Refining Human Risk Assessment through Comparisons of Human and Animal Internal Dosimetry: PFOA as a Case Study

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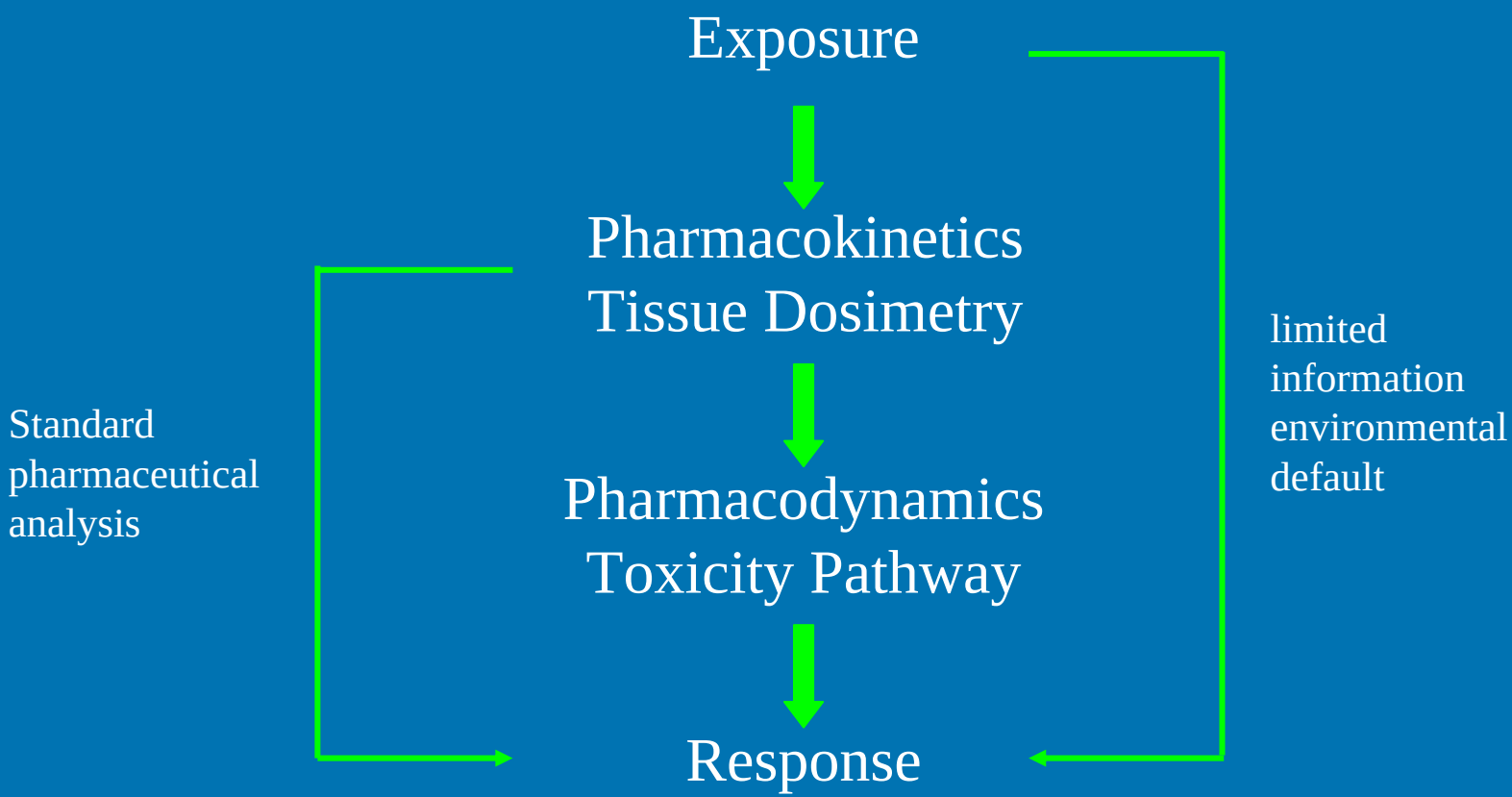
