Population-based pharmacokinetic modeling of perfluoroalkyl substances

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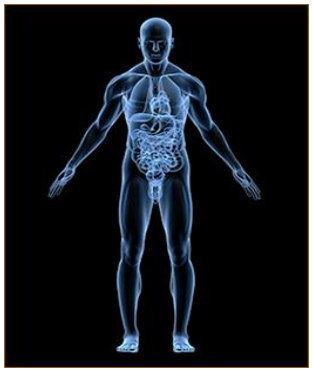
March 7 2023

We all have chemicals in our bodies…

The balance between exposure and elimination determines how much!

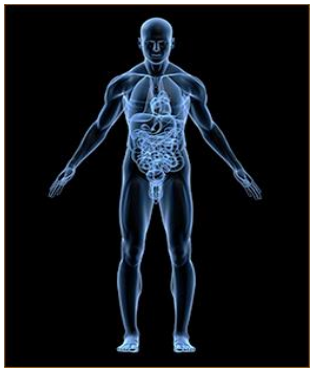


Exposure

Concentration

Elimination

A 1-box pharmacokinetic model…



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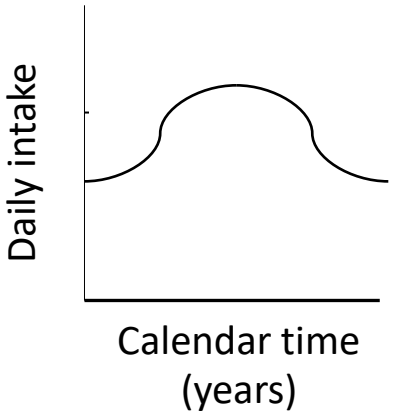

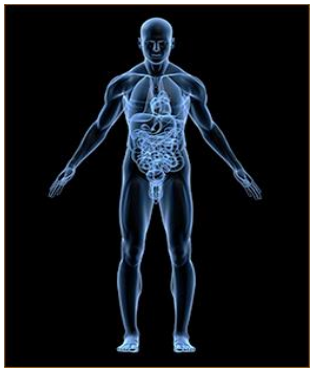

Exposure

Concentration

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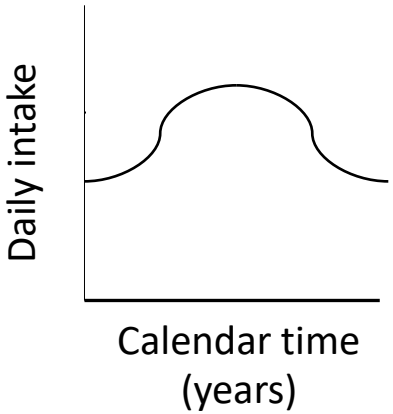
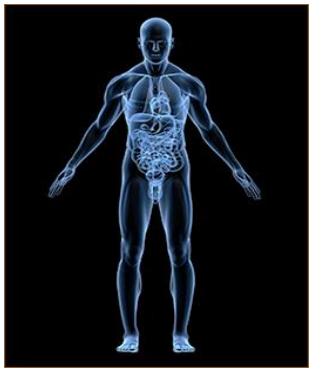
A 1-box pharmacokinetic model…





Characterized as a first-order process using an estimated elimination half-life

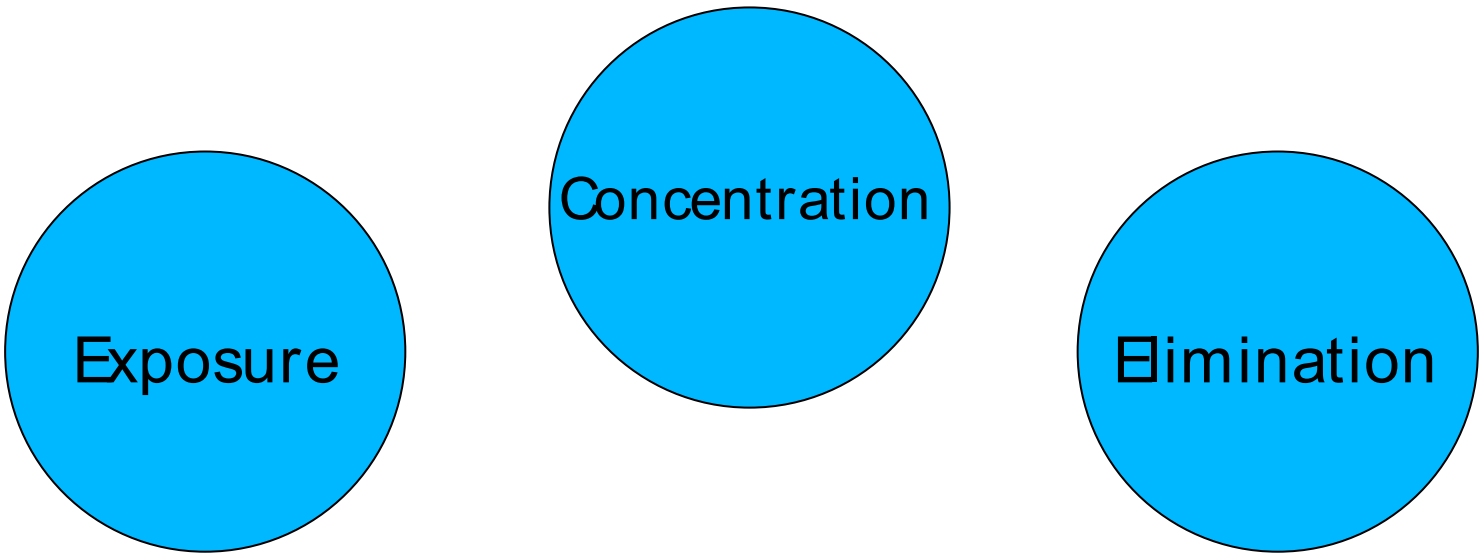
Exposure

Concentration

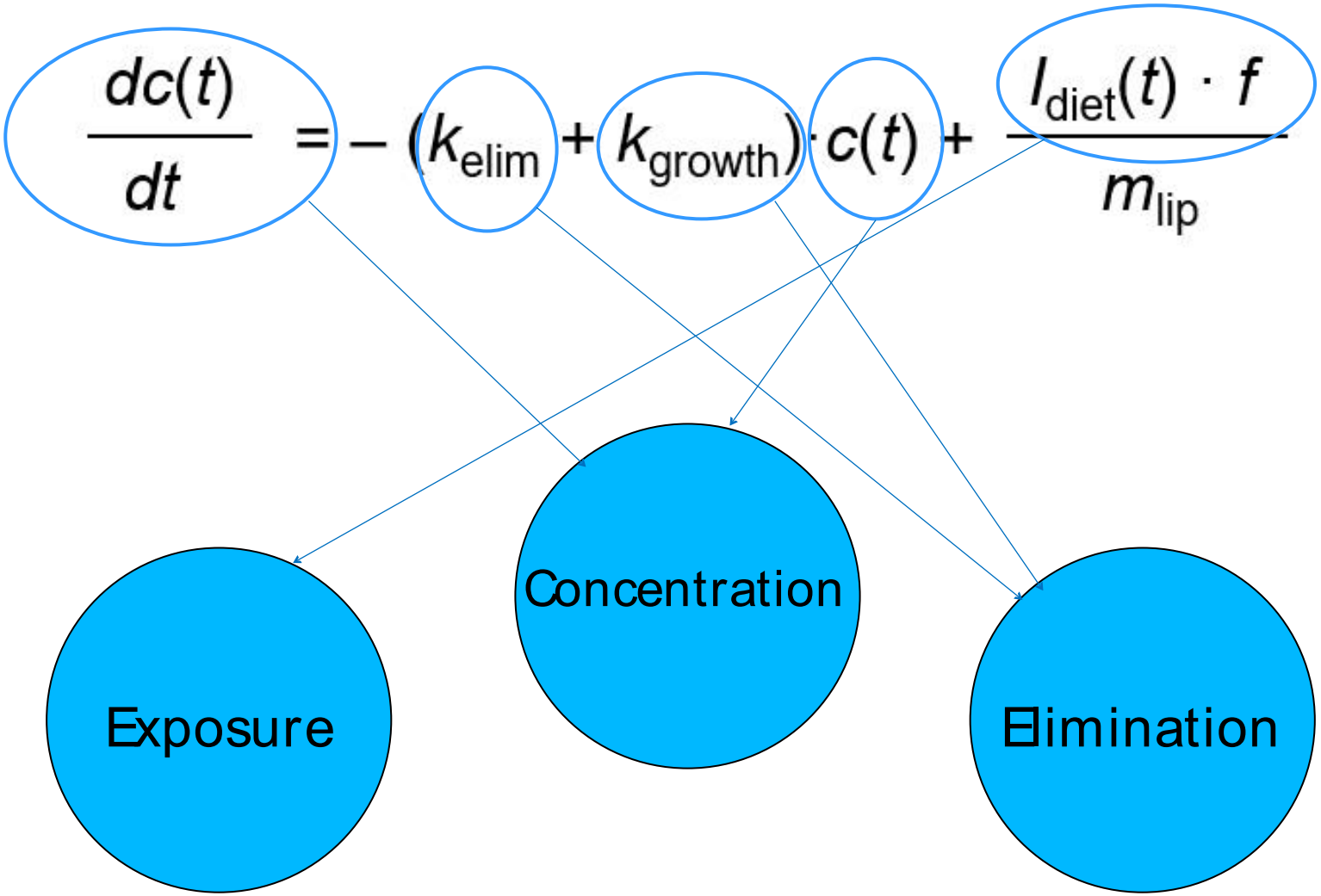
Elimination

A 1-box pharmacokinetic model…

$$\frac{dc(t)}{dt} = -(k_{elim} + k_{growth}) \cdot c(t) + \frac{I_{diet}(t) \cdot f}{m_{lip}}$$

