

UNDERSTANDING PFAS RETENTION MECHANISMS THROUGH TOXICOKINETIC MODELLING

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Implementations

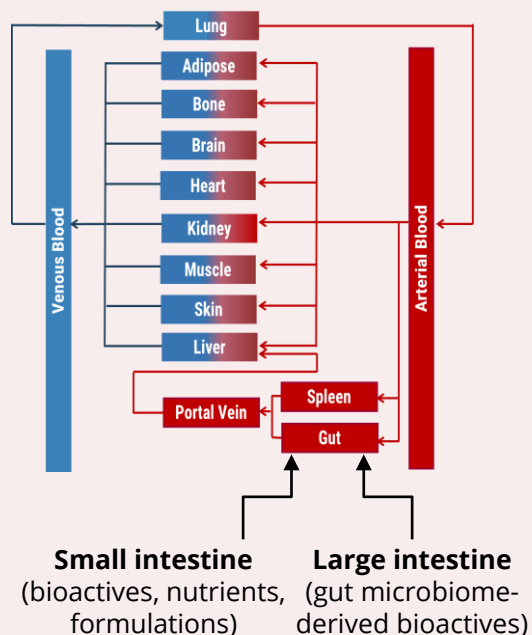
27 Sep 2023

Toxicokinetic modelling as a NAM – a digital twin



Physiologically-based toxicokinetic (PBTK) models

PBTK model (virtual human subject)

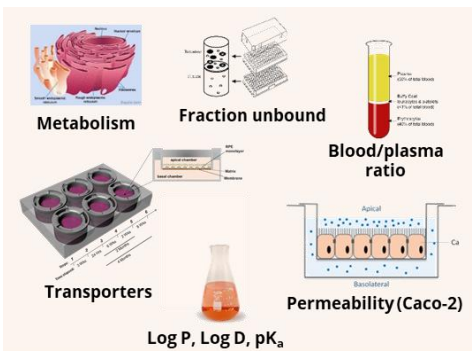


**Physiology data adjusted to
recapitulate other populations**

In vitro digestion models

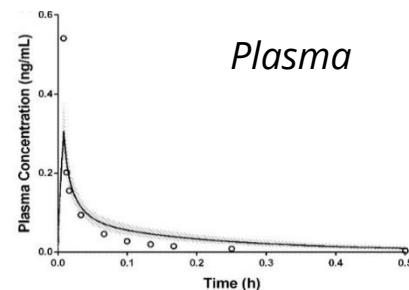


In vitro ADME assays

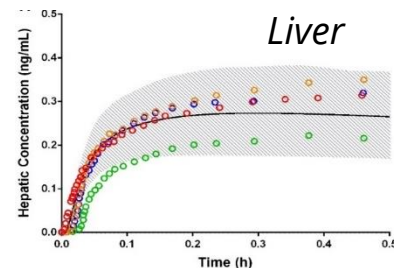


***In vitro*-to-*in vivo*
extrapolation (IVIVE)**

Prediction of plasma concentrations



Prediction of tissue concentrations



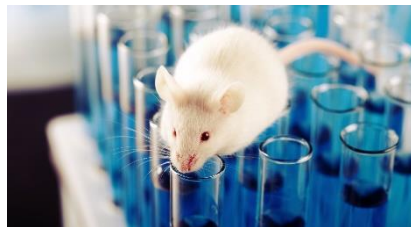
Why are tissue concentrations
important? Site of action,
efficacy/safety and dose-response
(e.g. skin, heart, brain, joint, muscle)

PFAS: The “forever” chemicals





Published studies disagree on the half-lives of PFOA



- PFOA half-life
 - hours/days in rats
 - weeks in mice
 - months in monkeys
- Poor inter-species correlation

(19) **United States**

(12) **Patent Application Publication**
Elcombe et al.