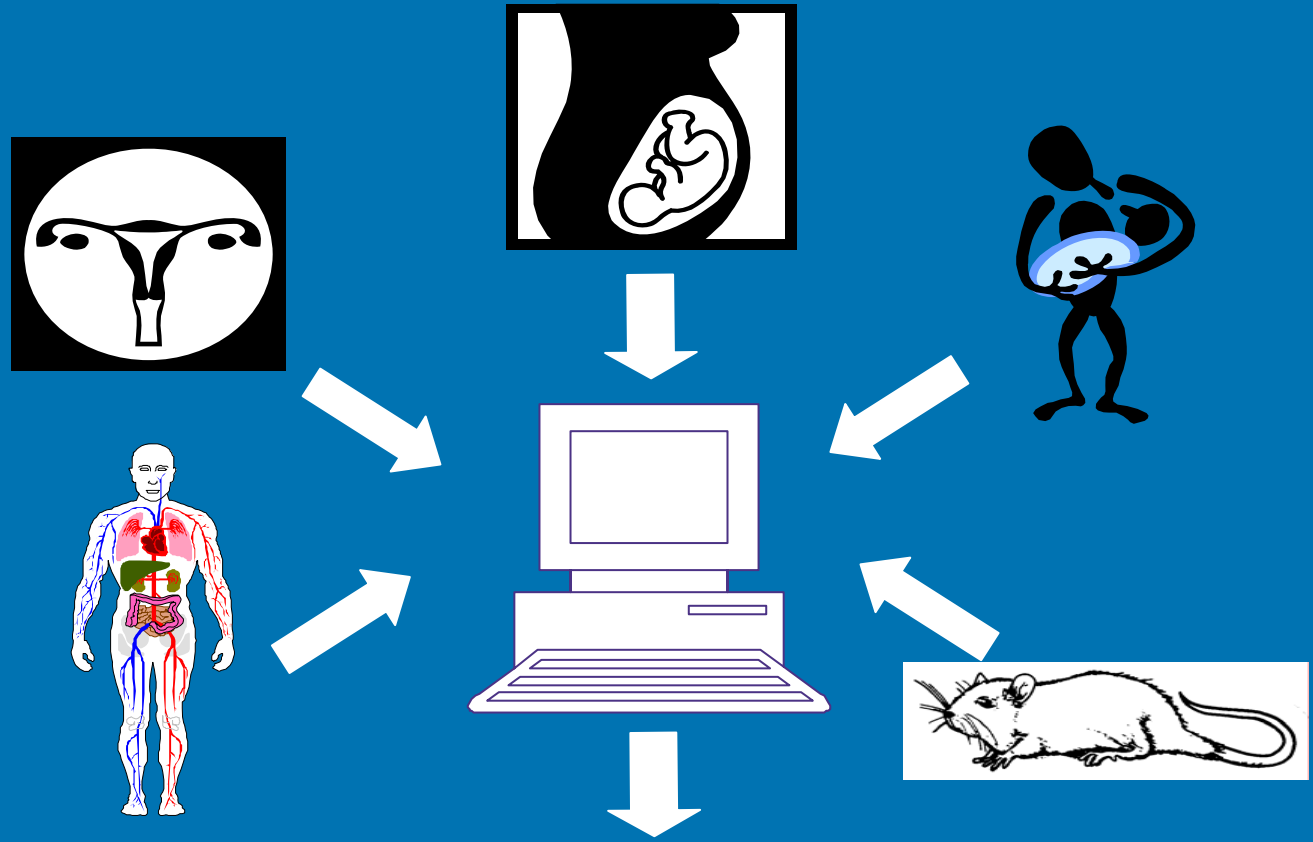
Risk Assessment in a Mode of Action Context





Cross Species, cross lifestage extrapolations

Perfluorooctanoic Acid (PFOA)