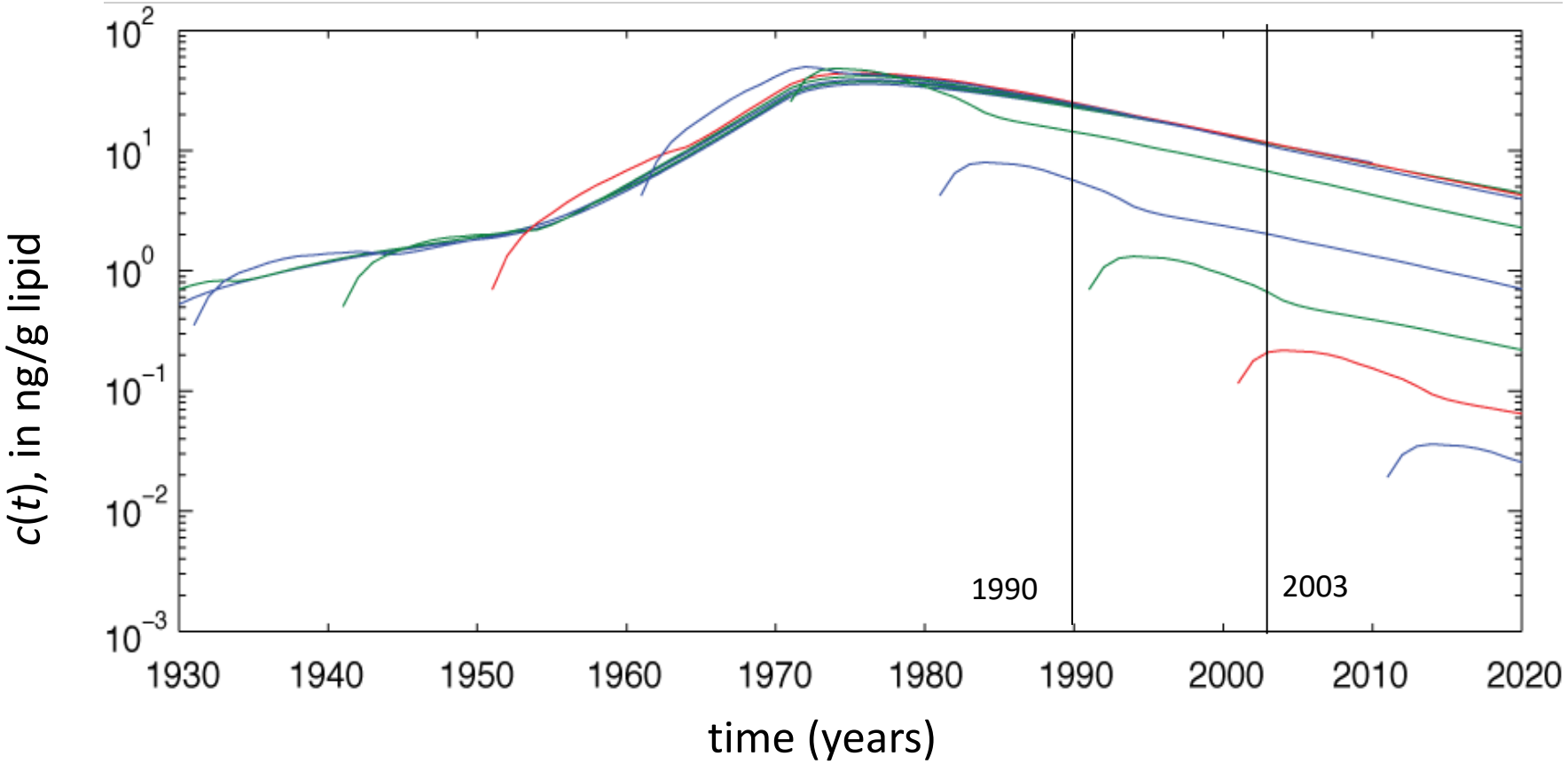


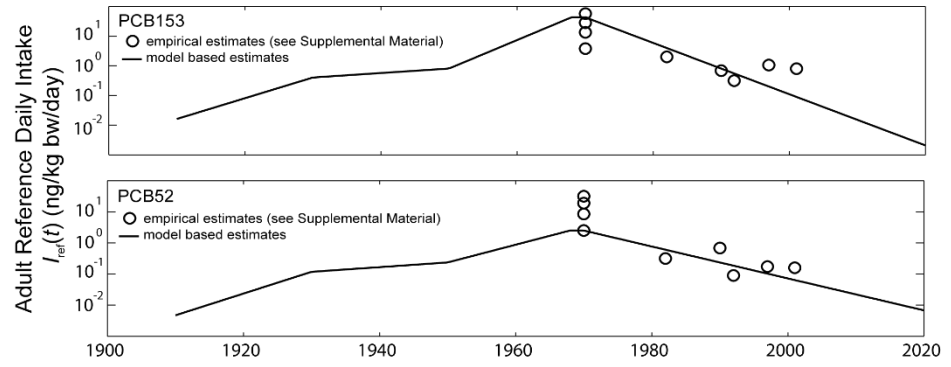
A 1-box pharmacokinetic model…

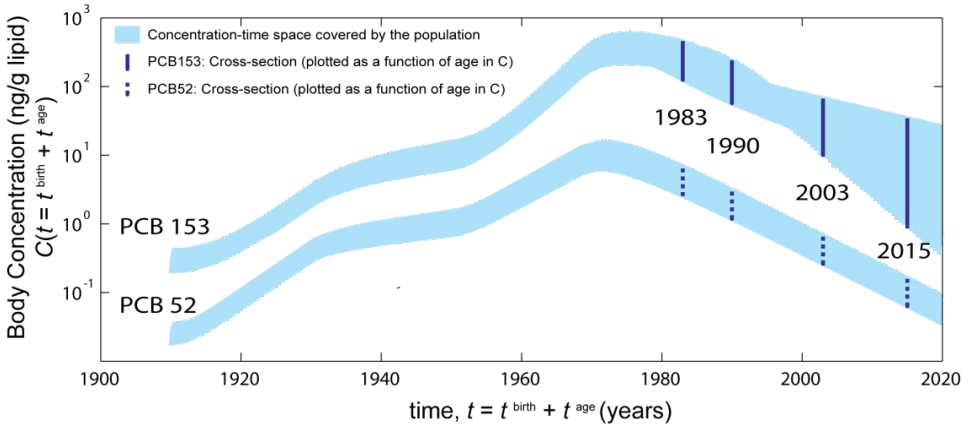


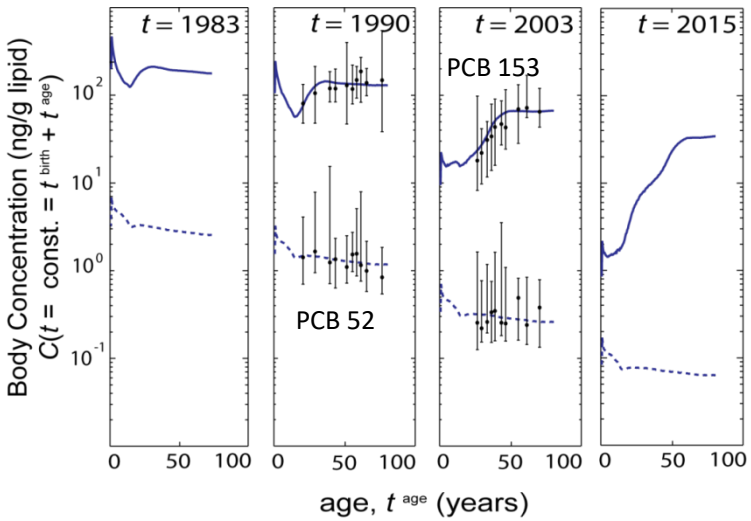
- Model representative individuals born every year for a century to create a population-based pharmacokinetic model…

9 individuals, one born every 10 years starting in 1931









Exposure Time Trends

Intrinsic Elimination

Concentration Time Trends

Age-Concentration Structure

Duarte-Davidson et al. 1994

Thomas et al. 2006

Complete information

A Multi-Individual Pharmacokinetic Model Framework for Interpreting Time Trends of Persistent Chemicals in Human Populations: Application to a Postban Situation

Roland Ritter, Martin Scheringer, Matthew MacLeod, Urs Schenker, and Konrad Hungerbühler

Safety and Environmental Technology Group, ETH Zurich, Zurich, Switzerland

BACKGROUND: Human milk and blood are monitored to detect time trends of persistent organic pollutants (POPs) in humans. It is current practice to use log-linear regression to fit time series of averaged cross-sectional biomonitoring data, here referred to as cross-sectional trend data (CSTD).

OBJECTIVE: The goals of our study are to clarify the interpretation of half-lives derived from fitting

in exposure (UNEP 2007; World Health Organization 2007). The second factor that has been reported to influence CSTD-based half-lives is the rate of elimination of a substance from the body by all possible pathways.

Intrinsic Human Elimination Half-Lives of Polychlorinated Biphenyls Derived from the Temporal Evolution of Cross-Sectional Biomonitoring Data from the United Kingdom

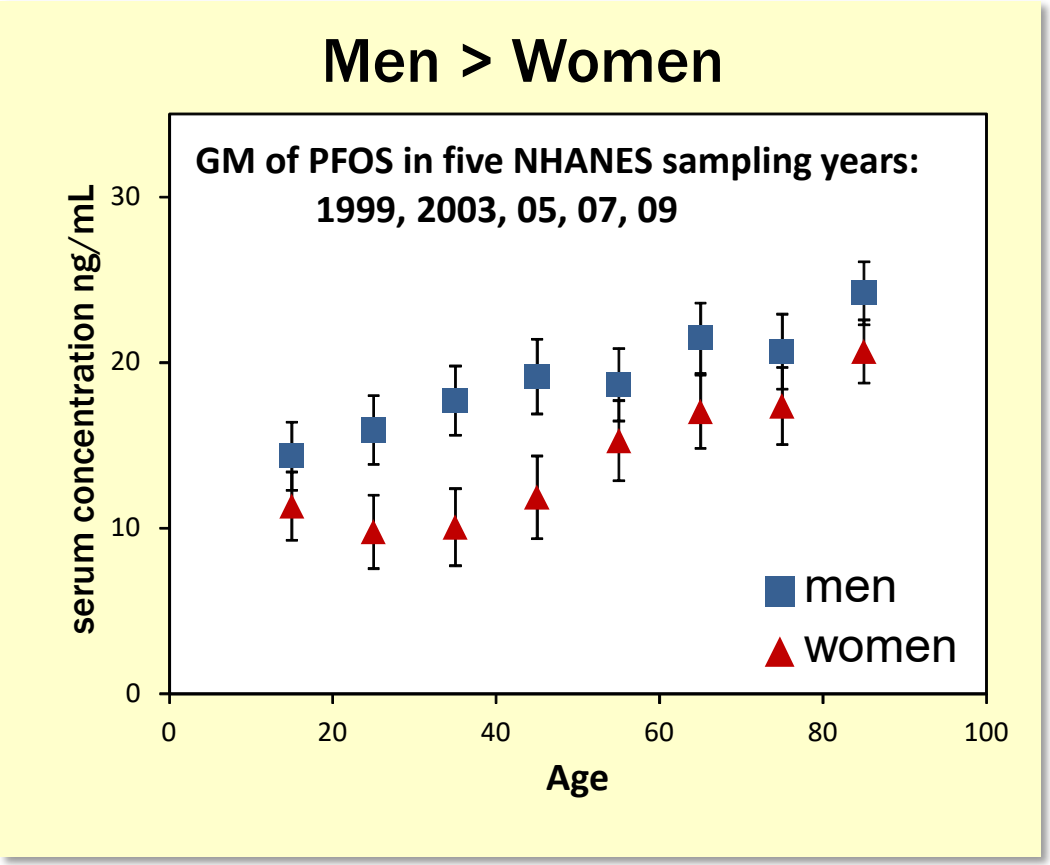
Roland Ritter,[1] Martin Scheringer,[1] Matthew MacLeod,[1] Claudia Moeckel,[2] Kevin C. Jones,[2] and Konrad Hungerbühler[1]

[1]Safety and Environmental Technology Group, ETH Zurich, Zurich, Switzerland; [2]Lancaster Environment Centre, Lancaster University, Lancaster, United Kingdom

BACKGROUND: Most empirical estimates of human elimination kinetics for persistent chemicals reflect apparent elimination half-lives that represent the aggregated effect of intrinsic elimination, ongoing exposure, and changes in body weight. However, estimates of intrinsic elimination at back-

substances range from < 1 year to several decades, and even negative values have been reported (Matsumoto et al. 2009; Milbrath et al. 2009; Shirai and Kissel 1996). We use

PFOS (Perfluorooctane sulfonate) is the most abundant POP measured in humans



NHANES = National Health and Nutrition Examination Survey

2014: Research Question:

Could loss of PFOS by menstruation explain the different body burdens in women and men?

