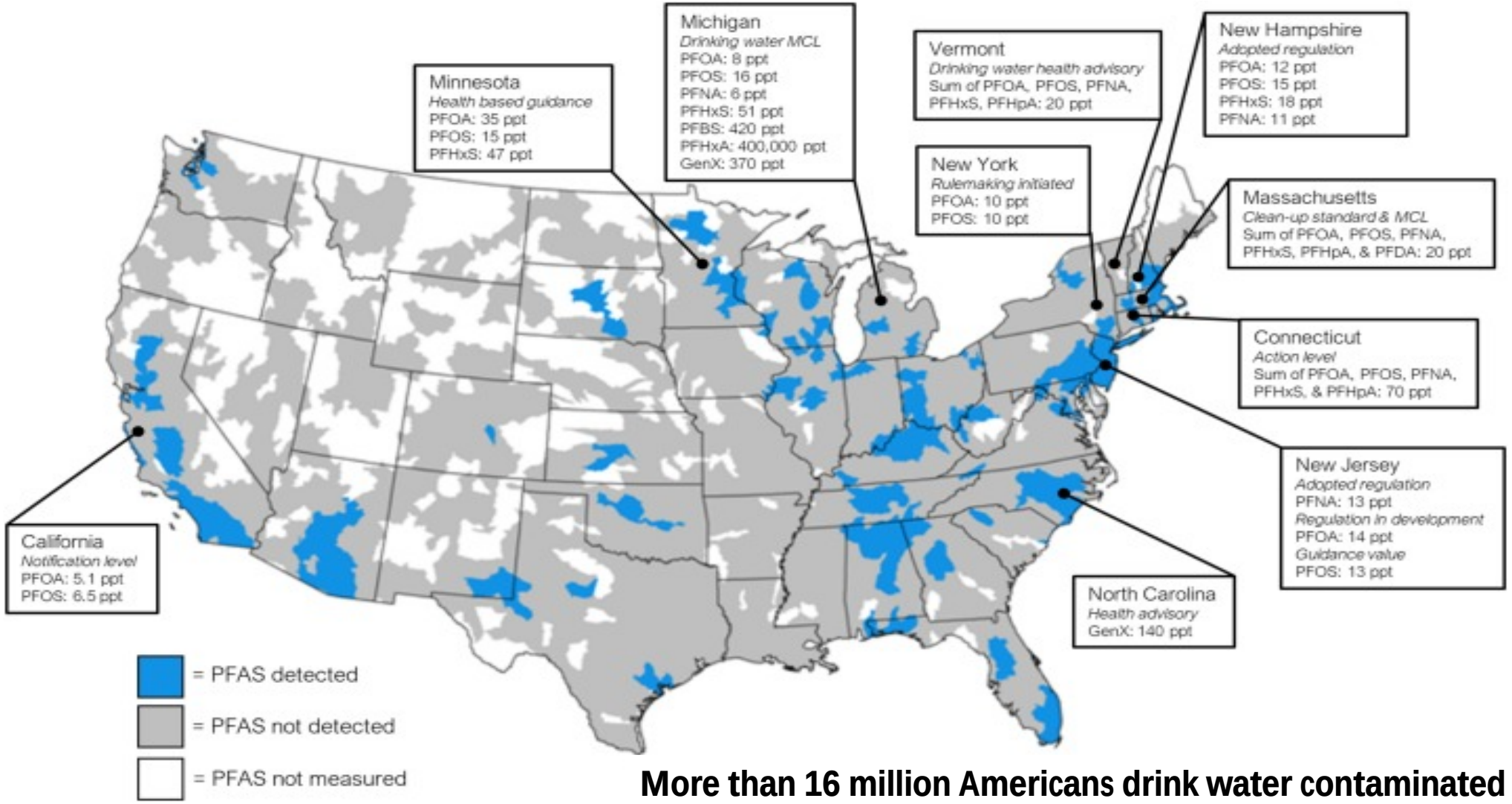
Aqueous Film-Forming **Foam** Concentrates (**AFFF**)

PFAS: Per- and polyfluoroalkyl substances
PFC : Perfluorinated compound
PFOA: Perfluorooctanoic acid

Sources: Sunderland et al. (2018).

Importance of assessing PFAS exposure in human

PFAS contamination in U.S. states



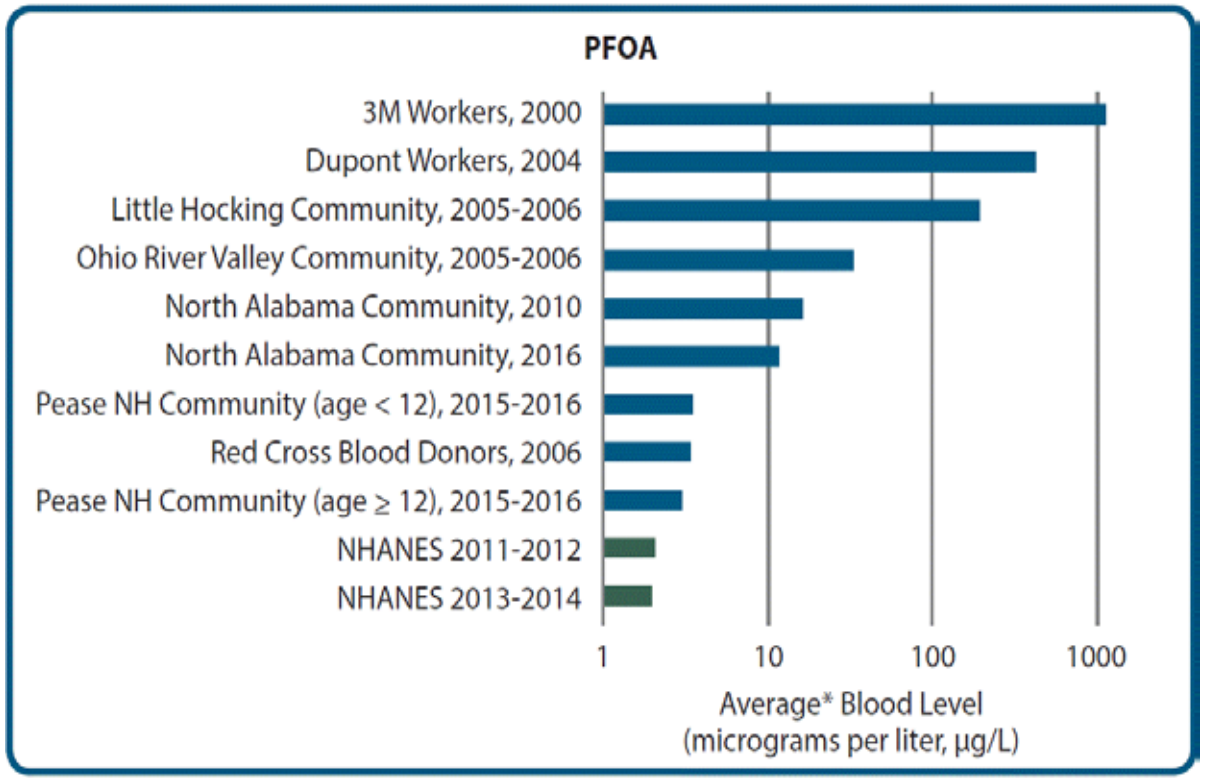
More than 16 million Americans drink water contaminated with toxic chemicals