$CF_3(CF_2)_6COOH$

Background

- Unique chemical properties which make perfluorinated compounds commercially valuable
- However, some members of the class:
  - Persistent in the environment
  - Persistent in many biological organisms
  - Toxic to many biological organisms
  - Present in blood of the general US population

Database on PFOA for Human Health Risk Assessment

- Epidemiology studies in workers
- Data in rodents and monkeys
  - Carcinogenicity in rats
  - Systemic Toxicity in rats and monkeys
  - Developmental and Reproductive Toxicity in rabbits and rats
  - Immunotoxicity in mice
  - Pharmacokinetics in rats and monkeys
- Human biomonitoring data

Animal Carcinogenicity Data

- Two 2-year bioassays in Sprague-Dawley rats
  - liver adenomas, Leydig cell adenomas , and pancreatic acinar cell tumors, mammary tumors?
- Quantitative analyses were not presented in the draft risk assessment as evidence was considered 'suggestive'.
- Quantitative analyses could use blood dose metrics for chronic exposure (e.g., AUC)

Endpoints Used in Risk Assessment for Adult Toxicity

- Cynomolgus monkey
  - liver weight and possible mortality in 6-month study
  - LOAEL = 3 mg/kg-day; no NOAEL
- Male rat
  - F1 body weight from 2-generation reproductive toxicity study
  - LOAEL = 1 mg/kg-day; no NOAEL
- Female rat
  - body weight from 2-year study
  - NOAEL = 10 mg/kg-day

Developmental Endpoints Used in Risk Assessment

- All endpoints are from a rat 2-generation reproductive toxicity study
  - Decreased preweaning litter body weight in F1 pups – NOAEL = 10 mg/kg-day
  - Decreased postweaning body weight in F1 males – NOAEL = 3 mg/kg-day
  - Decreased postweaning body weight in F1 females – NOAEL = 10 mg/kg-day
  - Increased postweaning mortality and delayed sexual maturation in F1 males and females – NOAEL = 10 mg/kg-day
- Unknown whether prenatal, lactational and/or postweaning exposures are critical. Therefore, important to assess risks for each of these periods.