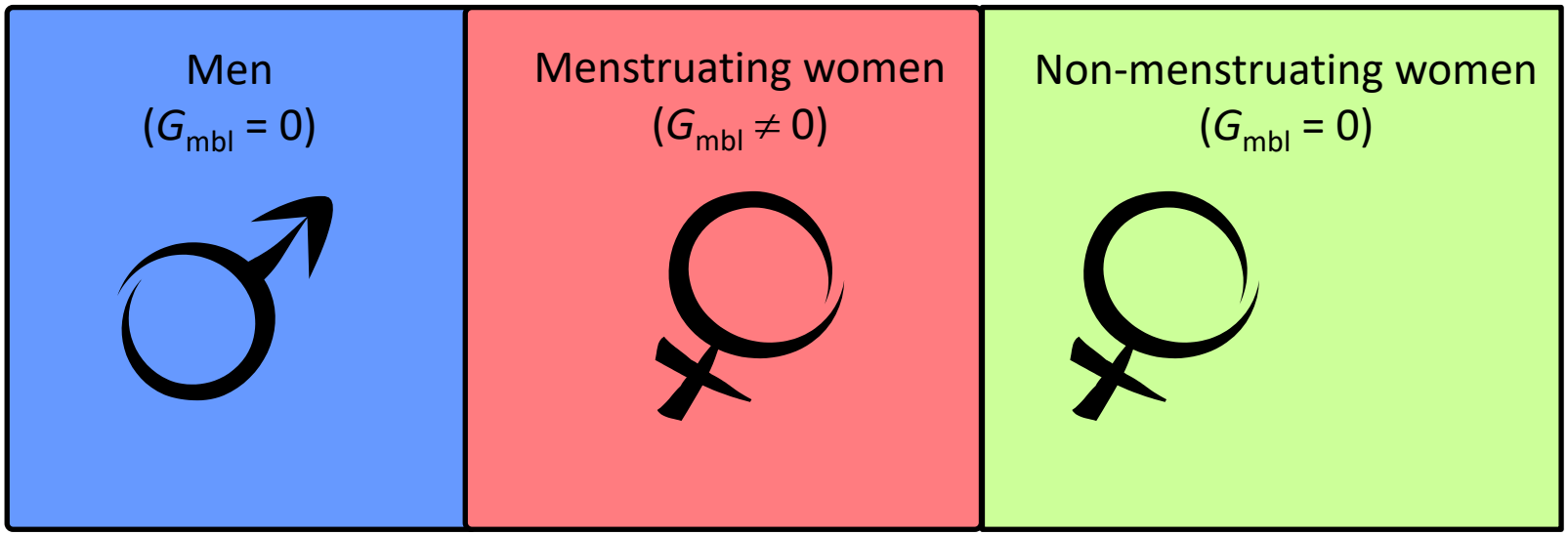
Our population-based model is based on an intrinsic elimination rate constant (k_{elim})

$$\frac{dc(t)}{dt} = -(k_{elim} + k_{growth}) \cdot c(t) + \frac{I_{diet}(t) \cdot f}{m_{lip}}$$

- Chemical specific
- Constant regardless of one's sex, age, body weight, ongoing exposure, and physiology

Add a new process to the model…

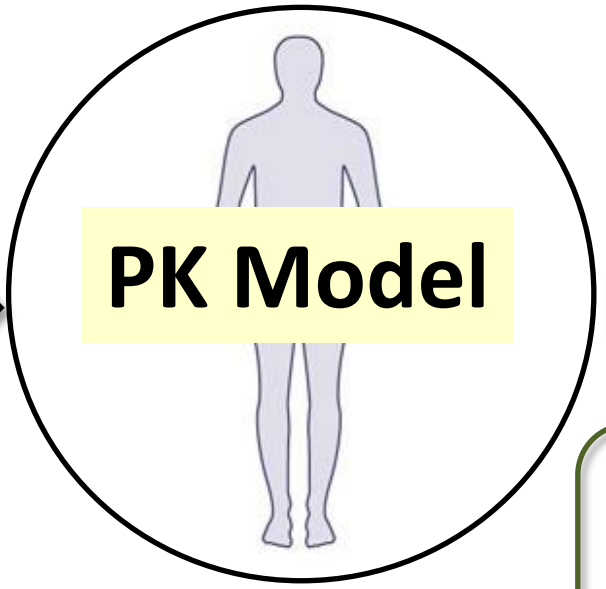
- Introduce a new term to describe losses with menstrual blood ($G_{\underline{\mathbf{m}}\text{enstrual }\underline{\mathbf{b}}\text{lood }\underline{\mathbf{l}}\text{oss}}$ / V_D)
- V_D – Volume of distribution (mL/kg)
  - $C_{\text{whole-body}}$ (ng/kg) / C_{blood} (ng/mL)



Population-based Pharmacokinetic Model

INPUT

- 5 years of cross-section data on PFOS in men and women in the US
- Intake function for PFOS based on product use data



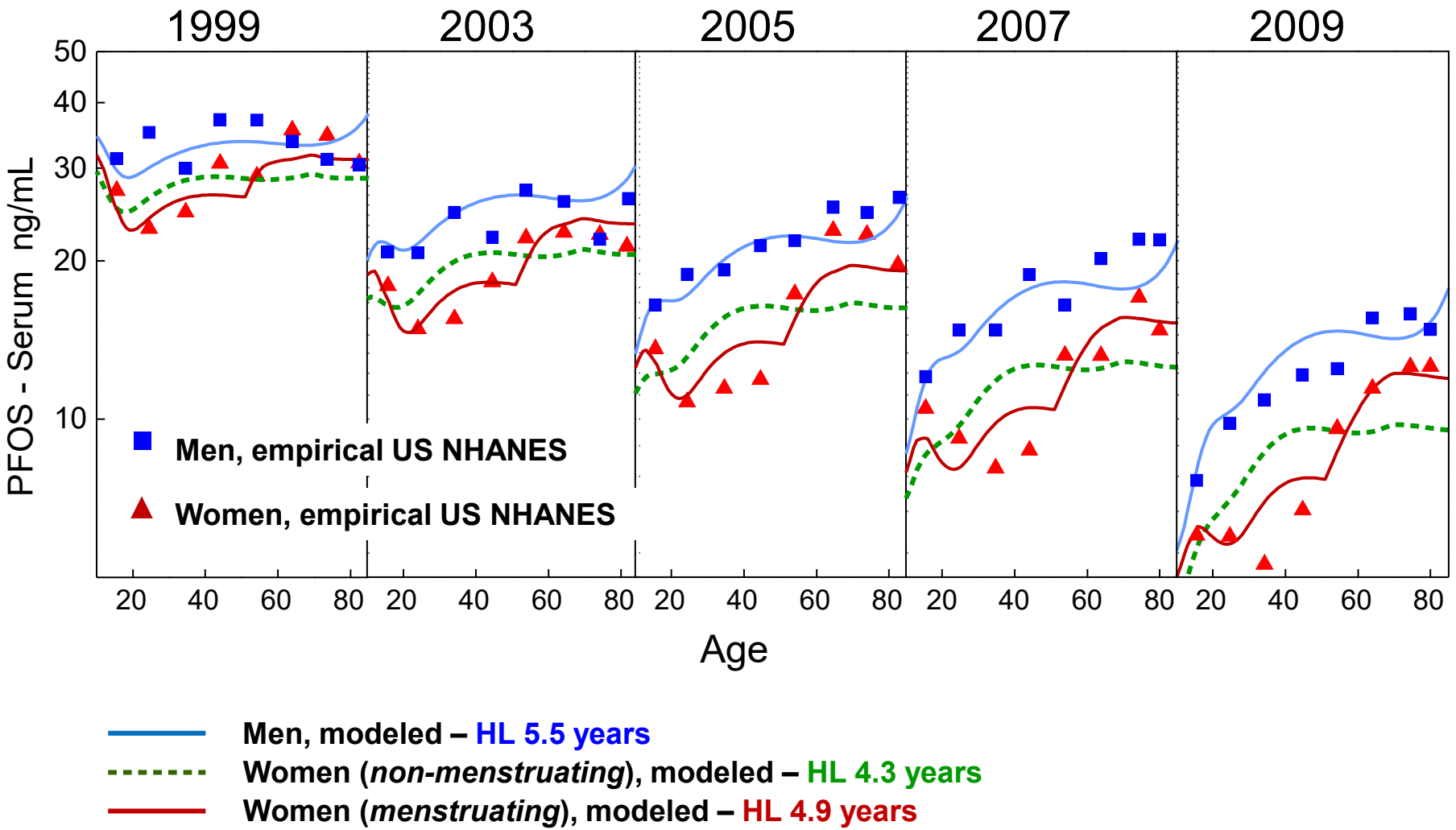
OUTPUT

k_e

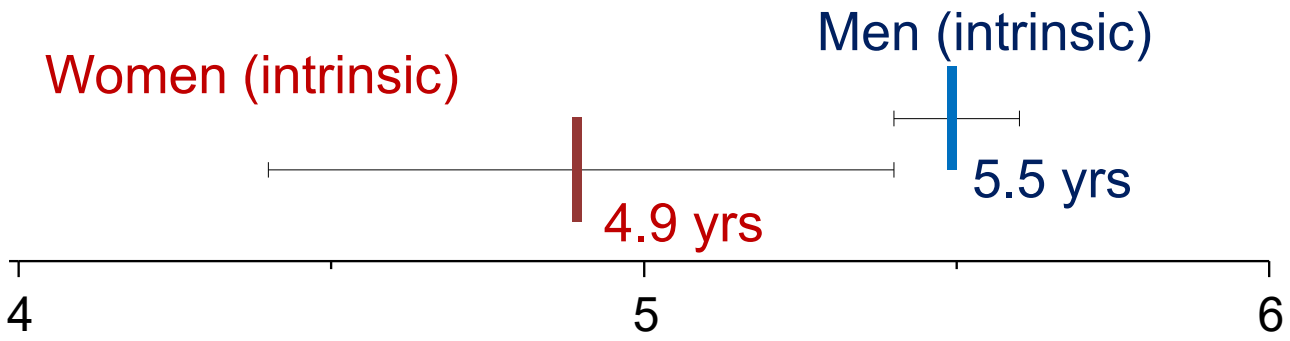
Refined intake function

NHANES = National Health and Nutrition Examination Survey

Results – PFOS in the US population



When menstruation is modeled as a sex & age specific loss process the difference in k_{elim} between women and men is *almost* gone!



PFOS half-lives in the US population (years)

2014: Research Question:

Could loss of PFOS by menstruation explain the different body burdens in women and men?

Yes.

Assuming the same body-weight normalized intake, the model fits data for women just as well as for men when menstruation is included

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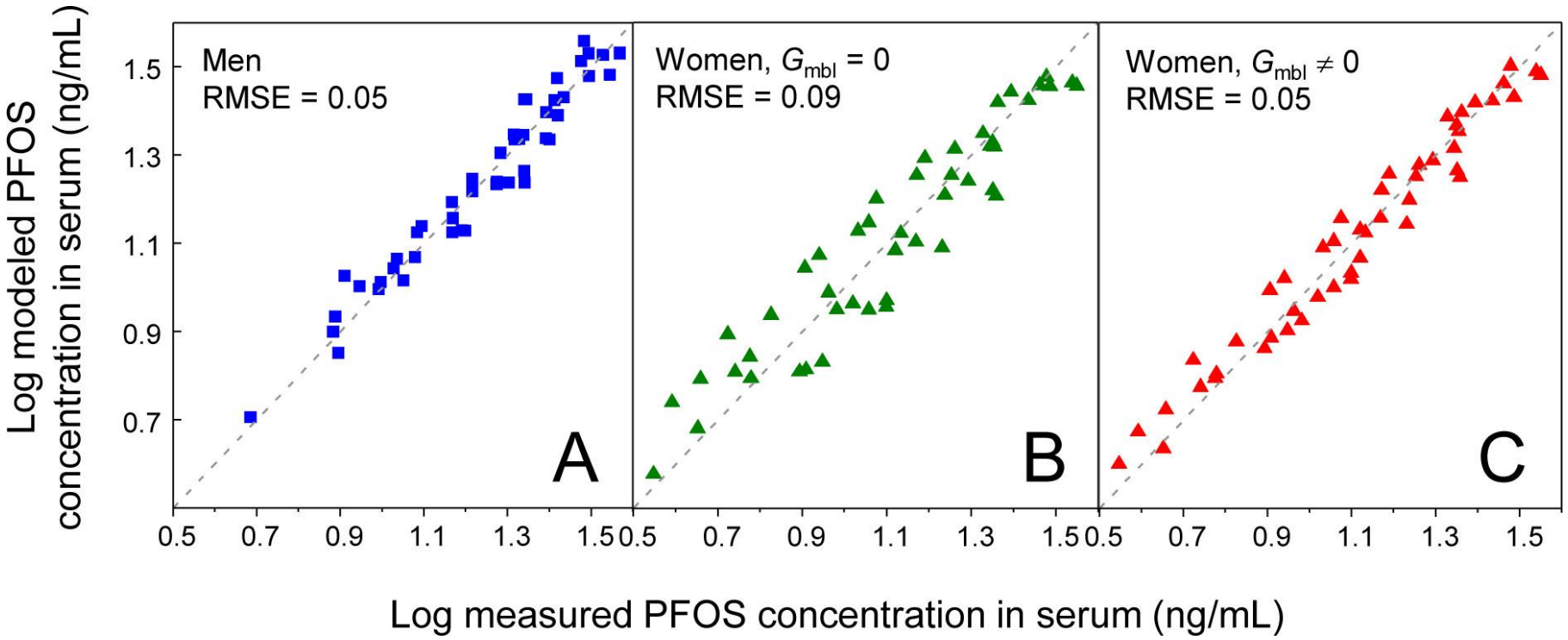