(10) **Pub. No.:** US 2013/0029928 A1

(43) **Pub. Date:** Jan. 31, 2013

(54) **COMPOSITIONS COMPRISING
PERFLUOROOCTANOIC ACID**

Publication Classification

(76) **Inventors:** Clifford Roy Elcombe, Dundee (GB);
Charles Roland Wolf, Dundee (GB);
Anna Louise Westwood, Dundee (GB)

(51)	Int. Cl.	
	A61K 31/20	(2006.01)
	A61K 31/704	(2006.01)
	A61K 31/7068	(2006.01)
	A61K 31/52	(2006.01)
	A61P 35/02	(2006.01)

- PFOA administered to cancer patients at extremely high doses (50 mg single dose, 50 mg weekly dose)
- Half-life estimated at **116 days** (3.8 months)



Centers for Disease
Control and Prevention

National Biomonitoring Program

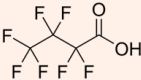




Biomonitoring Summary

Perfluorochemicals

- Consensus estimates place PFOA half-life at **~1.3-3.9 years**

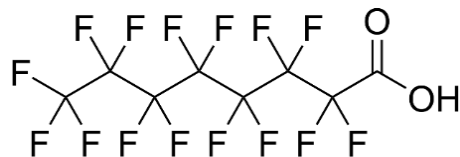


Biological half-life appears related to the carbon chain length

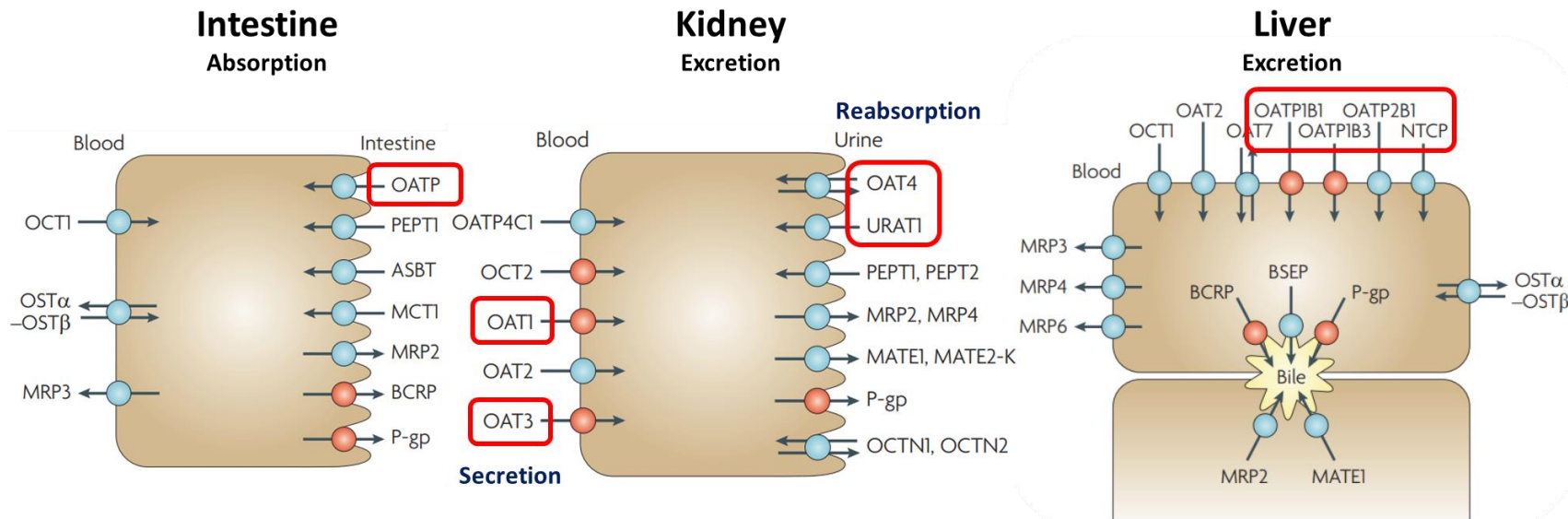
PFAS	Structure	Carbon chain length	Half-life
Perfluorobutanoic acid (PFBA)		4 (Short)	2 – 3 days
Perfluorobutane sulfonic acid (PFBS)		4 (Short)	28 days
Perfluorooctanoic acid (PFOA)		8 (Long)	1.3 – 3.9 years
Perfluorooctane sulfonic acid (PFOS)		8 (Long)	3.3 - 5.4 years
Perfluorohexane sulfonic acid (PFHxS)		6 (Long)	7 years

- Why do biomonitoring and clinical studies disagree on PFOA half-life?
- How do we identify PFAS with long half-lives? (risk prioritization)