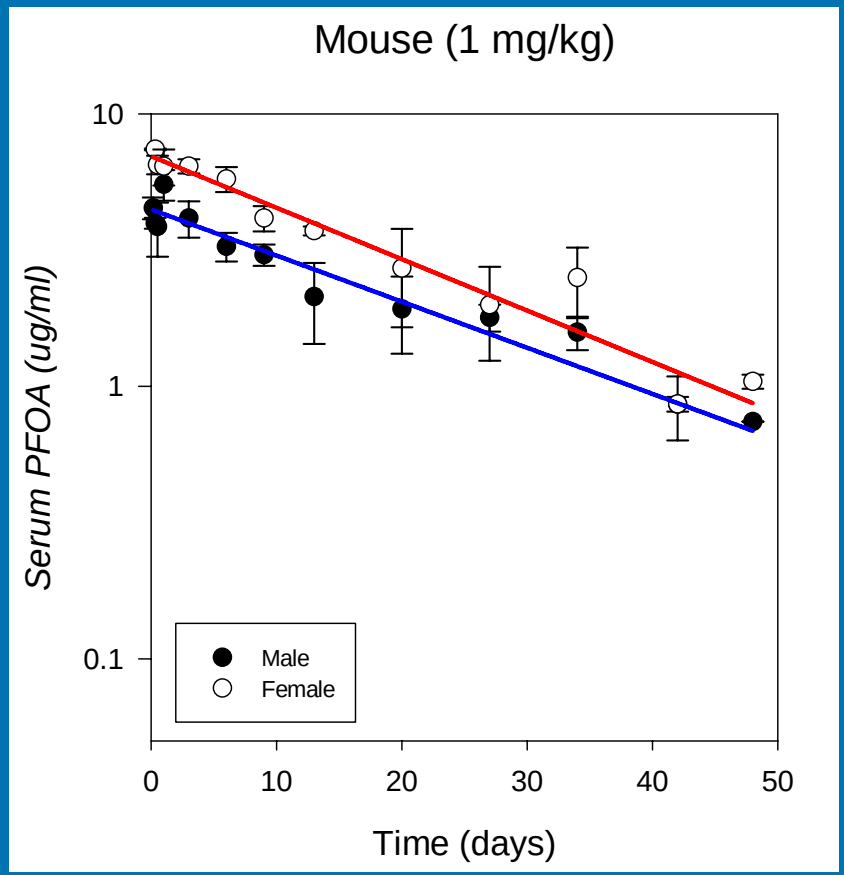
Pharmacokinetics and Distribution

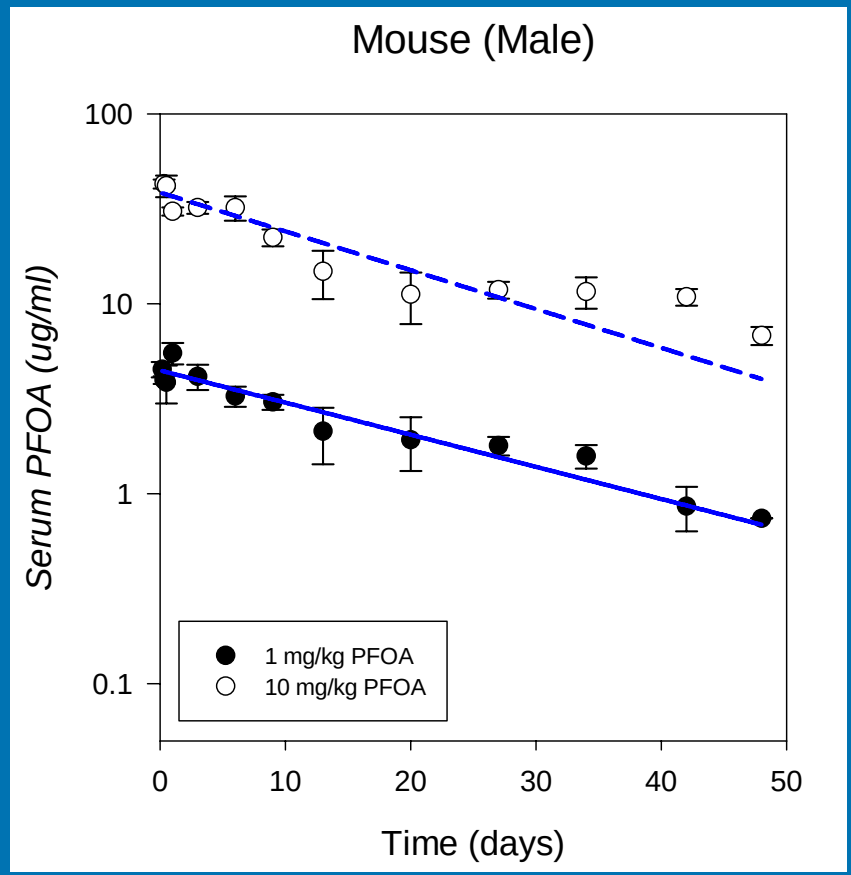
- Well absorbed
- Not metabolized
- Distributed mainly in serum and liver
- Urinary & biliary elimination
- Enterohepatic circulation

Pharmacokinetics and Distribution

- Half-life:
  - Female rats – estimates range from 2.8 – 16 hours
  - Male rats – estimates range from 5.75 – 8.4 days
  - Elimination in young male and female rats is developmentally regulated
  - Male & female mice – 12 – 20 days
  - Female monkey – 20.9 days
  - Male monkey – 32.6 days
  - Human – 4.4 years (Burris et al., 2002)

Mouse Oral Gavage PK





Lau C, Strynar MJ, Lindstrom A, Hanson RG, Thibodeaux JR and Barton HA. (2005) Pharmacokinetic evaluation of perfluorooctanoic acid in the mouse. Toxicol Sci 84, S-1 (The Toxicologist) Abstract #1232.