2014: Research Question:

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Assuming the same body-weight normalized intake, the model fits data for women just as well as for men when menstruation is included

But…

Modeled k_{elim} for women still did not convincingly overlap with k_{elim} for men…

Environmental Science & Technology

Article

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Enhanced Elimination of Perfluorooctane Sulfonic Acid by Menstruating Women: Evidence from Population-Based Pharmacokinetic Modeling

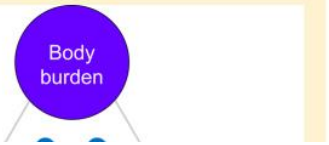
Fiona Wong,*[,†] Matthew MacLeod,[†] Jochen F. Mueller,[§] and Ian T. Cousins[†]

[†]Department of Applied Environmental Science (ITM), Stockholm University, Svante Arrhenius väg 8, SE-10691, Stockholm, Sweden

[§]National Research Centre for Environmental Toxicology, The University of Queensland, 39 Kessels Road, Coopers Plains, Queensland 4108, Australia

Supporting Information

ABSTRACT: Human biomonitoring studies have shown that concentrations of perfluorooctane sulfonic acid (PFOS) in men are higher than in women. We investigate sex differences in elimination of PFOS by fitting a population-based pharmacokinetic model to six cross-sectional data sets from 1999 to 2012 from the US National Health and Nutrition Examination Survey (NHANES) and derive human first-order elimination rate cor
corresponding elimination half-lives ($t_{1/2}$) for PFOS, where $t_{1/}$
use a modified version of the Ritter population-based pharma
and derive elimination rate constants separately for men an
model accounts for population-average lifetime changes in PF
weight, and menstruation rate. We compare the model-deri
rate constant for hypothetical nonmenstruating women to the



Environmental Science & Technology

Correspondence/Rebuttal

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Response to Comment on "Enhanced Elimination of Perfluorooctane Sulfonic Acid by Menstruating Women: Evidence from Population-based Pharmacokinetic Modeling"

We thank Verner and Longnecker[1] for their insightful comments on the rate of menstrual blood serum loss (G_{mbl}, mL/kg-bw/year). We agree with the authors that the parameter G_{mbl} is subject to uncertainty and that there are limited literature available for characterizing the composition and volume of menstrual fluid loss.

In our paper,[2] we assumed that monthly menstrual blood serum loss is 36 mL/month, which amounts to 432 mL/year and G_{mbl} = 6.1 mL/kg-bw/year, assuming a body weight of 71 kg. During our uncertainty and sensitivity analysis, we assigned

difference in the elimination rate of PFOS between men and women. Figure 1 shows the modeled data fits well to the measured data when the adjusted G_{mbl} is applied. When we plotted the modeled vs measured data using the adjusted G_{mbl}, the root mean squared error (RMSE) = 0.04, which is smaller than the RMSE estimated from the G_{mbl} of Wong et al.,[2] that is, 0.05.

Finally, we acknowledge the lack of information for parametrizing G_{mbl} and are therefore grateful for Verner and Longnecker's[1] contribution. In the absence of even newer

2022 – Update PFOS & model other PFAS

1) New NHANES data for 2011, 2013 and 2015, and 1999 data retracted (!)

2) Assume menstrual blood loss accounts for difference between men & women and treat V_D as a fitting parameter