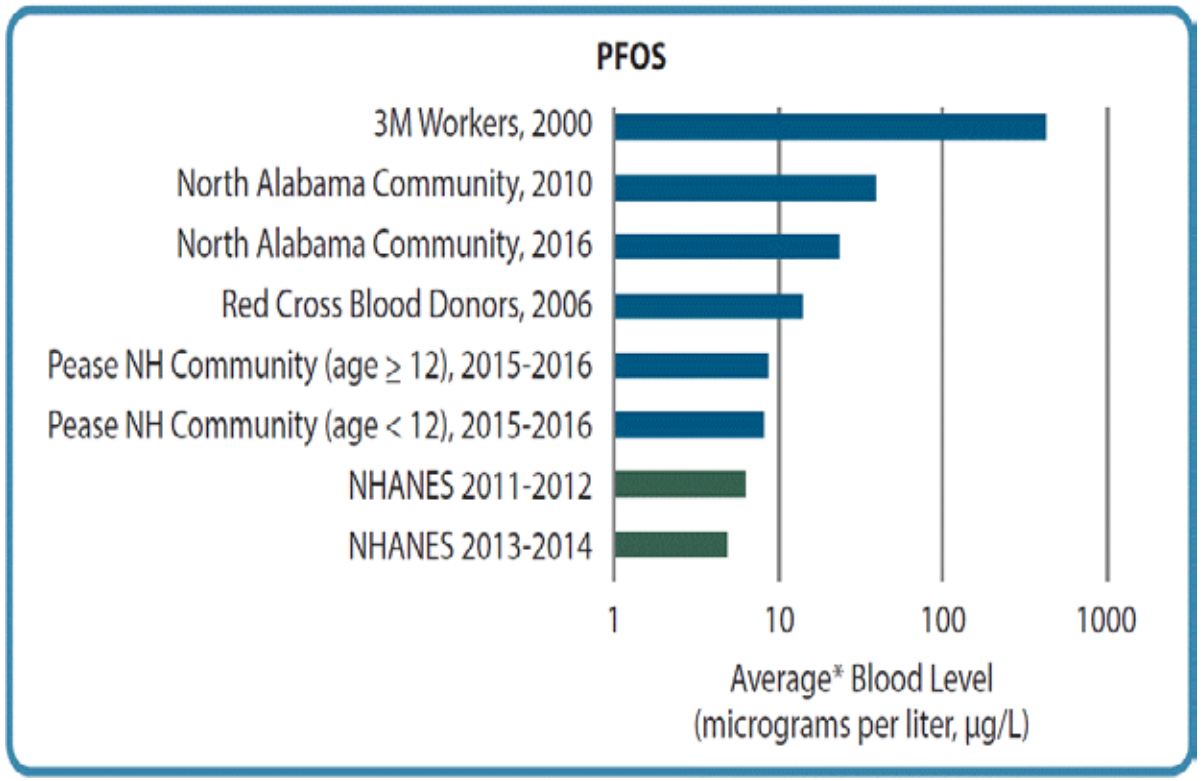
Sources: Blake et al., (2020).

Importance of assessing PFAS exposure in human

PFAS serum concentration in U.S. population

PFOA and PFOS detectable in >90% of the U.S. population

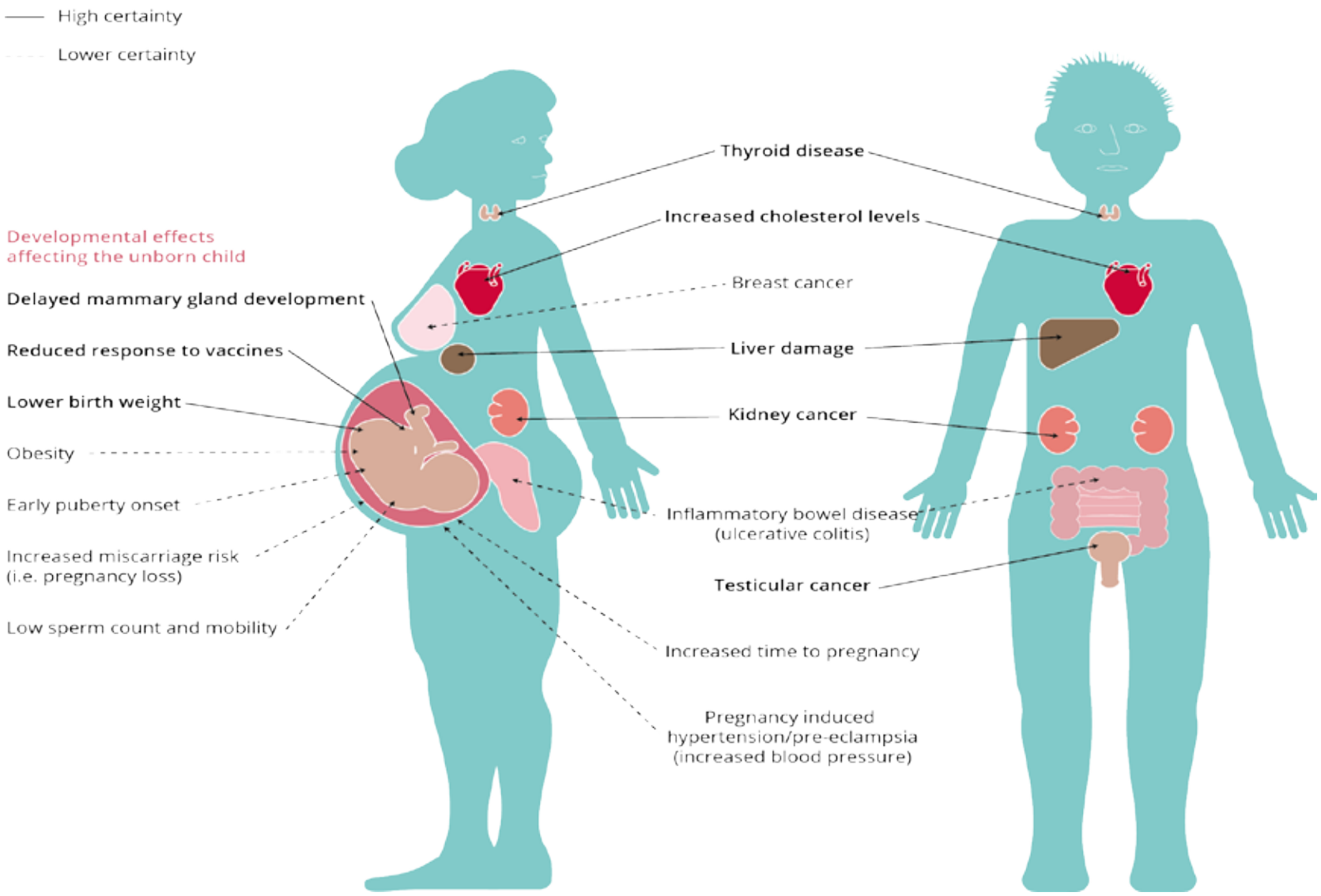




Sources: ATSDR, 2018

The adverse outcomes of PFAS exposure in human

Summary of current knowledge of the health impacts of PFAS.



Sources: US National Toxicology Program, (2016); C8 Health Project Reports, (2012); WHO IARC, (2017); Barry et al., (2013); Fenton et al., (2009); and White et al., (2011).

Challenges in the PFOS risk Assessment

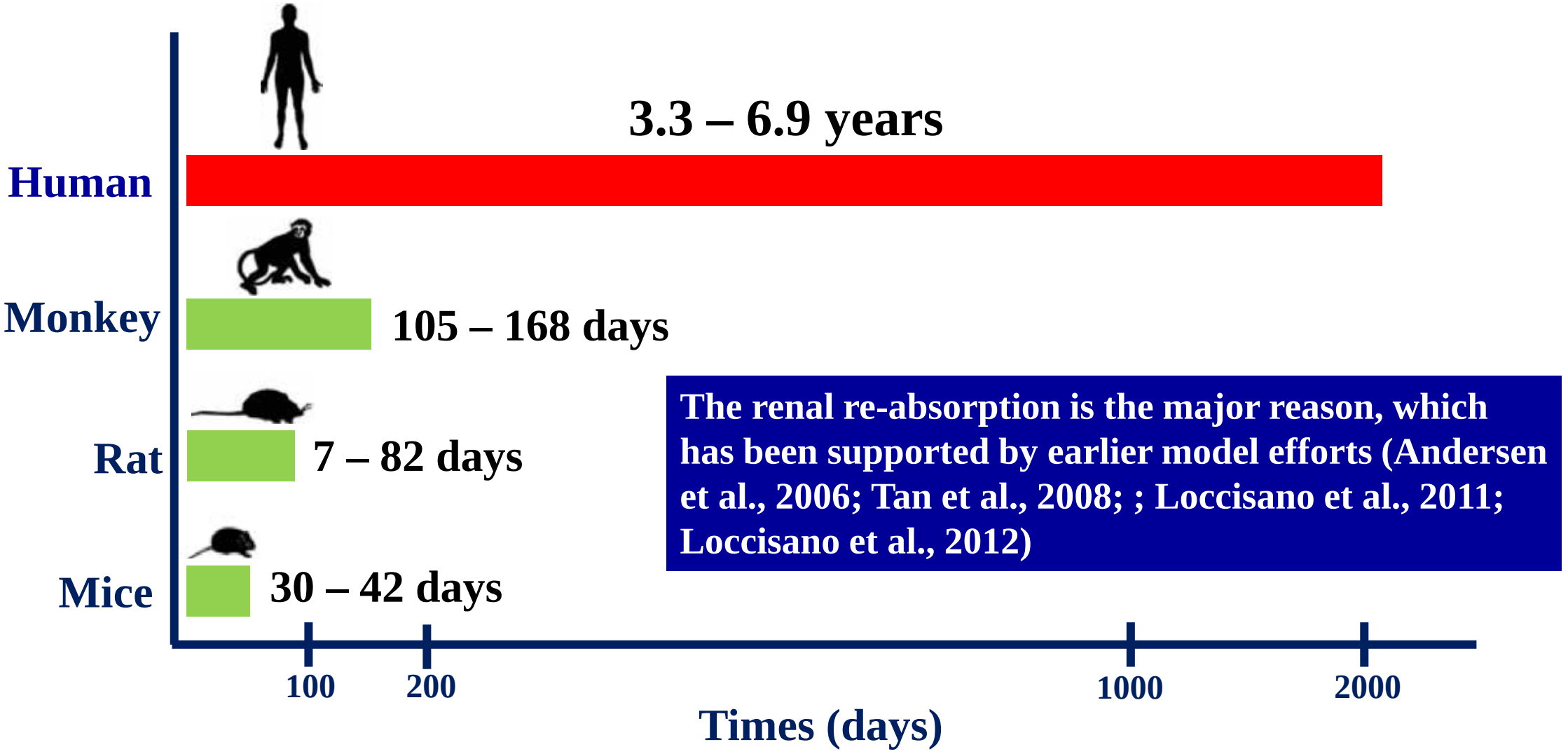
The reference dose is decreasing over the years (Dong et al., 2017).