Transporters are essential for the disposition of PFAS

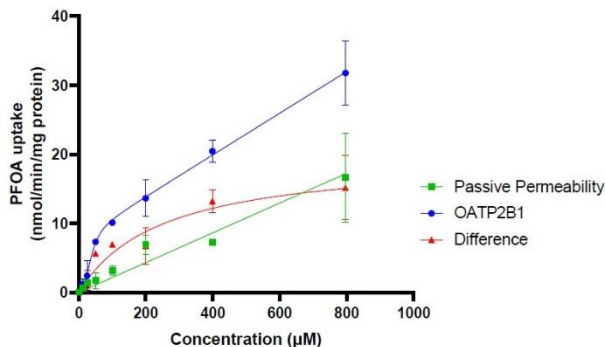


PFOA - pK_a 3.8



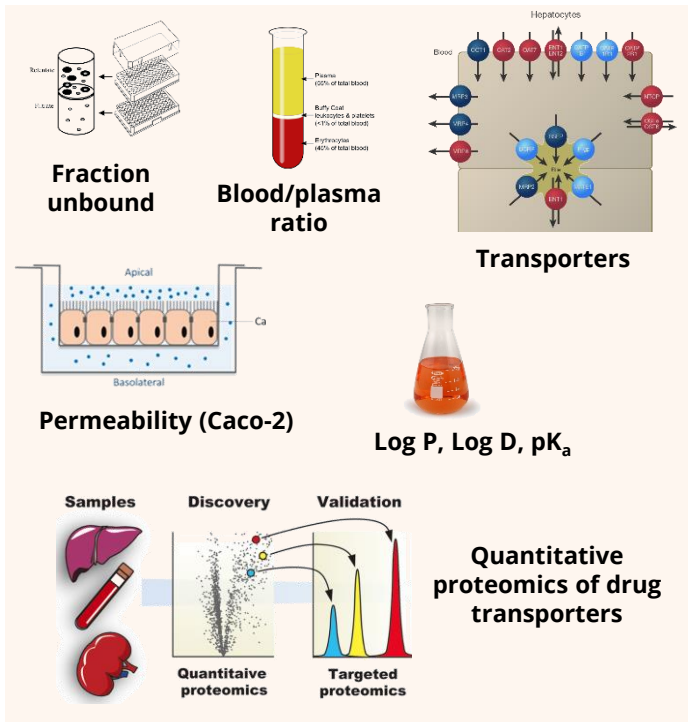
Approach to model the toxicokinetics of PFOA and other PFAS