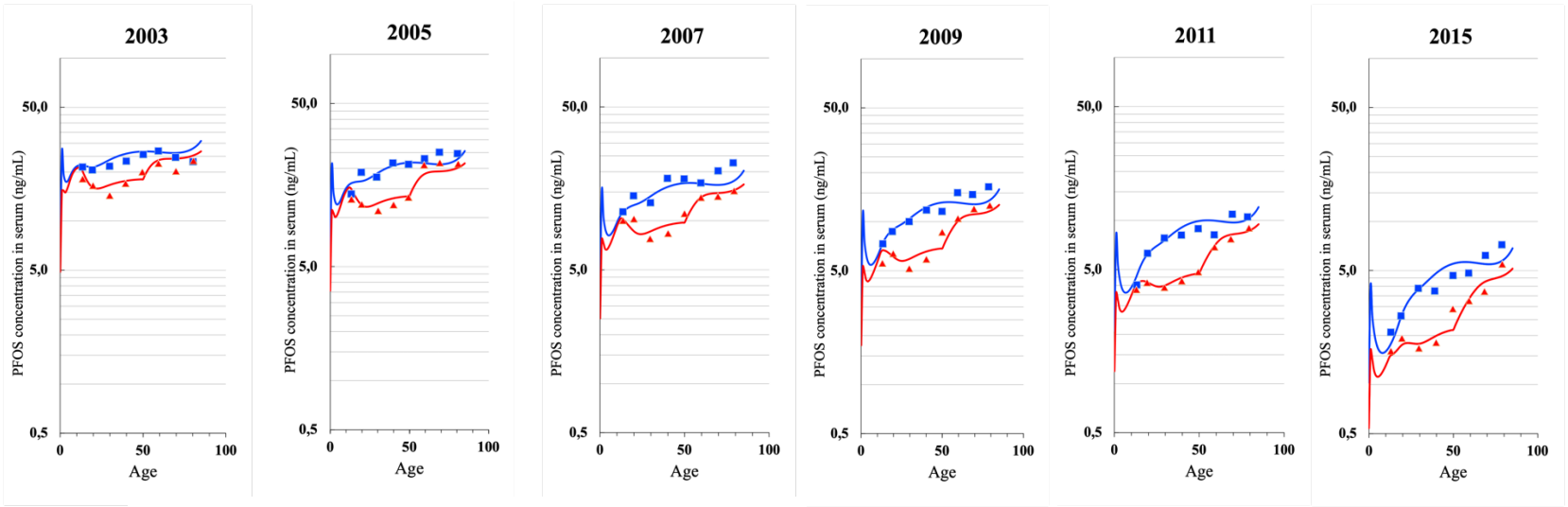
PFOS

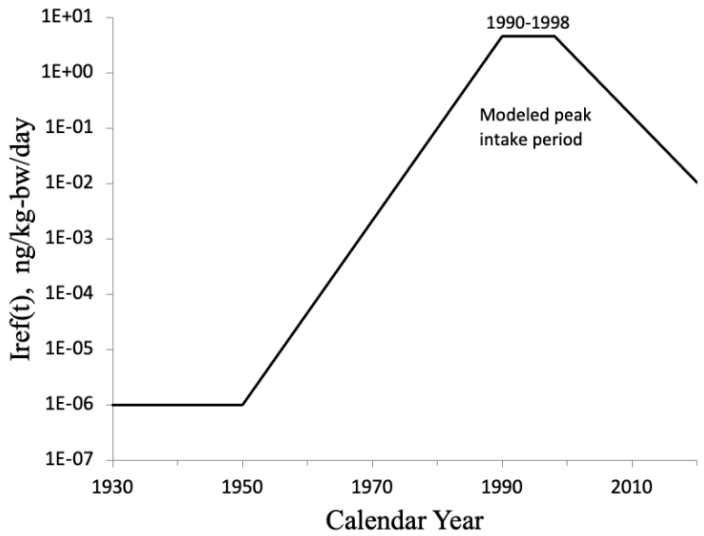
Men, empirical US NHANES

Women, empirical US NHANES

Men, modeled

Women, modeled





Intrinsic elimination half-life

Men: 4.3 years

Women: 4.0 years

V_D: 256 mL/kg

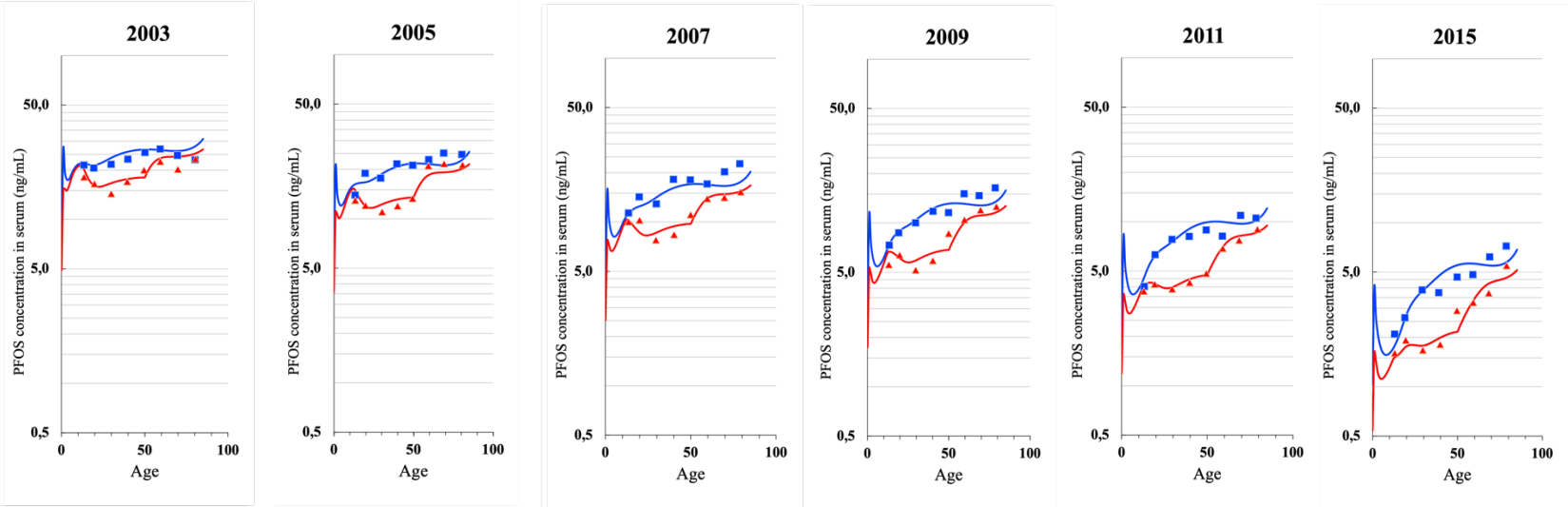
PFOS

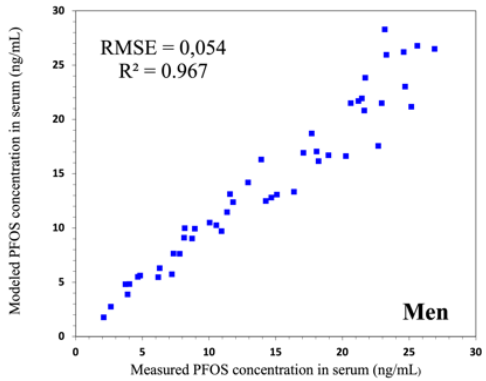
Men, empirical US NHANES

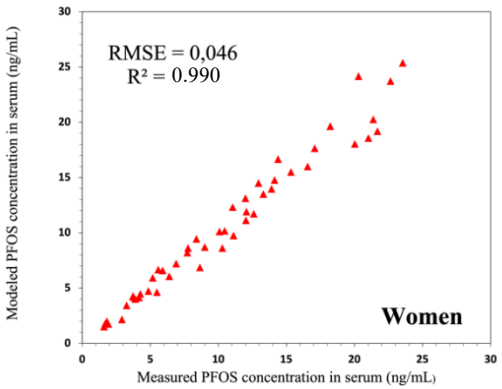
Women, empirical US NHANES

Men, modeled

Women, modeled







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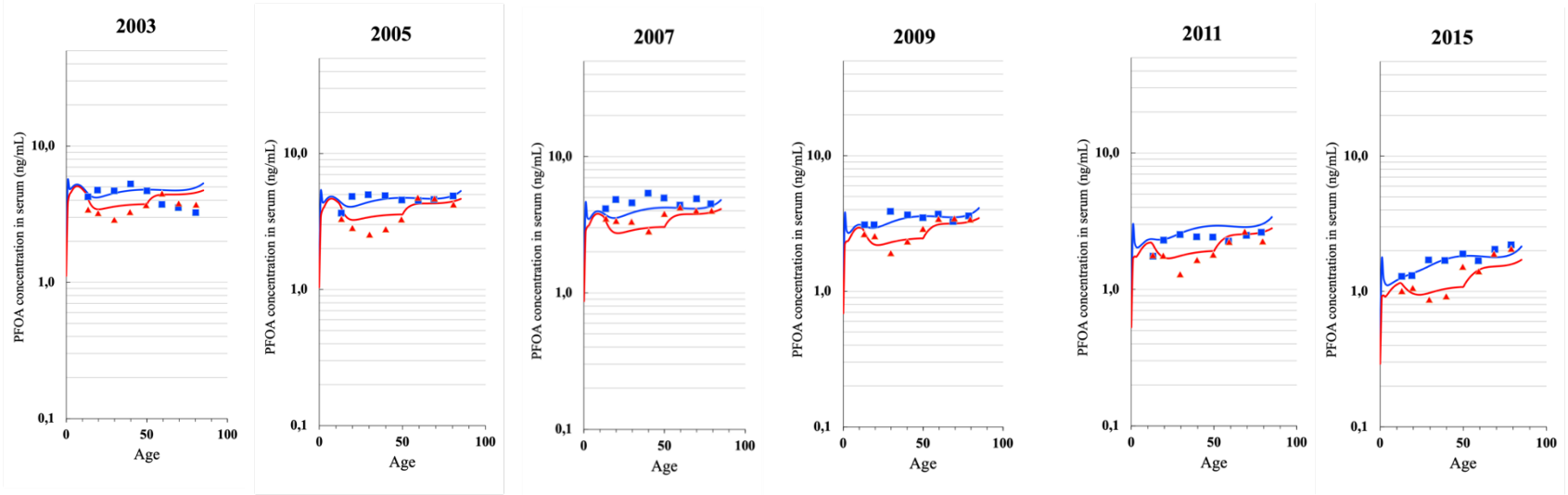
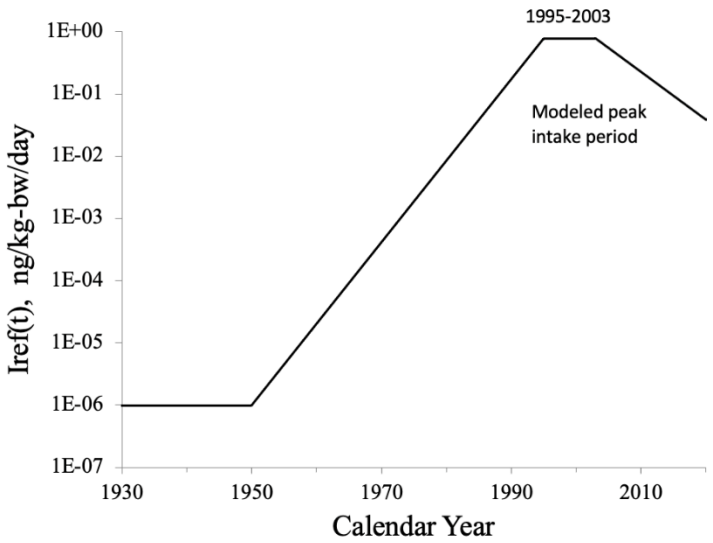