Table 1
Developments of proposed reference doses for PFOS and PFOA.

Chemical	Organisation	Species, duration	Endpoint	Tolerable Daily Intake or Reference Doses (ng/kg/day)	PoD (mg/kg/day)	UFs			
						UF_1[a]	UF_2[b]	UF_3[c]	UF_4[d]
PFOS	UK COT(UK COT, 2006a)	Cynomolgus monkeys, 26 weeks	decreased serum T3 levels	300	NOAEL, 0.03	10	10	NA	NA
PFOS	EFSA(EFSA, 2008)	Cynomolgus monkeys, 26 weeks	decreased serum T3 levels	150	NOAEL, 0.03	10	10	2	NA
PFOS	U.S. EPA(U.S. EPA, 2009)	Cynomolgus monkeys, 26 weeks	decreased serum T3 levels	77[e]	NOAEL, 0.03	39[f]	10	NA	NA
PFOS	Danish EPA(Danish EPA, 2015)	Rats, 104 weeks	liver hypertrophy	30[e]	$BMDL_{10}$, 0.033	123[g]	10	NA	NA
PFOS	U.S. EPA(U.S. EPA, 2016a)	Rats, 12 weeks	pup body weight	20[e]	HED, 0.00051	3	10	NA	NA
PFOS	EFSA (2018)	Human	Serum cholesterol	1.8	PBPK model				

UF1, interspecies uncertainty factor; UF2, intraspecies uncertainty factor; UF3, uncertainty factor to account for studies with less than lifetime exposure;

Challenges in the PFOS risk Assessment:
The differences in half-lives across species

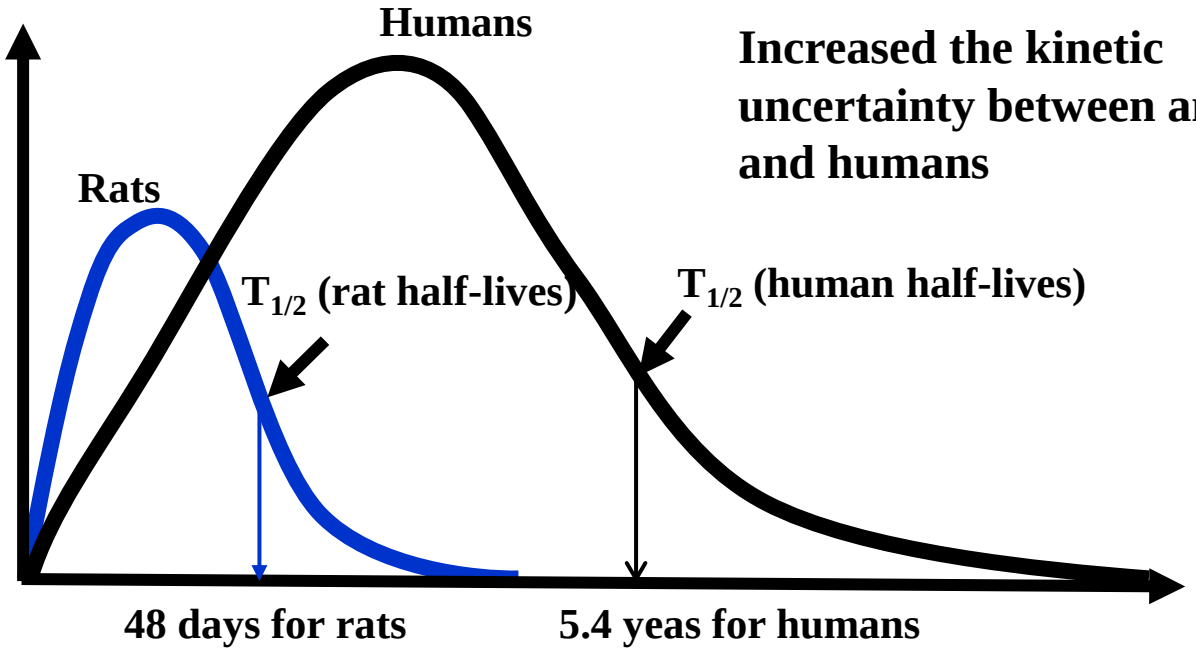


Reference: ATSDR (2018); Chang et al. (2012); Kim et al. (2016); Seacat et al. (2002); Olsen et al. (2012)

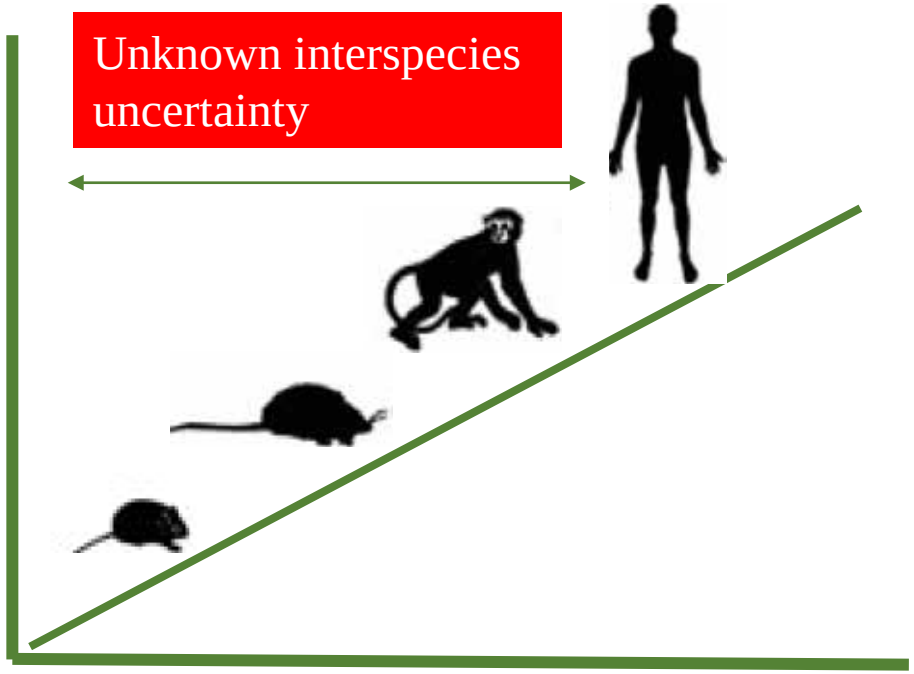
Challenges in the PFOS risk Assessment:

The differences in the half-lives lead to..