Transporter kinetics

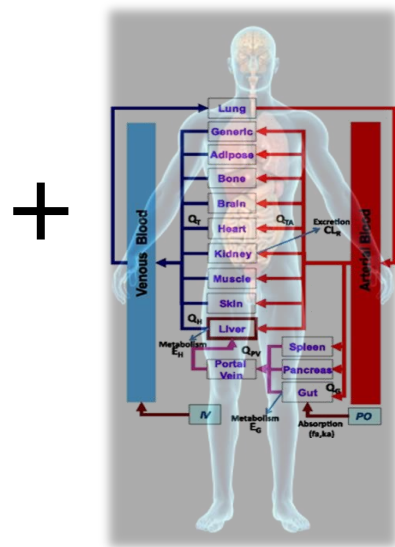


8 transporters in triplicates were screened for each PFAS

Chemical data: *In vitro* ADME assays



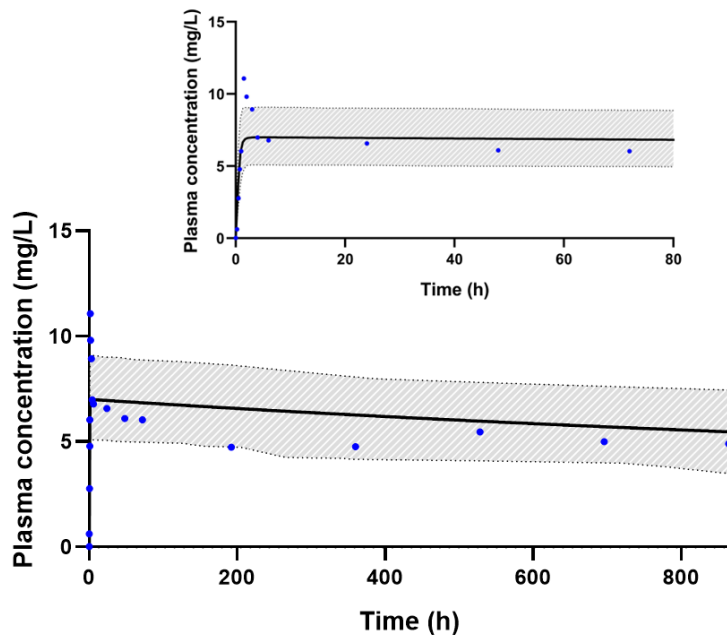
Systems data: Human physiology



Simcyp® Simulator



Clinical PFOA toxicokinetics were recapitulated



• Clinical data
— Predicted Mean

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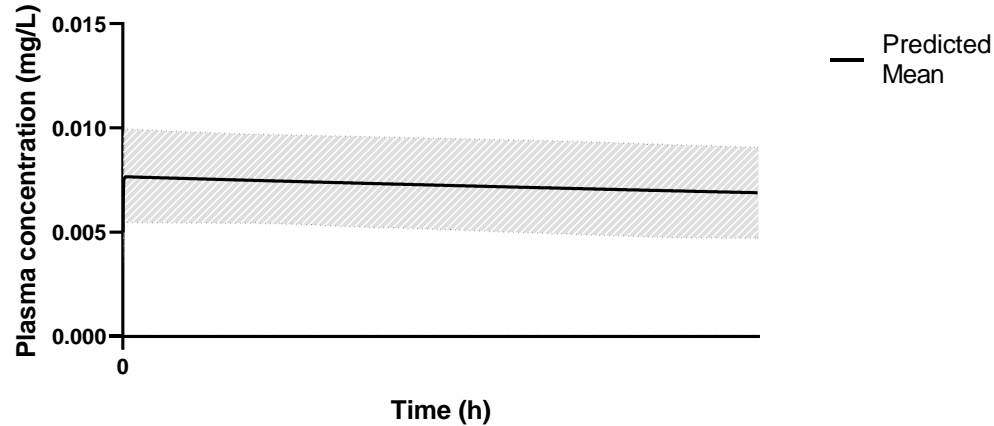
PFOA 50 mg single dose

TK parameter	Observed	Predicted	Predicted/ Observed ratio
AUC _{0-t} (mg/L·h)	4470.80	5268.57	1.18
C _{max} (mg/L)	9.25	6.97	0.75
T _{max} (h)	3.00	3.16	1.05
CL (L/h)	0.0112	0.0095	0.85
t _{1/2} (days)	116	124	1.07



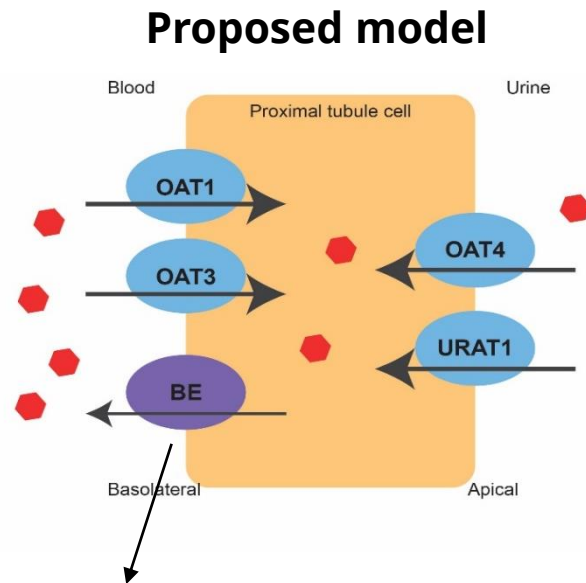
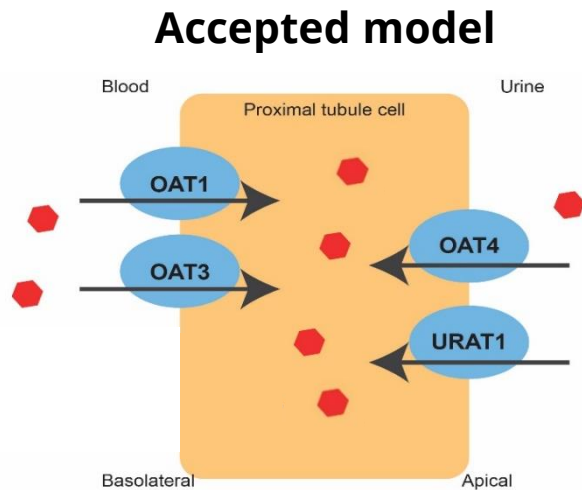
Long half-life in low exposure settings was recapitulated

- Low exposure (70 ng/day) of PFOA similar to biomonitoring studies
- Recapitulated years-long $t_{1/2}$ (1.3 years) observed in biomonitoring studies (1.3-3.9 years)



Why are clinical and biomonitoring estimates of PFOA half-life so different?