Intrinsic elimination half-life

Men: 3.5 years

Women: 3.1 years

V_D: 261 mL/kg

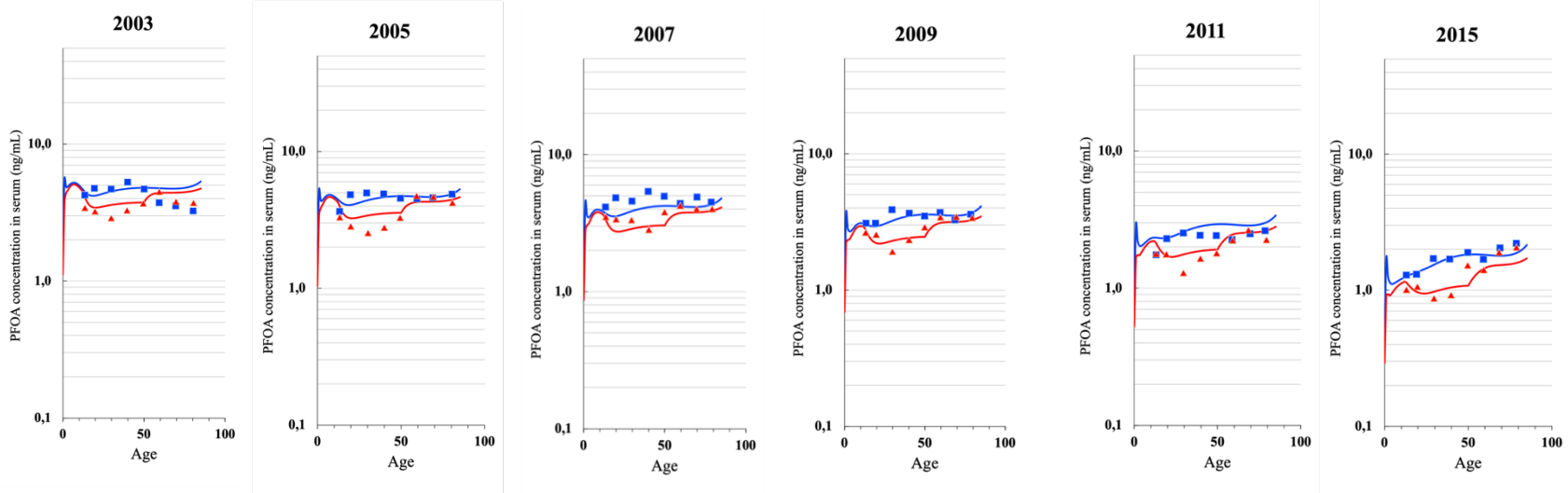
PFOA

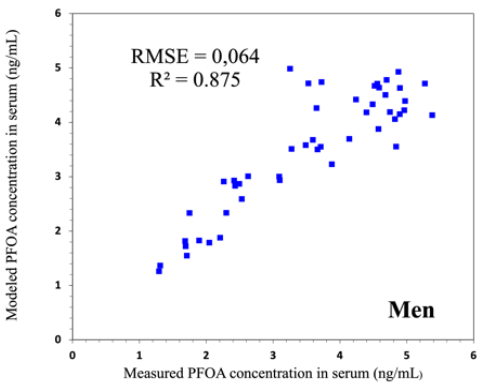
Men, empirical US NHANES

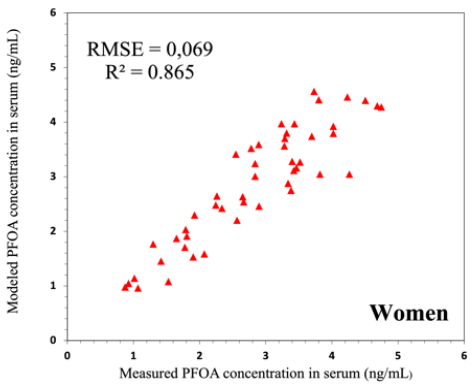
Women, empirical US NHANES

Men, modeled

Women, modeled







Intrinsic elimination half-life

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V_D: 261 mL/kg

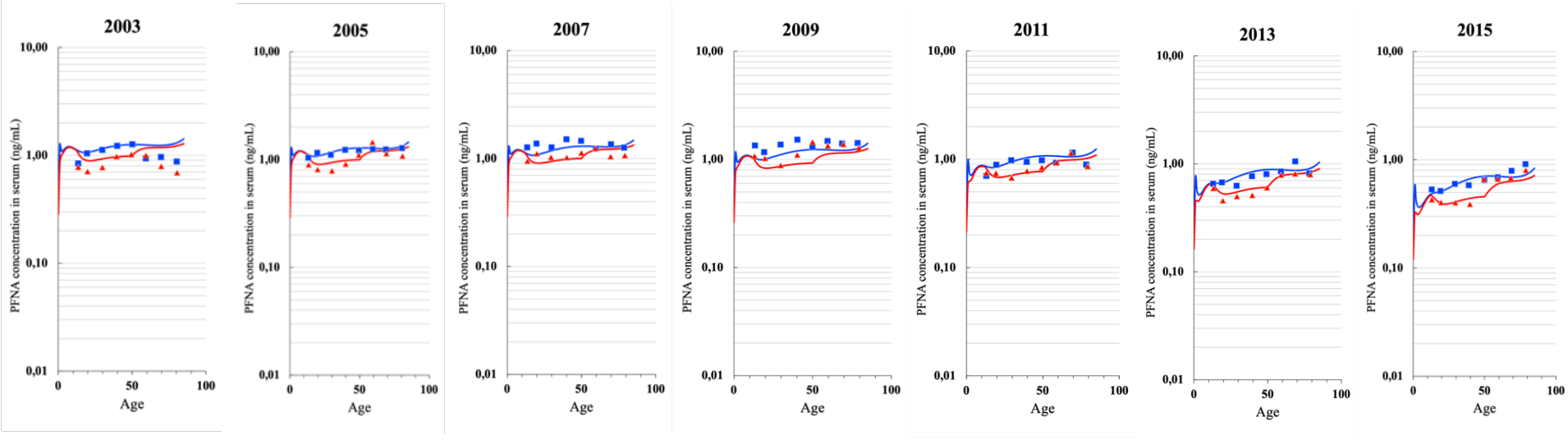
PFNA

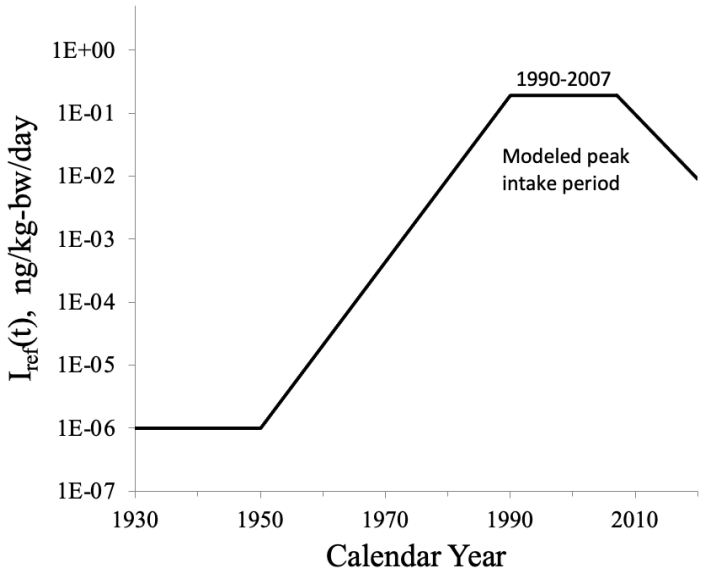
Men, empirical US NHANES

Women, empirical US NHANES

Men, modeled

Women, modeled





Intrinsic elimination half-life

Men: 4.1 years

Women: 3.8 years

V_D: 305 mL/kg

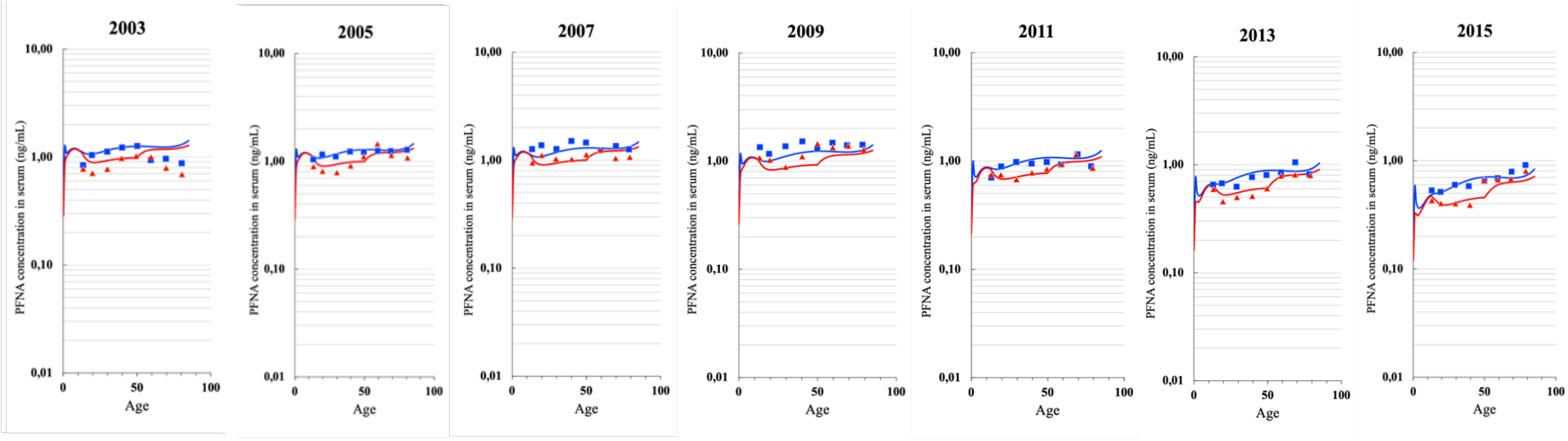
PFNA

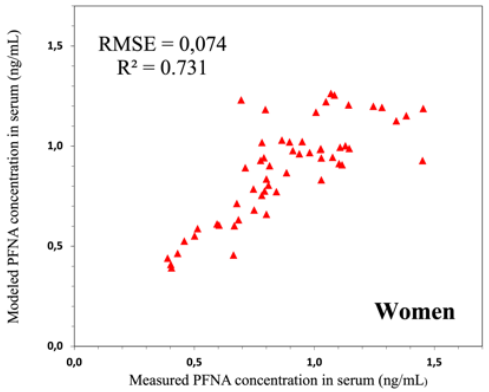
Men, empirical US NHANES

Women, empirical US NHANES

Men, modeled

Women, modeled





Intrinsic elimination half-life

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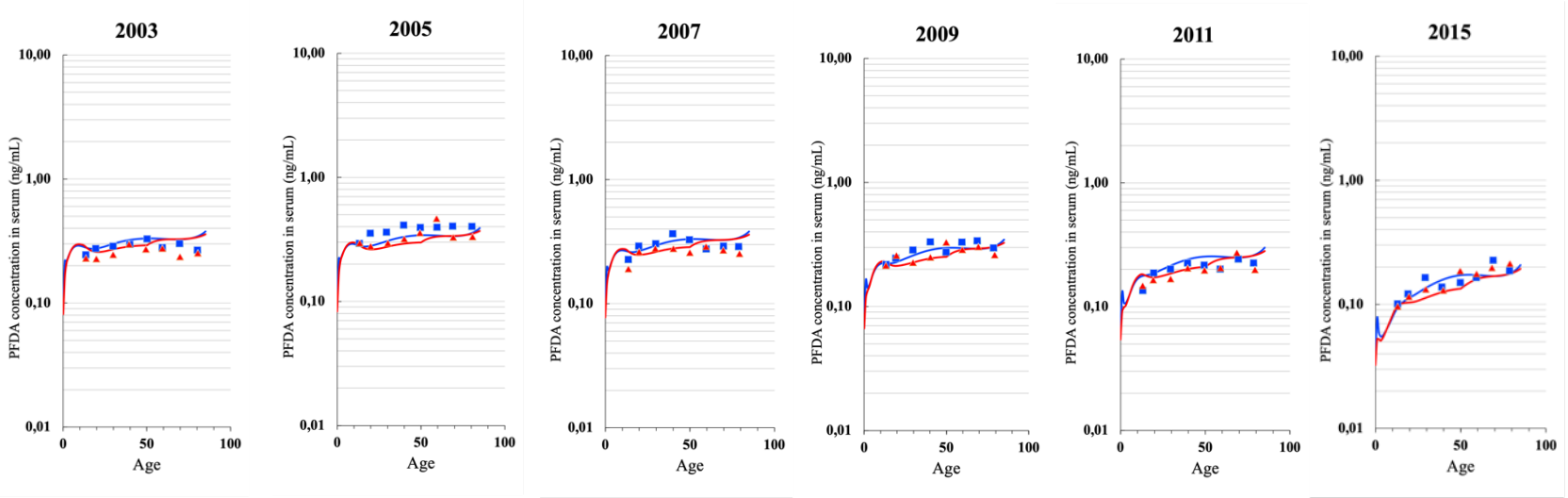
PFDA

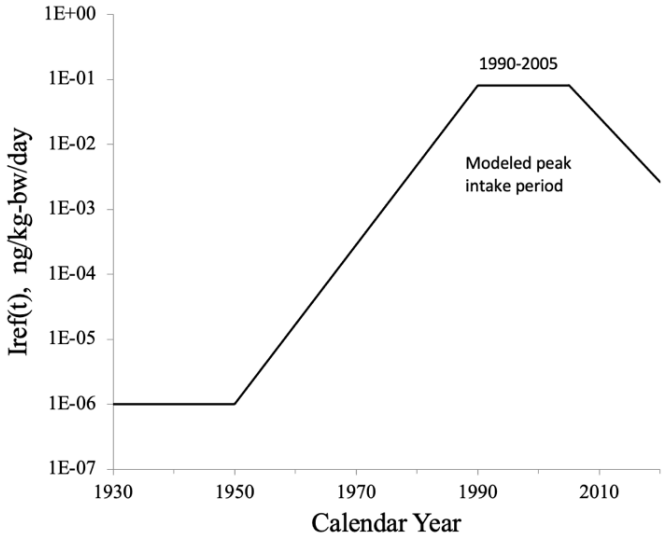
Men, empirical US NHANES

Women, empirical US NHANES

Men, modeled

Women, modeled





Intrinsic elimination half-life

Men: 5.0 years

Women: 5.0 years

V_D: 590 mL/kg

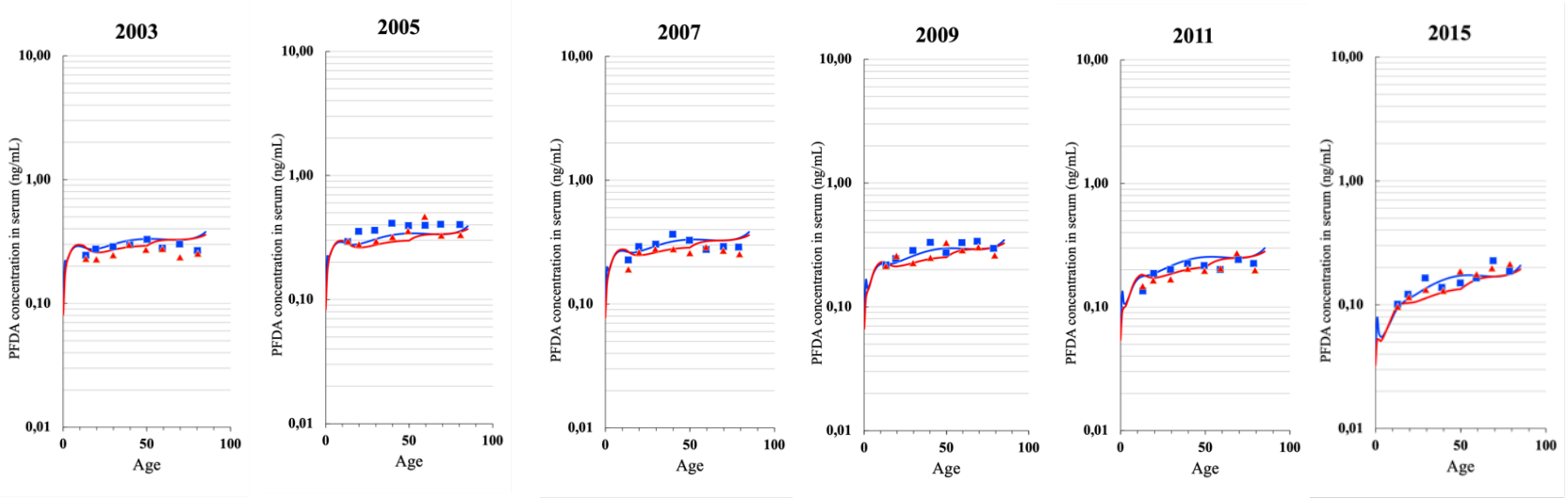
PFDA

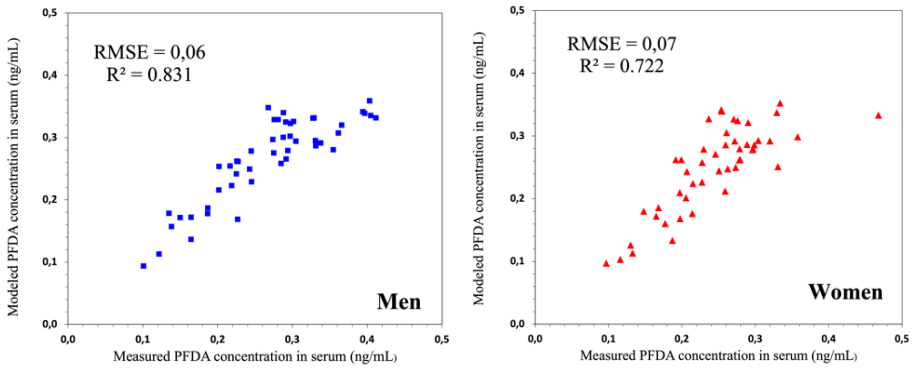
Men, empirical US NHANES

Women, empirical US NHANES

Men, modeled

Women, modeled





Intrinsic elimination half-life

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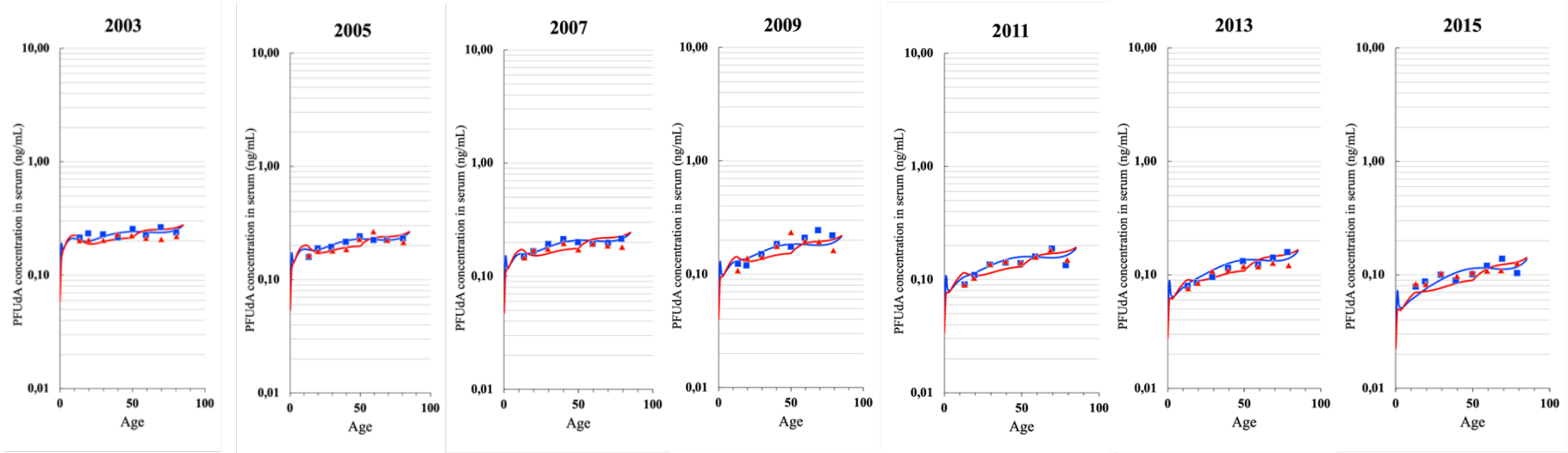
PFUdA