Large difference in internal dose (e.g., AUC) with the same external dose between animals and humans



Increased the kinetic uncertainty between animals and humans

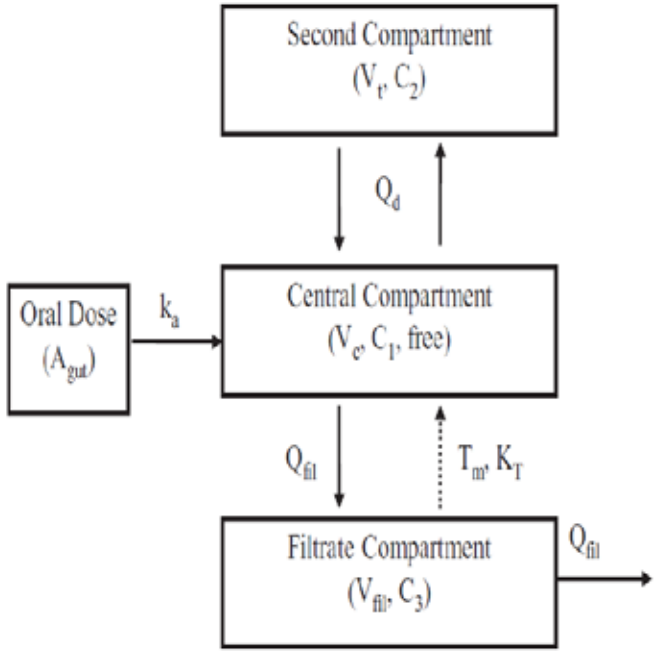


Challenges in the PFOS risk Assessment

Some limitations and uncertainties exist in the derivation of RfD from U.S. EPA guidance (EFSA, 2018, Dong et al., 2017, FSANZ et al., 2016).

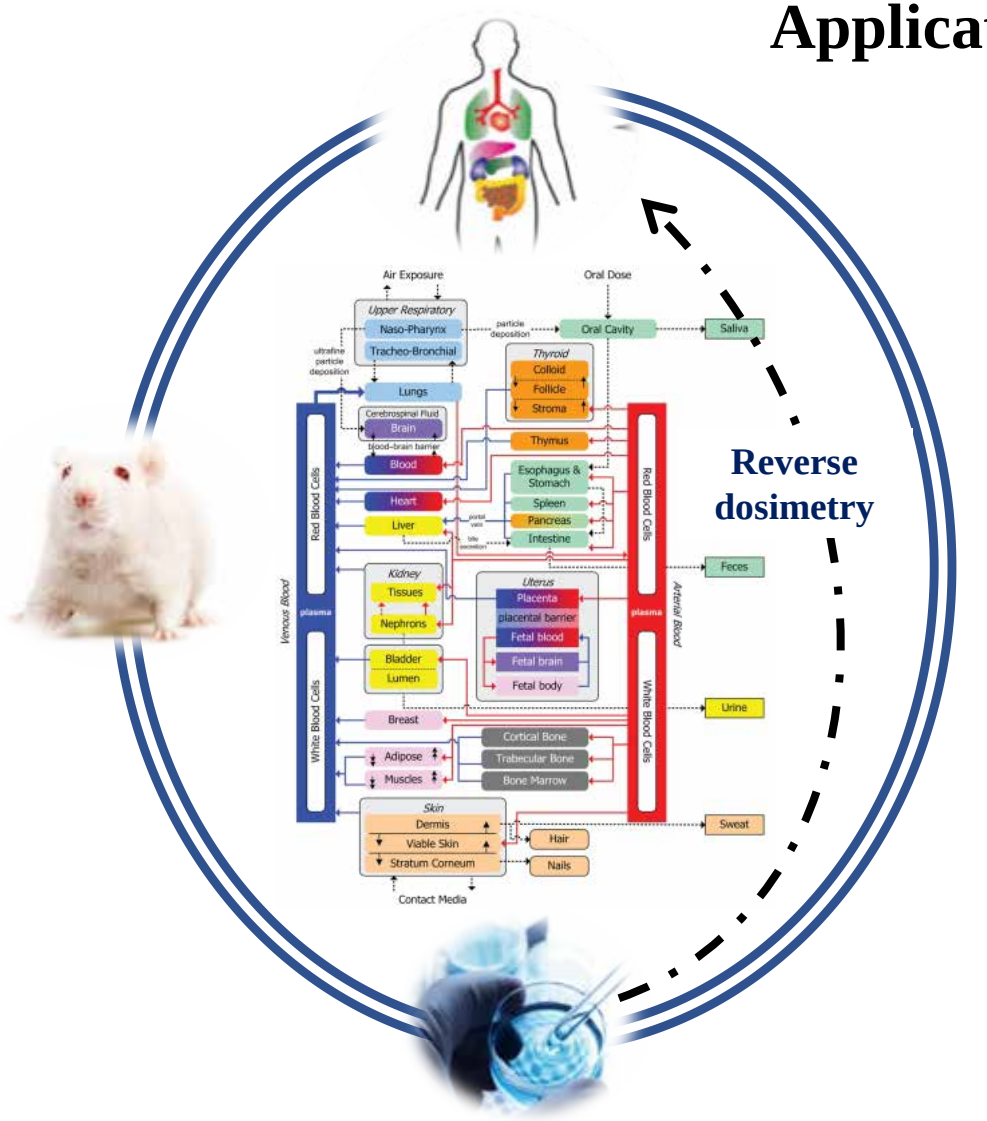
1. **The U.S. EPA's model (Wambaugh et al., 2013) is not physiologically based and the parameters are not biologically plausible and thus might affect the derivation of RfD.**

   - **Lack of the ability to predict the amount of PFAS in specific organ**
   - **Lack of the biological mechanisms to describe the chemical deposition.**
   - **The model can not extrapolation to other life-stage population and sensitive population (infant, children, pregnant women)**



Considering the toxicokinetic difference between animals and humans, a more physiologically relevant and robust model should be developed.

What is Physiologically based pharmacokinetic (PBPK) model?



Application in risk assessment and toxicology

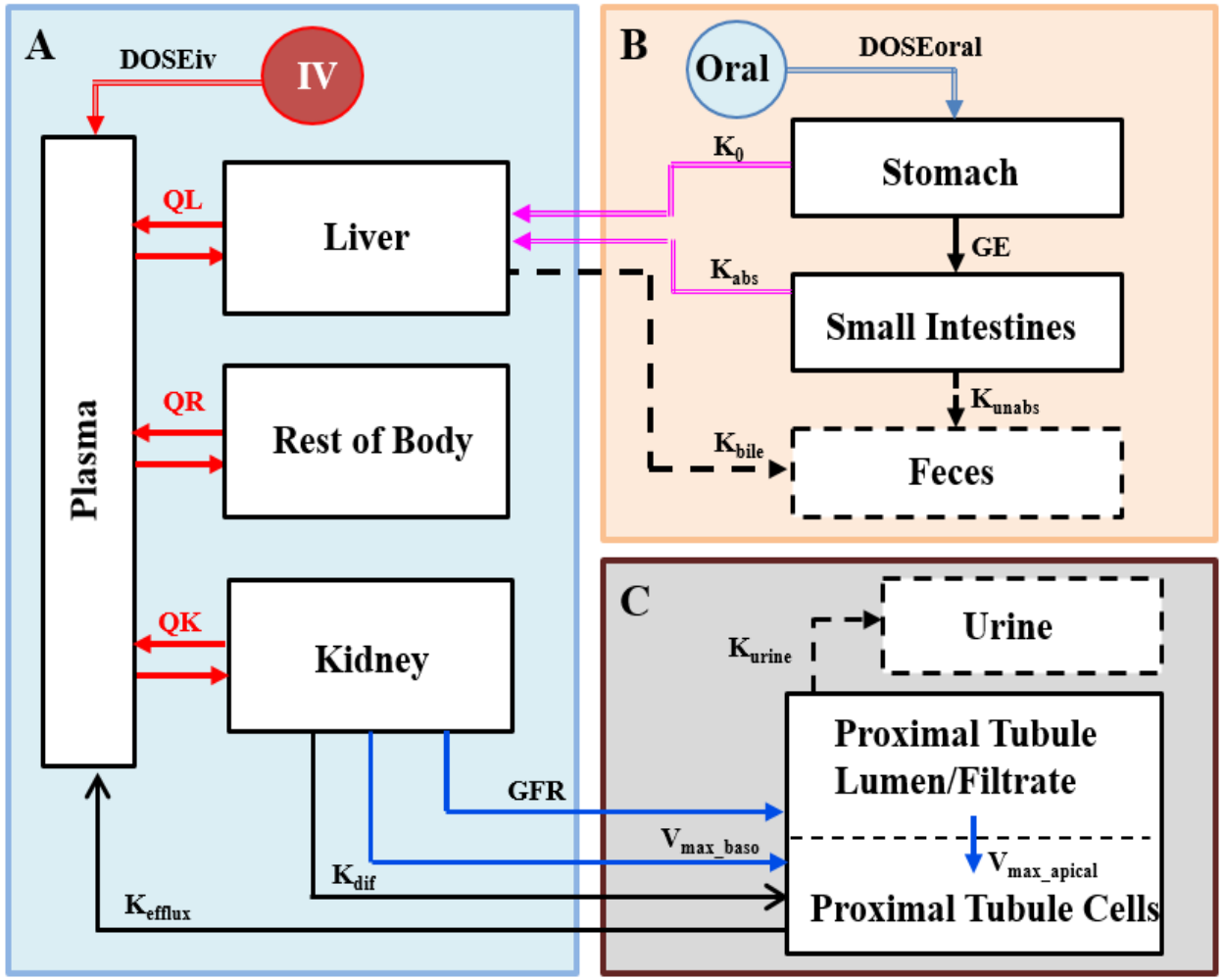
- Predict exposure from animal to human (HED)
- Simulate the individual/population exposure (forward dosimetry)
- Estimate population daily exposure intakes that are consistent with blood or urine measures found in biomonitoring surveys (reverse dosimetry)
- Precision medicine: Dosing recommendation for sensitive population
- **In vitro to in vivo extrapolation (IVIVE) (21st toxicology science)**