A missing kidney transporter provides a unified explanation for the divergent half-life estimates



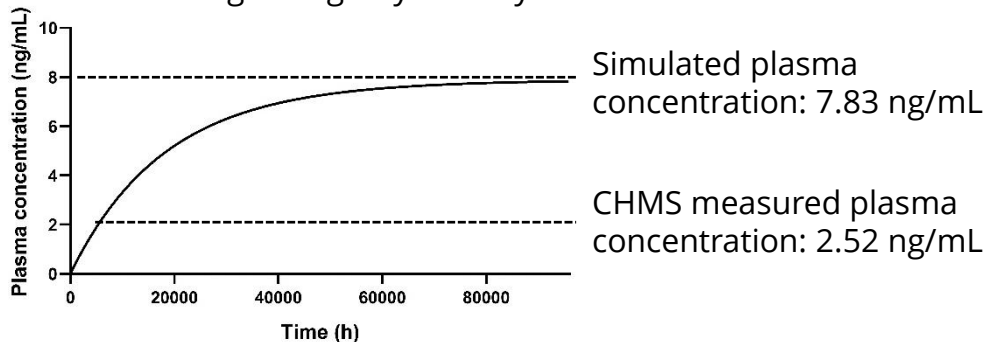
Saturable, renal basolateral efflux transporter



How does our model compare with other estimates of PFOA exposure?

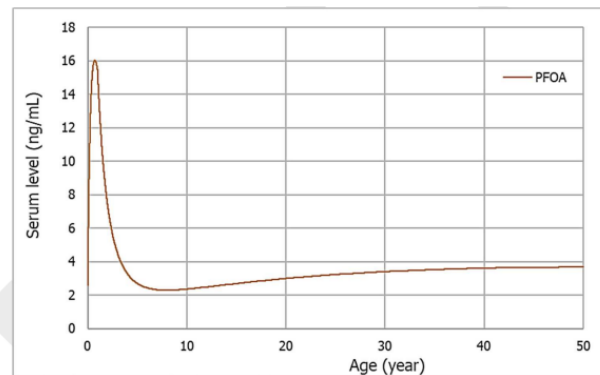
Forward dosimetry

Dosing: 70 ng/day for 11 years



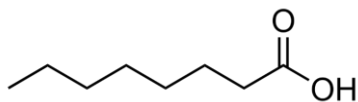
- Canadian total diet study: 70 ng/day
- Canadian Health Measures Survey (CHMS) (2.52 ng/mL)

Reverse dosimetry

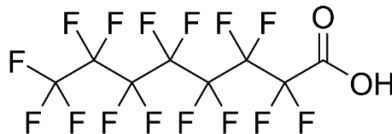


- EFSA estimates for steady state serum level of 2 ng/mL of PFOA, a daily intake of 0.187 ng/kg is needed
- Our estimates to achieve 2 ng/mL PFOA are 0.28 ng/kg