Risk Assessment Approach

- Margin of Exposure (MOE) compares animal NOAEL/LOAEL with human exposure to evaluate potential for adverse outcomes.

$$\frac{\text{Exposure Dose NOAEL Rat (mg/kg/day)}}{\text{Exposure Dose Human (mg/kg/day)}} \qquad \frac{\text{Internal Dose NOAEL Rat (AUC)}}{\text{Internal Dose Human (AUC)}}$$

Risk Assessment Approach

- Human blood concentrations have been measured. Apply directly or assume steady state.
- Animal blood concentrations in toxicity studies or in pharmacokinetic studies permit prediction of NOAEL/LOAEL blood concentrations.

MOE
Adult Toxicity

- Monkey Data
  - Steady-state for liver and mortality (LOAEL)

    Steady-state for adult humans

- Male Rat Data
  - AUC for body weight (LOAEL 2-gen)

    AUC for adult humans

- Female Rat Data
  - AUC for body weight (NOAEL 2-year)

    AUC for adult humans

MOE: Developmental Toxicity

- Prenatal Rat Data
  - Cmax or AUC pregnant rat male pup body weight (NOAEL)

    Css or AUC for adult human females

- Lactation Rat Data – MOE not calculated

- Postweaning Rat Data
  - AUC for 4-week weanlings pup mortality (NOAEL)

    AUC for humans age 2-12

  Delay Sexual Maturation and Postweaning Body Weight Rat Data
  - AUC for 4-5 week female delay/body weight (NOAEL)

    AUC for humans age 2-12
  - AUC for 4-8 week male delay/body weight (NOAEL)