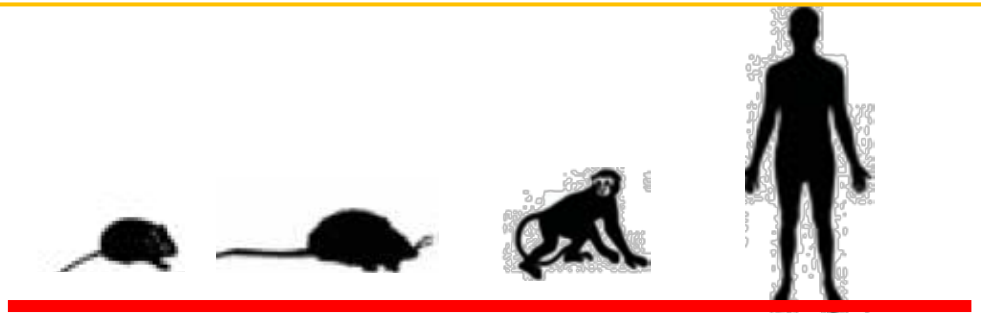
Figure modified from NTP

Multiple dataset across species were considered in the development of PFOS PBPK model

Species				
Strain	**CD-1**	**Sprague Dawley**	**Cynomolgus**	**General population**
Study	• Chang et al., 2012	• 3M unpublished data • Johanson et al., 1979 • Kim et al., 2016 • Chang et al., 2012	• Seacat et al., 2002 • Norker and Gorman, 2003 • Chang et al., 2012	• Olsen et al., 2003 • Olsen et al., 2008 • Fabrega et al., 2014 • Chang et al., 2012
Route	• Single oral dose	• Single oral dose • Single iv dose • Daily oral dose	• Single iv dose • Daily oral dose	• Assumed PFOS dose directly into the blood due to unknown exposure route
Dose	• 20 mg/kg • 1 mg/kg	• Daily oral dose of 1 mg/kg • Single iv dose at 2 or 4.2 mg/kg • Single oral dose at 2, 4.2 and 15 mg/kg	• Daily oral dose of 0.03, 0.15 and 0.75 mg/kg • Single iv dose at 2 mg/kg	• Assumed exposure 0.0045 (µg/kg) and 0.0118 (µg/kg)
Matrix	• Plasma • Kidney • Liver	• Plasma • Liver • Urine	• Plasma • Liver • Urine	• Plasma • Kidney • Liver