- MCT1 transports short and medium chain fatty acids e.g. octanoic acid

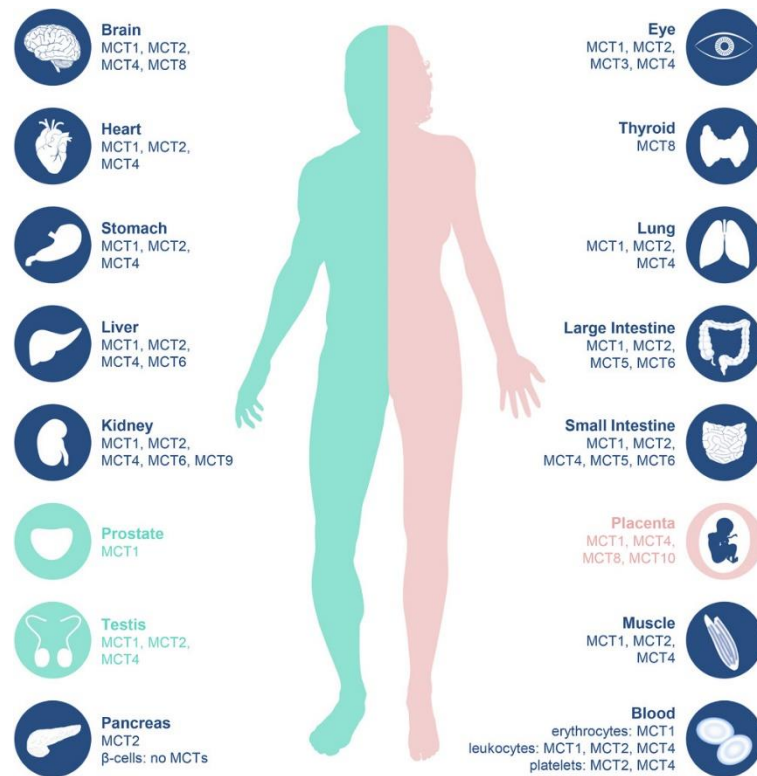


Octanoic acid



PFOA

- PFOA distribution not confined to liver and kidney
- May explain effects on other organs (thyroid, reproductive tissues), appearance in cord blood
- Greater **volume of distribution** than expected → implication on **half-life**?



Comparative analysis of 5 PFAS with differing half-lives identifies mechanisms of retention

CL _{int} ($\mu\text{L}/\text{min}/\text{mg}$ protein)	Kidney Transporter				Liver Transporter			
	OAT1	OAT3	OAT4	URAT1	NTCP	OATP1B1	OATP1B3	OATP2B1
PFBA	Non-substrate	Non-substrate	Non-substrate	1.31	1.06	Non-substrate	Non-substrate	Non-substrate
PFBS	6.62	5.63	5.33	3.41	28.83	1.58	2.78	3.38
PFOA	9.67	7.11	30.18	1.85	6.53	43.78	29.41	10.04
PFOS	44.40	9.41	17.10	23.37	15.46	65.99	48.28	31.90
PFHxS	2.39	76.31	15.00	1.46	2.53	90.03	52.57	77.18

PFAS	Observed half-life	Predicted half-life
PFBA	2-3 days	31 days
PFBS	28 days	162 days
PFOA	1.3-3.9 years	1.1 years
PFOS	3.3-5.4 years	3.6 years
PFHxS	7 years	5.9 years

PFAS	f_u	CL _F (L/h)	CL _R (L/h)	CL _S -CL _{reabs} (L/h)	% Reabsorbed
PFBA	0.1172	0.9293	0.375	-0.5543	59.65%
PFBS	0.0121	0.0959	2.650E-3	-0.0933	97.24%
PFOA	0.0048	0.0381	5.724E-4	-0.0375	98.50%
PFOS	0.0048	0.0381	2.826E-5	-0.0381	99.93%
PFHxS	0.0013	0.0103	7.068E-5	-0.0102	99.31%

Half-life increases with:

1. Greater transport by reuptake transporters
2. Greater plasma protein binding

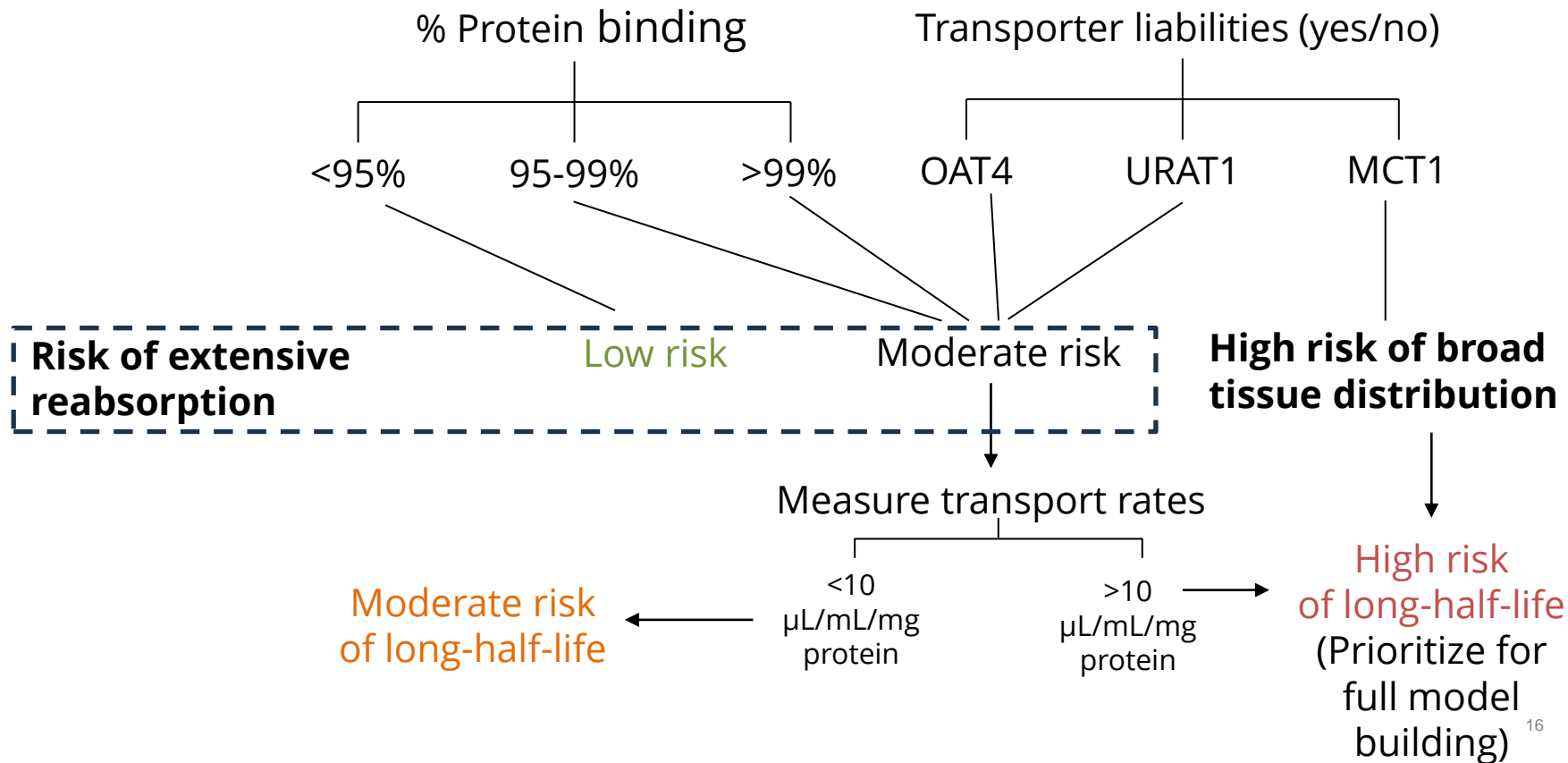
= greater reabsorption

3. Substrate of MCT1
(PFOA, PFOS, PFHxS)

= greater distribution



Translating these mechanisms to a risk prioritization strategy





Key learning points from our PFAS study

- PBTK models provide deep mechanistic insights that cannot be discerned from human clinical or biomonitoring studies
- The key organ that controls PFAS removal is the kidney
- Future PFAS should be designed to have **minimal plasma protein binding, low affinities to renal transporters** and **limited tissue uptake**
- Next steps: model placental transfer in the pregnant population



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Article

Mechanistic Middle-Out Physiologically Based Toxicokinetic Modeling of Transporter-Dependent Disposition of Perfluorooctanoic Acid in Humans

Jieying Lin, Sheng Yuan Chin, Shawn Pei Feng Tan, Hor Cheng Koh, Eleanor Jing Yi Cheong, Eric Chun Yong Chan, and James Chun Yip Chan*



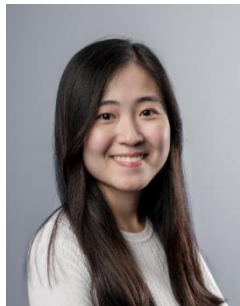
Cite This: *Environ. Sci. Technol.* 2023, 57, 6825–6834



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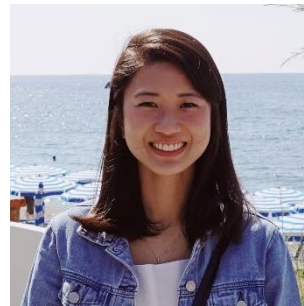
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