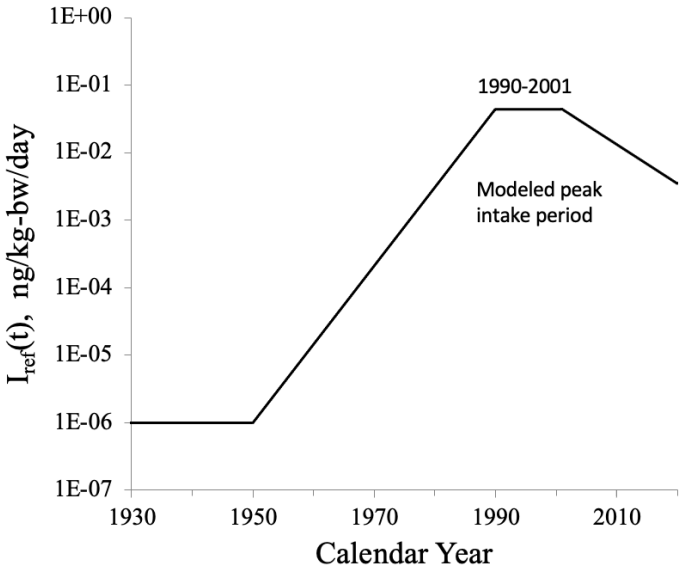
Men, empirical US NHANES

Women, empirical US NHANES

Men, modeled

Women, modeled





Intrinsic elimination half-life

Men: 4.9 years

Women: 5.2 years

V_D: 412 mL/kg

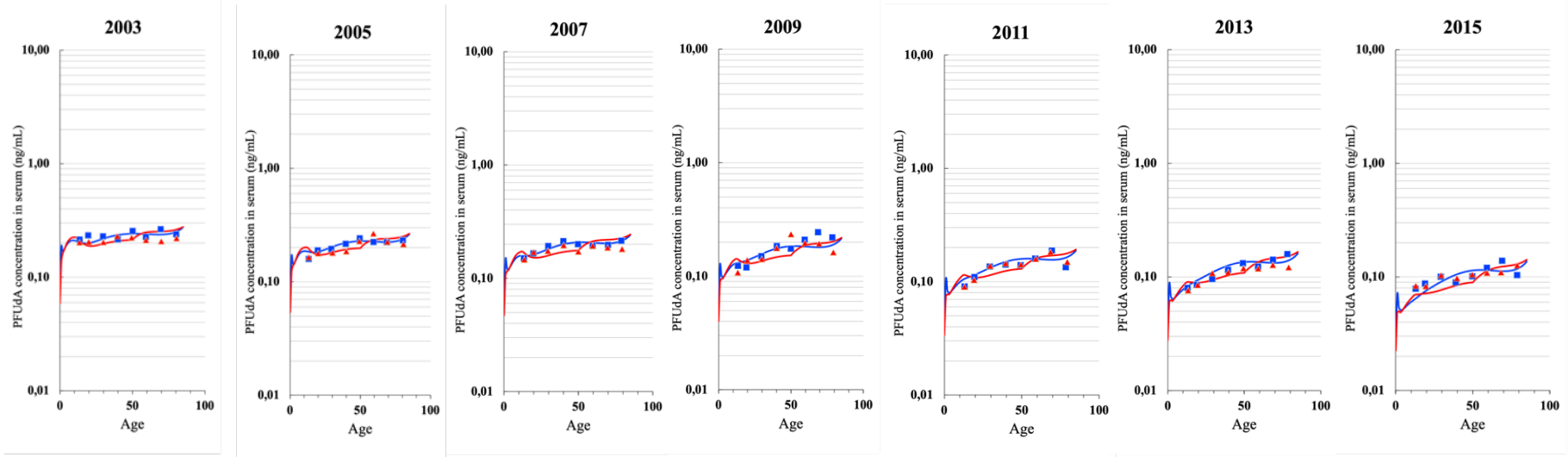
PFUdA

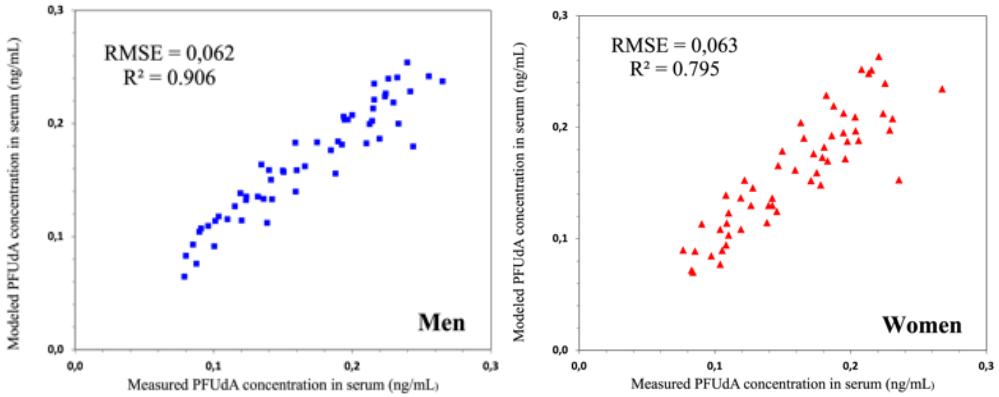
Men, empirical US NHANES

Women, empirical US NHANES

Men, modeled

Women, modeled





Intrinsic elimination half-life

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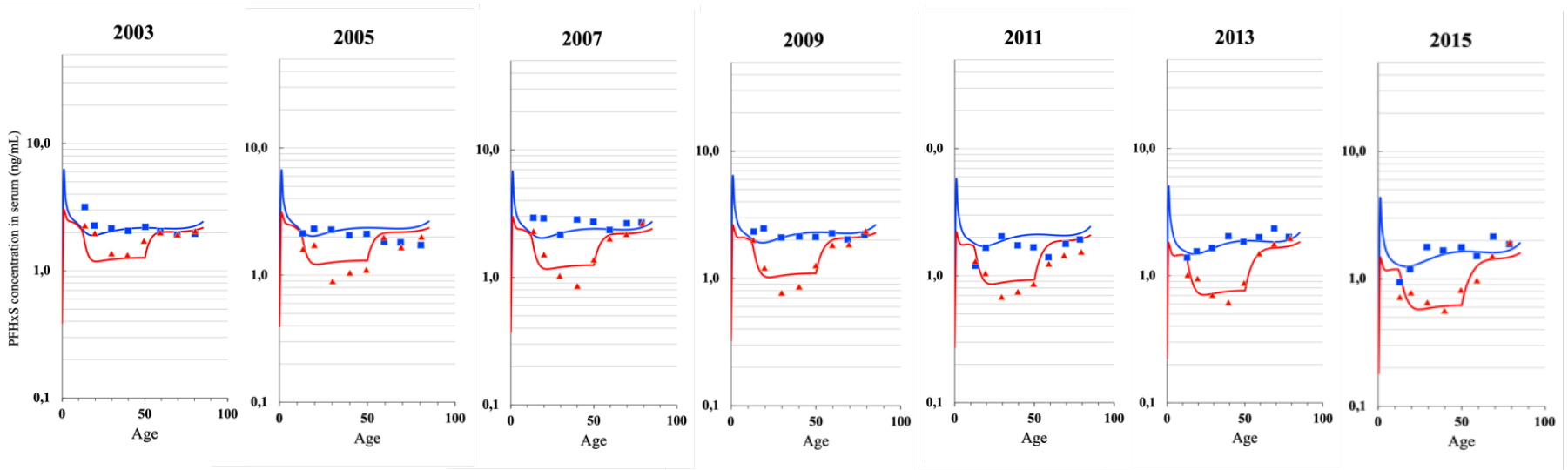
PFHxS