PBPK model structure

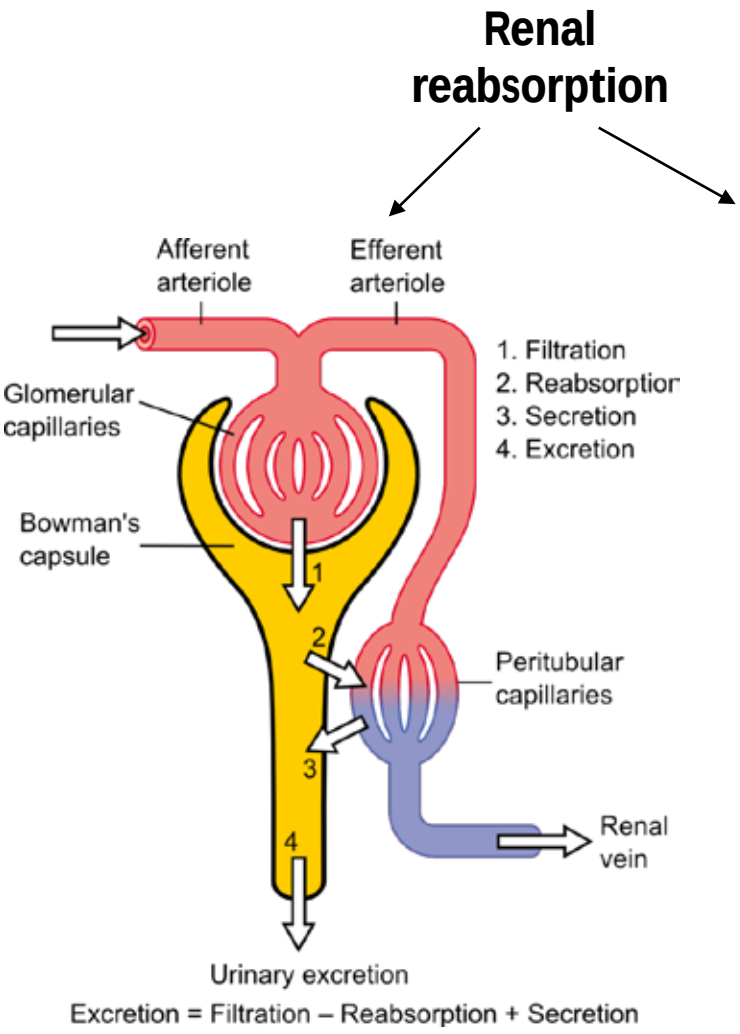


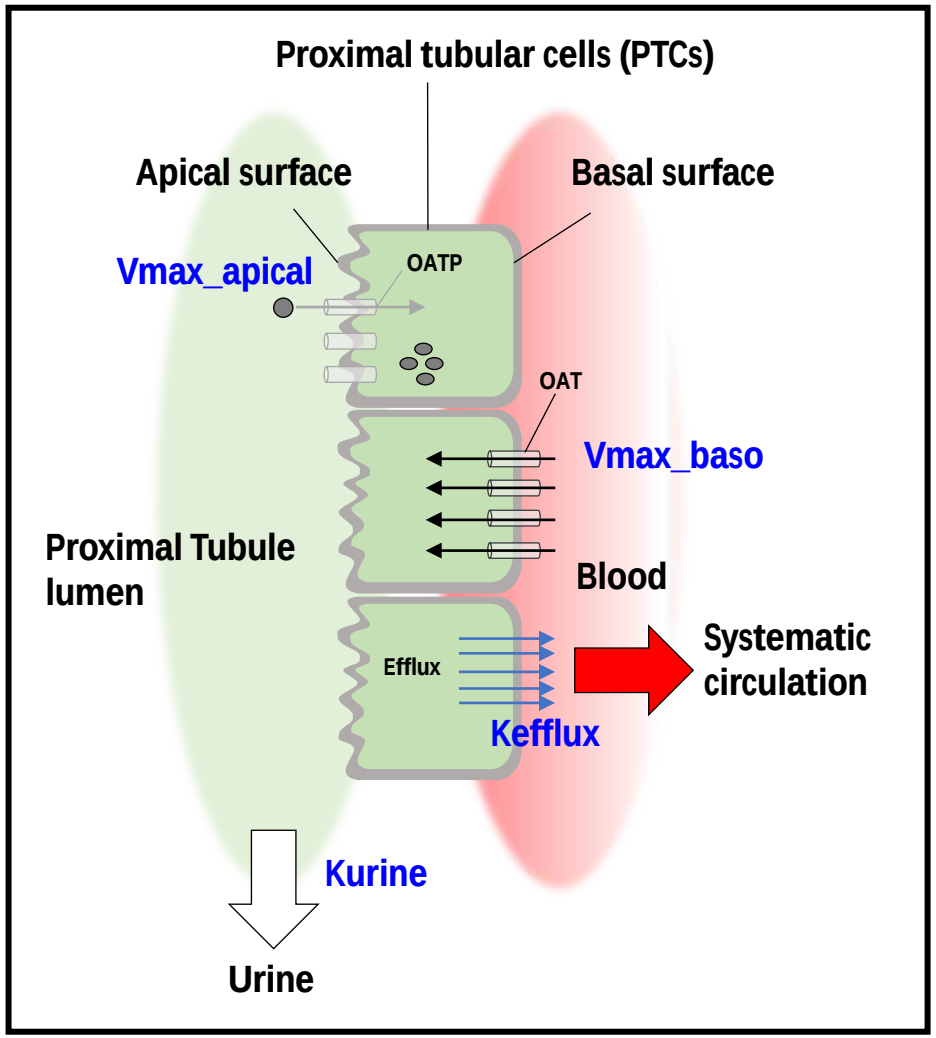


- **Consistent model structure across species was used in this study.**
- **Multiple exposure route (oral and IV dose)**
- **Kidney was described as a three-sub-compartments for the simulation of renal re-absorption.**

GFR: Glomerular Filtration Rate

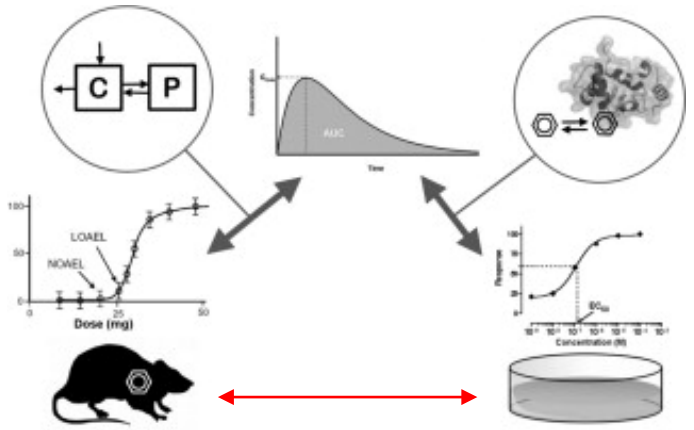
Mathematical description for renal absorption





Michaelis-Menten equation

$$\frac{dC}{dt} = \frac{Vmax \cdot C}{C + K_M}$$



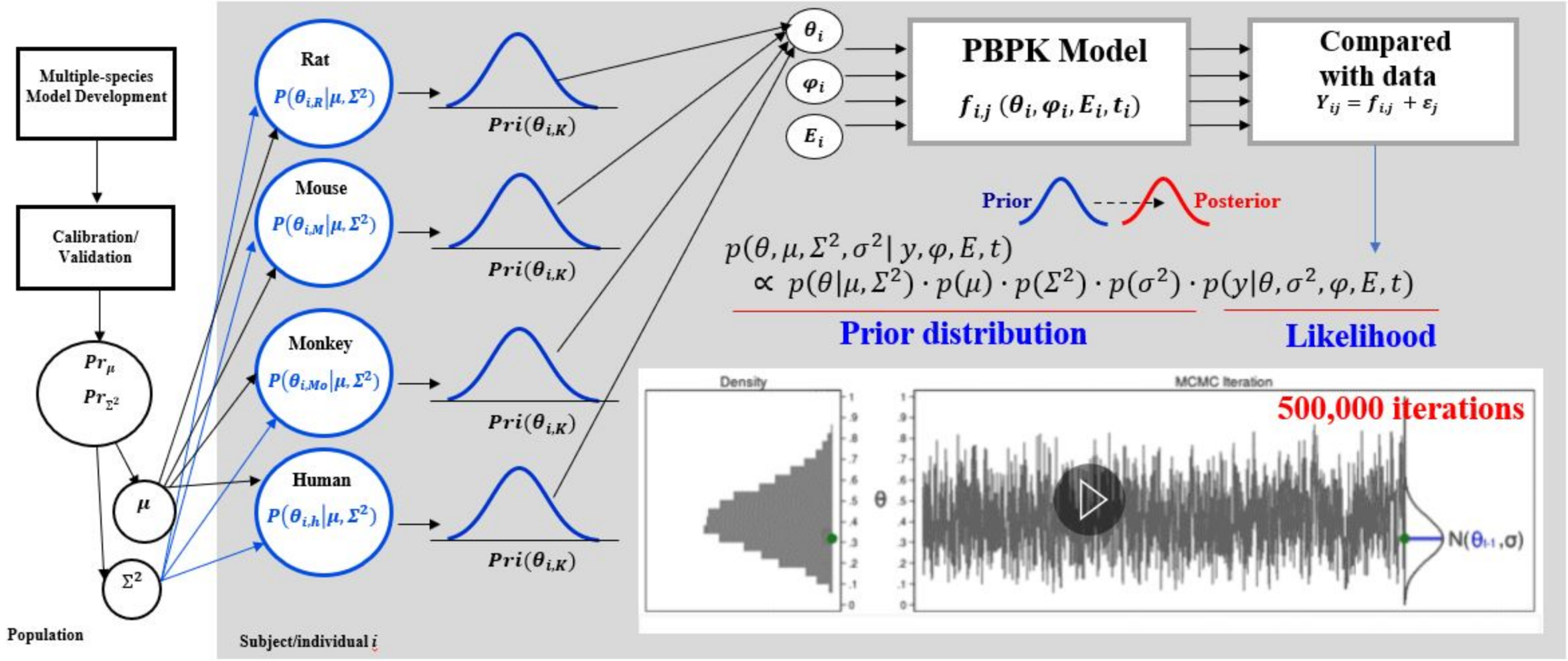
In vitro-to-in vivo extrapolation (IVIVE); Vmax_apical and Vmax_baso

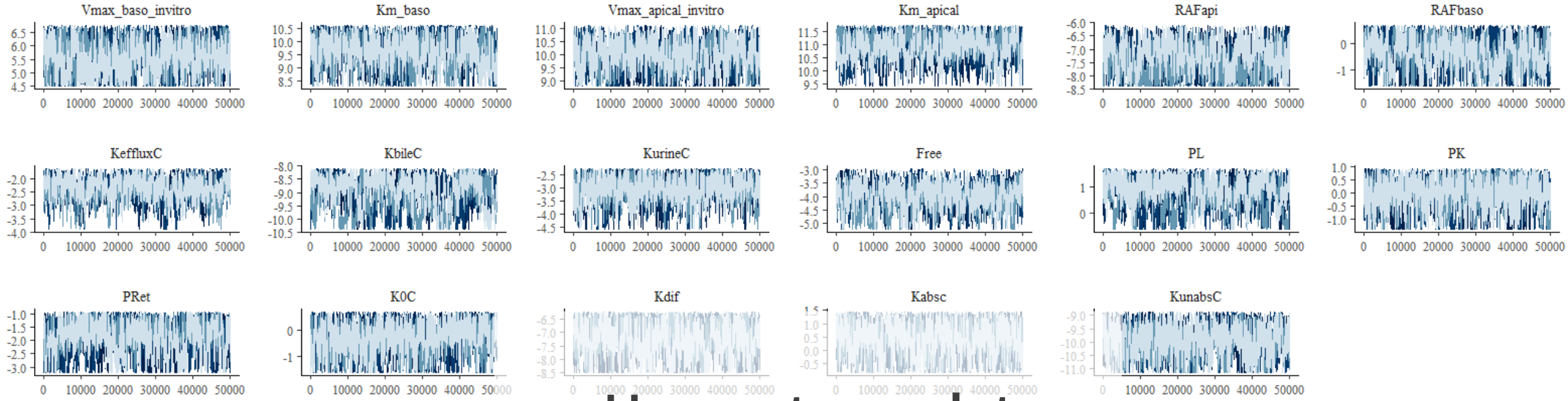
C: initial substrate concentration
Vmax: the maximum reaction rate
Km: Michaelis constant