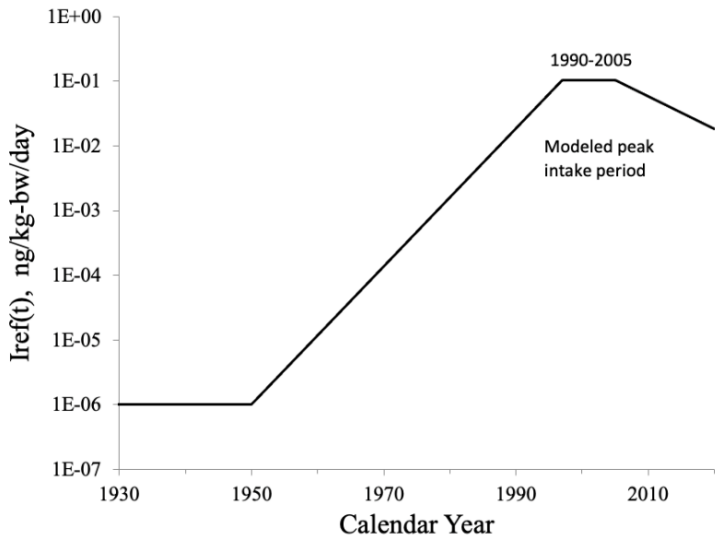
Men, empirical US NHANES

Women, empirical US NHANES

Men, modeled

Women, modeled





Intrinsic elimination half-life

Men: 4.3 years

Women: 3.9 years

V_D: 84 mL/kg

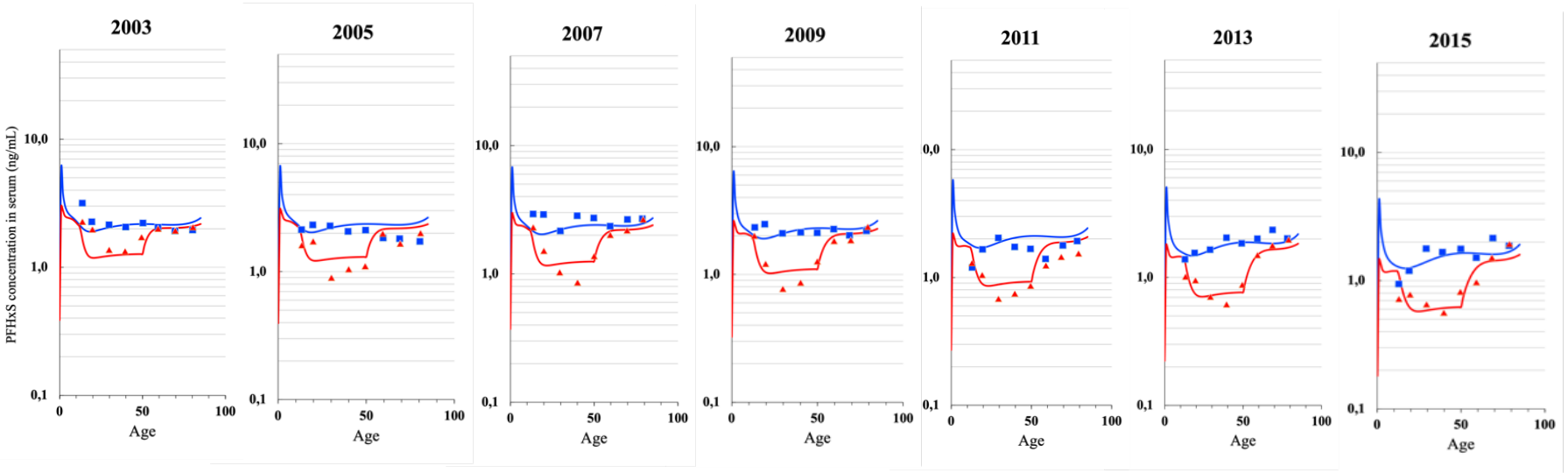
PFHxS

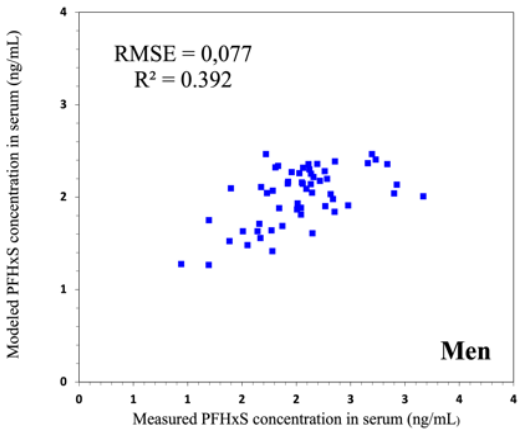
Men, empirical US NHANES

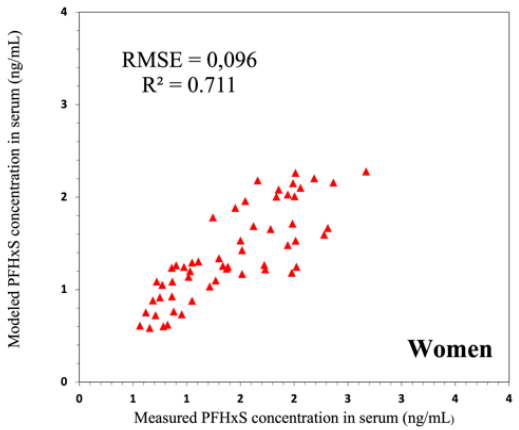
Women, empirical US NHANES

Men, modeled

Women, modeled







Intrinsic elimination half-life

Men: 4.3 years

Women: 3.9 years

V_D: 84 mL/kg

Summary - V_D

Compound	Modeled human volume of distribution (V_D) mL/kg	Reported volume of distribution (V_D), study mL/kg
PFOS	256	**230 human** (Thompson, et al., 2010) 274 (+/- 28) female monkeys, (*Chang et al. 2012*)
PFOA	261	**170 human** (Thompson, et al., 2010) 198 (+/- 69) female monkeys (*Butenhoff et al. 2004)*
PFNA	305	243 (+/-49) female rat (Ohmori et al. 2003) 46 (+/- 4) female rat *(Kim et al. 2019)*
PFHxS	84	213 (+/- 28) female monkeys. (*Sundström et al, 2012)*
PFDA	591	441 (+/- 55) female rats (Ohmori et al. 2003)
PFUdA	412	250 (+/- 80) female rats (*Fuji et al. 2015)*

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Highly uncertain – No "signal" to model

Summary - V_D

Also a modeling study!

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2022 – Model CARES Biomonitoring Data

1) 2018 – LA County 400 serum samples

2) 2019 – Southern California 350 serum samples

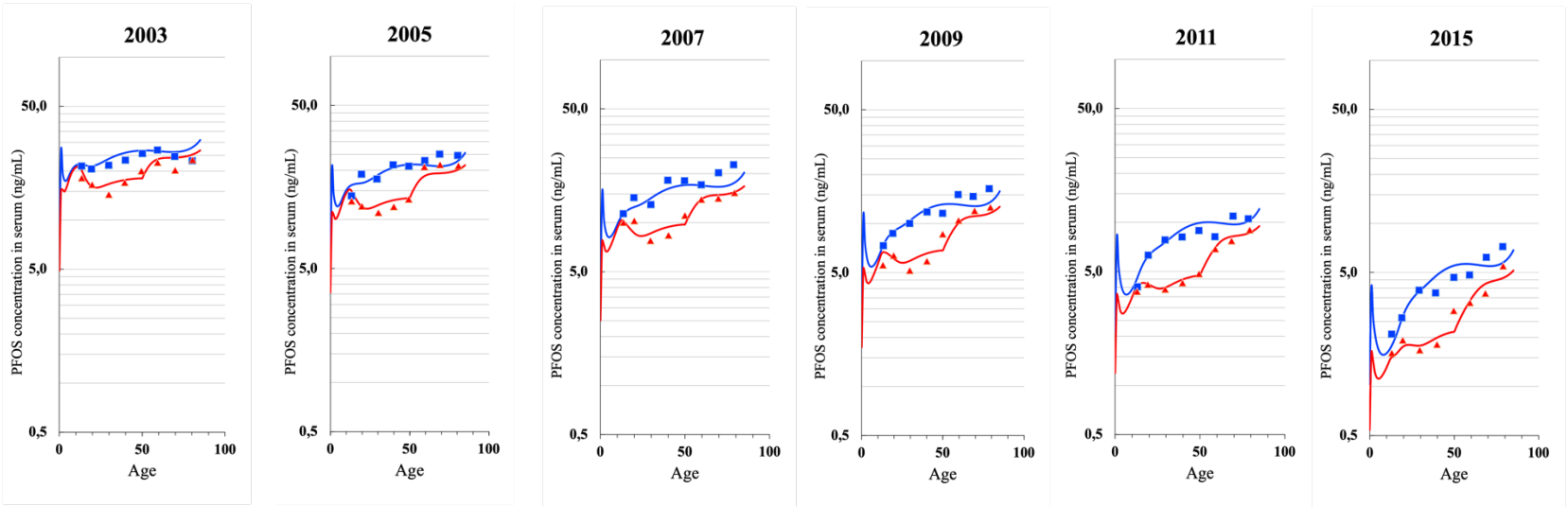
PFOS

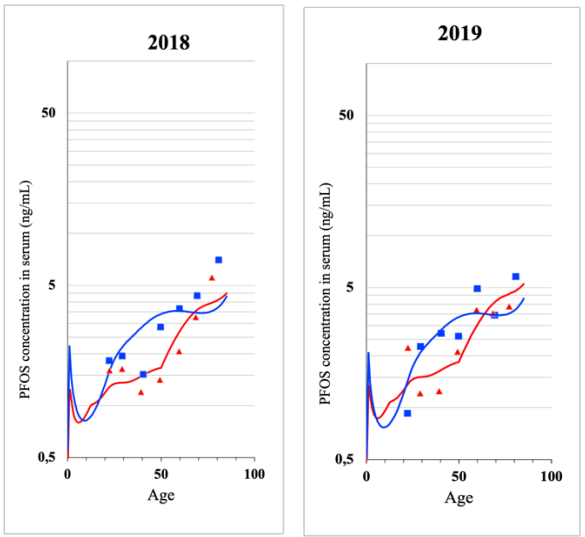
Men, empirical US NHANES

Women, empirical US NHANES

Men, modeled

Women, modeled





CARE Study

California Regional Exposure Study

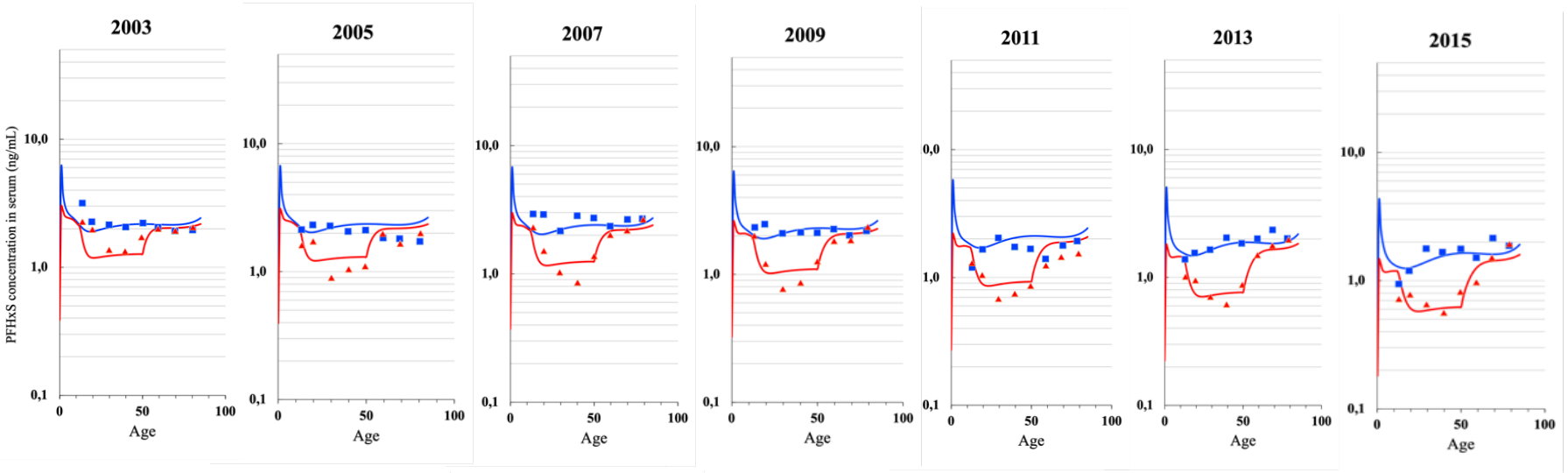
PFHxS

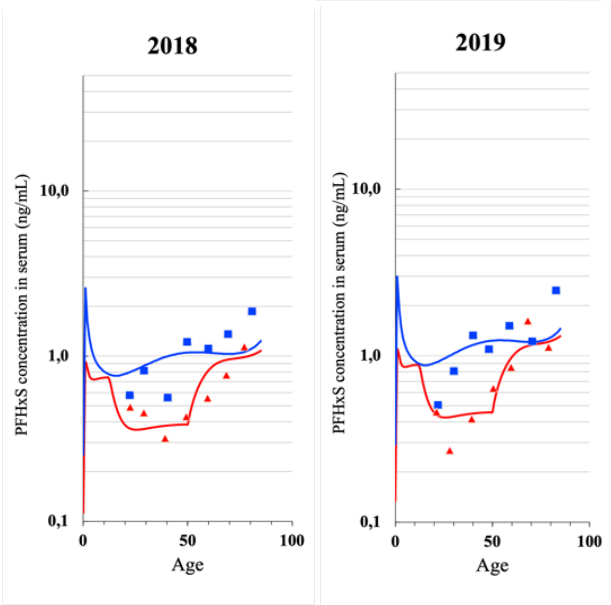
Men, empirical US NHANES

Women, empirical US NHANES

Men, modeled

Women, modeled





CARE Study

California Regional Exposure Study

Modeling CARES Data

- We assumed V_D and k_{elim} from the NHANES population would also apply to the CARES populations
- Tested the hypothesis that intake of PFAS by the CARES populations was different than NHANES…
  - No obvious evidence of that!

Conclusions

- New population-based pharmacokinetic modeling of NHANES biomonitoring data for 6 PFAS provides estimates of
  - Intake levels and trends
  - Intrinsic elimination half-lives (k_{elim})
  - Volumes of distribution (V_D)

Acknowledgments

- Swiss Federal Office for the Environment
- FORMAS

Even better with the correct composition of menstrual blood!