OAT: Organic anion transporter
OATP: Organic anion transporting polypeptides

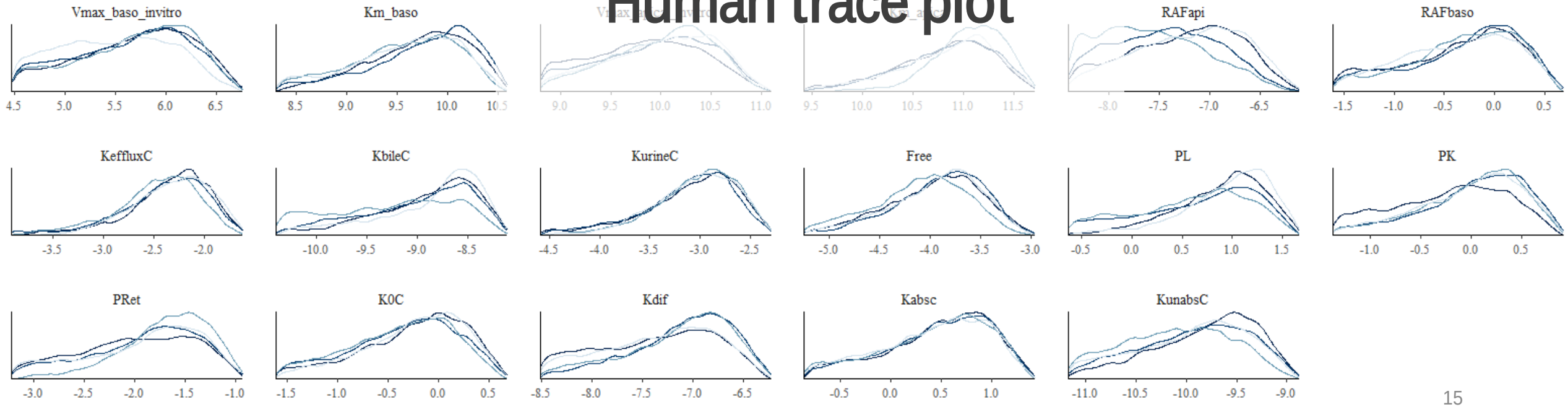
Bayesian hierarchical modeling

Develop multiple species PBPK model within Bayesian framework to characterize the variability and uncertainty within species and between species.





Human trace plot

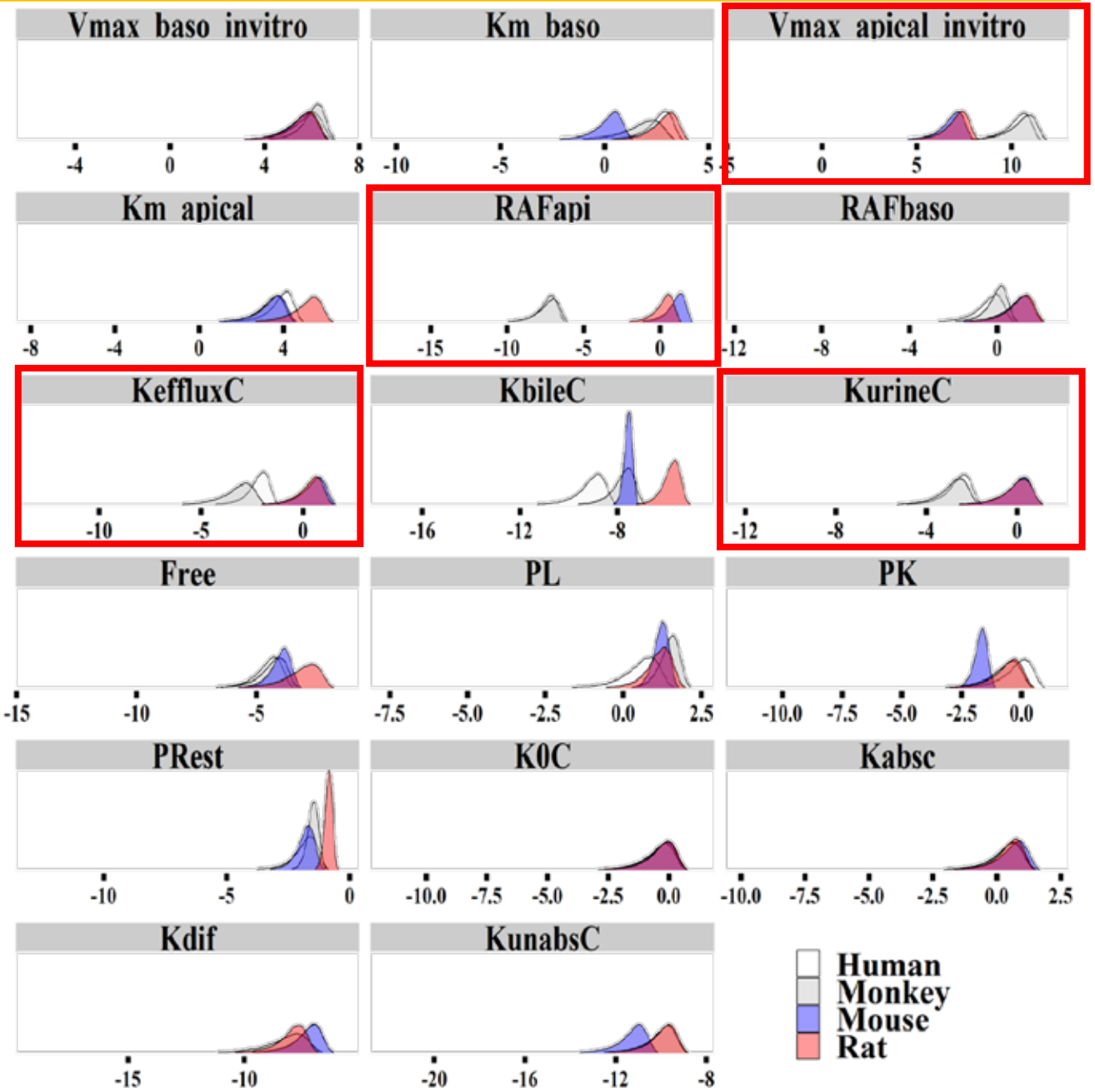


Interspecies uncertainty in model parameters

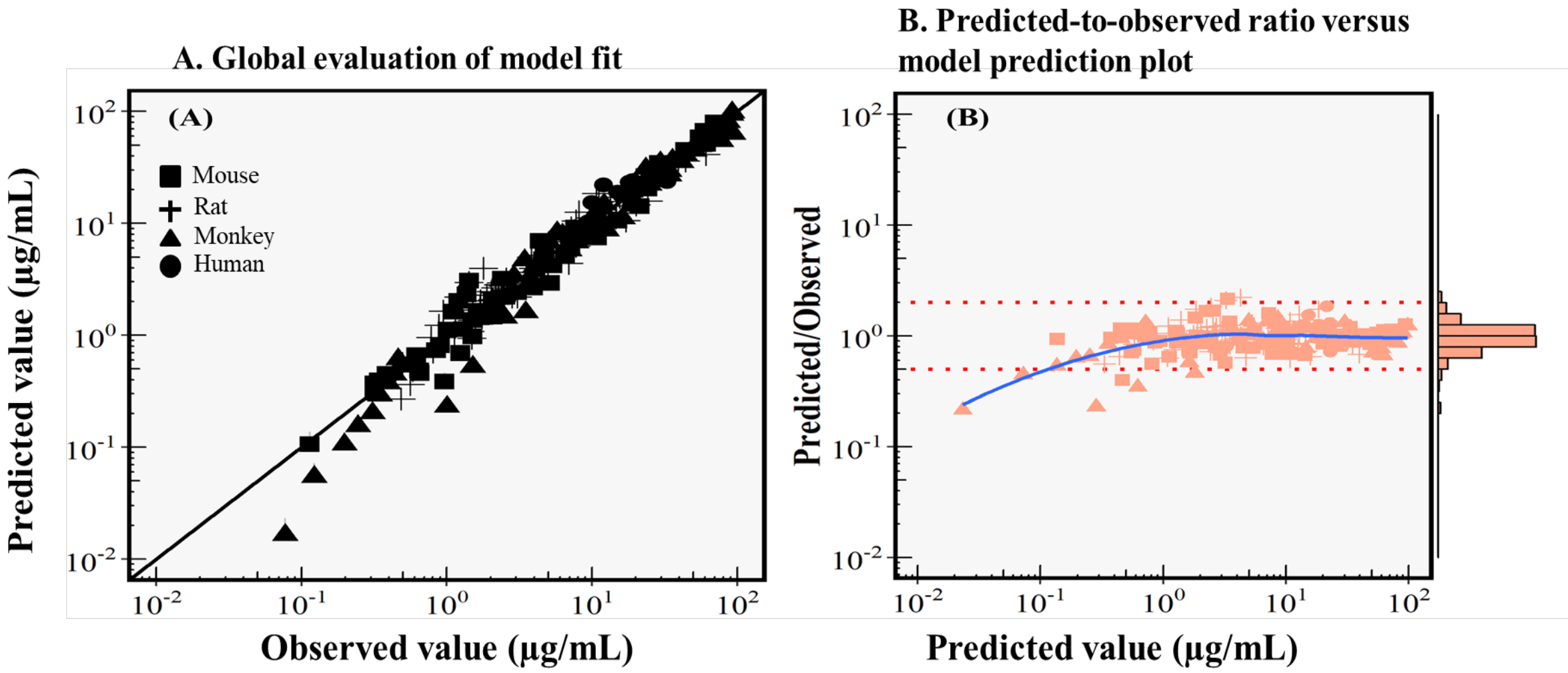
Kurine values in the human and monkey were significantly different from those for rodents, reflecting the variation in the plasma half-life

Vmax_apical_invitro values in the human and monkey were significantly different from those for rodents, supporting the finding from earlier modeling efforts.

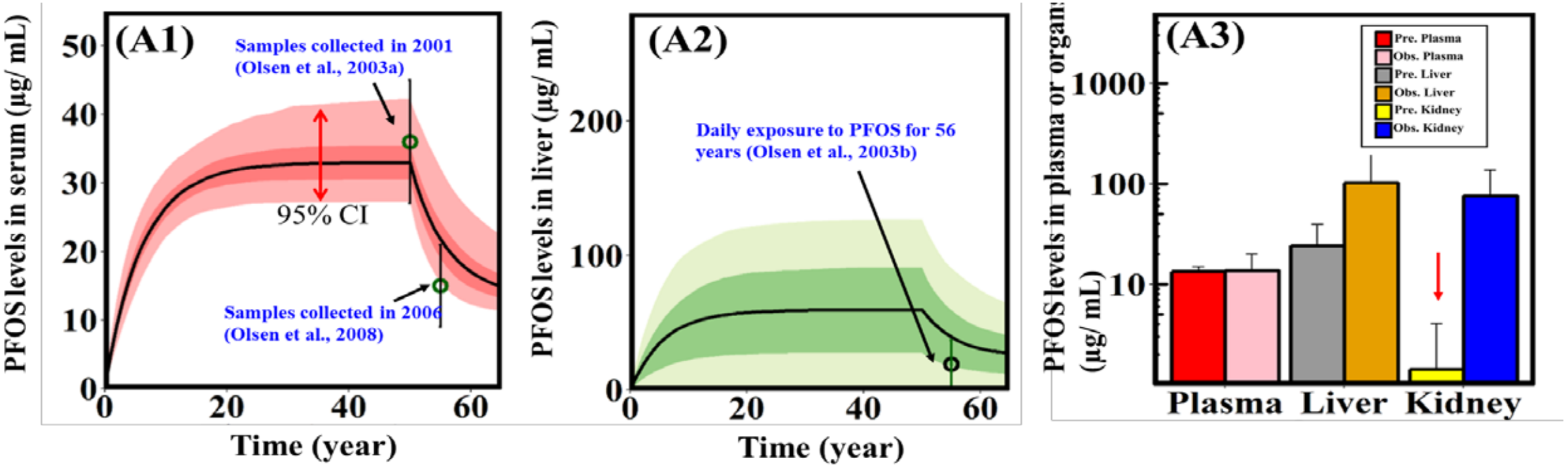
KeffluxC: The rate of efflux constant that pump the PFOS back into the blood might paly a critical role in the elimination kinetics between species



Goodness of Fit Plots



Model Evaluation based on real-world exposure scenario in human population



Study	Dosing duration (days)	NOAEL (mg/kg/day)	Human equivalent dose (HED) (mg/kg/d)	
			U.S. EPA	This study
Seacat et al., 2002: monkey;	182	0.15	0.0031	0.0055 (0.0001~ 0.14)
Seacat et al., 2003: rat;	98	0.34	0.0013	0.0057 (0.0002 ~ 0.17)

We recommend that the 5th percentile of the HED from the monkey study (0.0001) as the basis in the derivation of RfD

Model application: Reference dose derivation

EFSA, 2018

- EFSA guidance value (EFSA, 2018) based on the endpoint of elevated cholesterol levels in human study

1.8 ng/kg/day

Chou et al. (2019)

- Estimated value from our model based on liver toxicity effects in monkey study (Seacat et al., 2011)

3 ng/kg/day

(0.0001/30 mg/kg/day)

20 ng/kg/day

- USEPA guidance value (EPA, 2016) based on the endpoint from animal study

A series of extensional study related to PFAS studies

Environmental Science & Technology

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Article

Integration of Toxicogenomics and Physiologically Based Pharmacokinetic Modeling in Human Health Risk Assessment of Perfluorooctane Sulfonate

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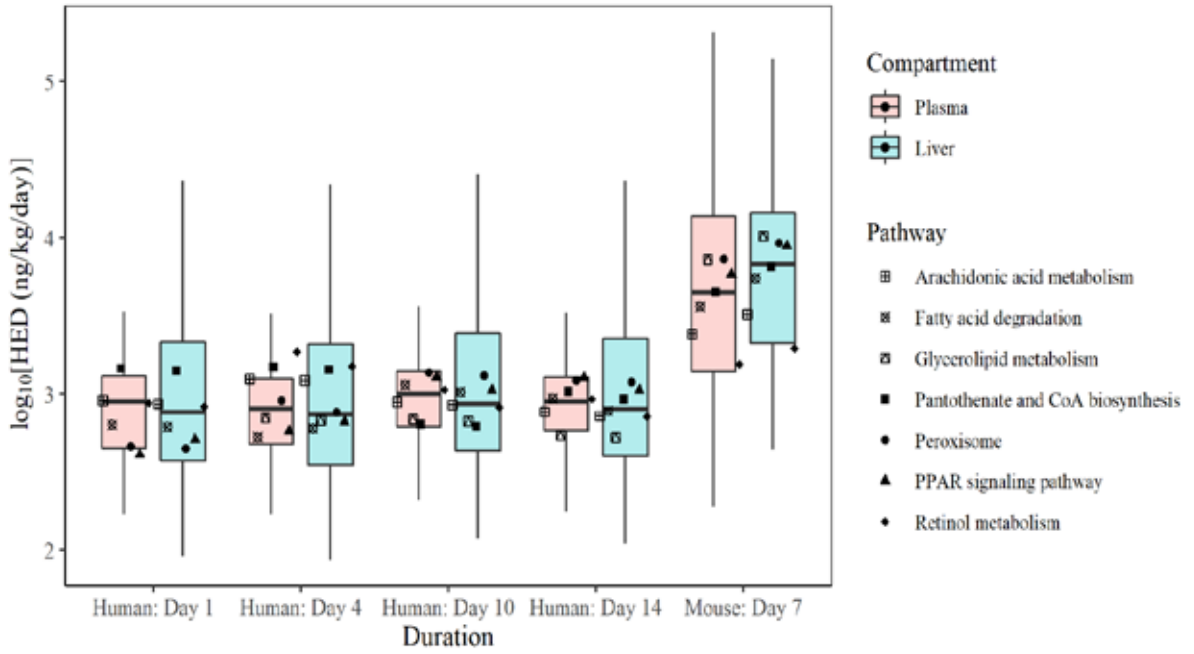

Research

A Section 508–conformant HTML version of this article is available at https://doi.org/10.1289/EHP7671.

Development of a Gestational and Lactational Physiologically Based Pharmacokinetic (PBPK) Model for Perfluorooctane Sulfonate (PFOS) in Rats and Humans and Its Implications in the Derivation of Health-Based Toxicity Values

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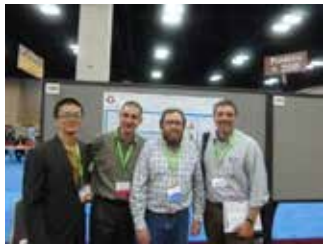

UGA 2013

KSU 2017

KSU Lab 2019

UF Lab 2021

National FARAD 2019

UF FARAD 2021

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Thank you for your attention

Questions