    AUC for humans age 2-12

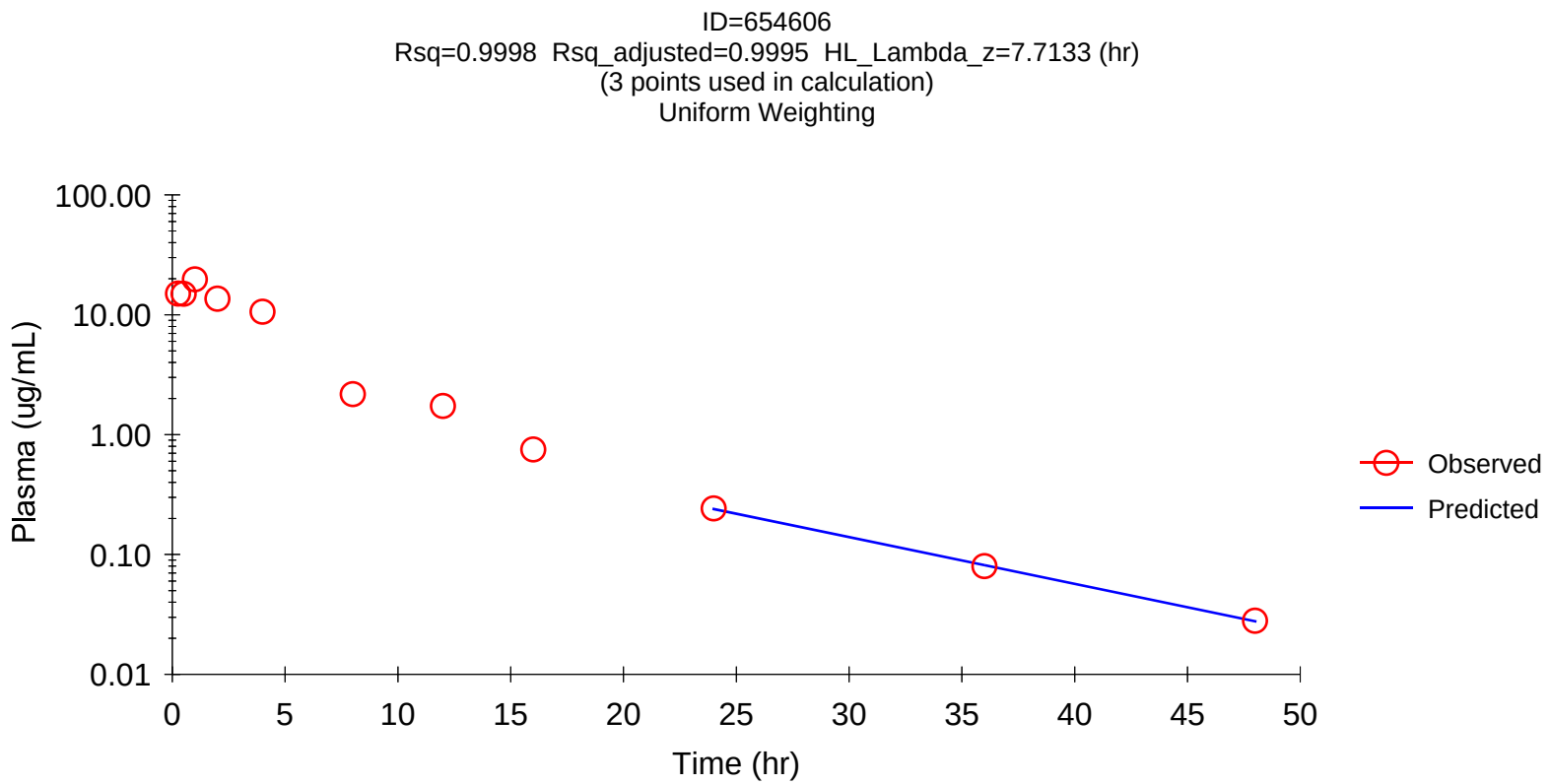
Predicting Rat Dose Metrics

- Measured blood levels in some toxicity studies:
  - steady state analysis for males would be possible,
  - rapid clearance in females precludes similar analysis
- Use pharmacokinetic model to predict blood dose metric
  - AUC (chronic, two-generation)
  - Cmax (two-generation)

PK Model Options

- Noncompartmental analysis
  - Used in several reports of rat PK
- Compartmental analysis
  - Human blood concentrations interpretable as approximating steady state levels given estimates of long half life
  - Extensive rat PK studies permit estimation of parameters in compartmental models (4 rats/dose/sex, 0.1, 1, 5, 25 mg/kg oral, 1 mg/kg intravenous)
- PBPK Model
  - Potentially gives comprehensive description of determinants of kinetics,
  - Very limited data available in humans and even for rodents appears to require a research effort

Noncompartmental Fitting (model independent)



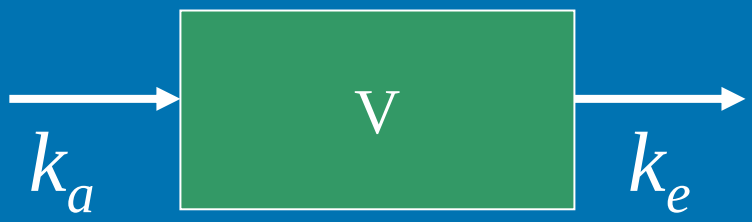
Noncompartmental Modeling AUC_{INF}/D (hr·ug/mL/mg/kg)

	Male	Female
0.1 mg/kg oral	1097 ± 310	31.7 ± 5.9
0.1x mg/kg oral	2111 ± 587	34.4 ± 3.3
1 mg/kg oral	1194 ± 216	39.1 ± 10.2
1 mg/kg iv	1123 ± 100	30.7 ± 6.8
5 mg/kg oral	1222 ± 250	20.8 ± 2.0
25 mg/kg oral	942 ± 285	29.5 ± 7.0

Kemper 2003

One Compartment Model

$$C = \frac{k_a D}{V(k_a - k_e)}(e^{-k_e t} - e^{-k_a t}).$$



AUC = D /(V × ke)

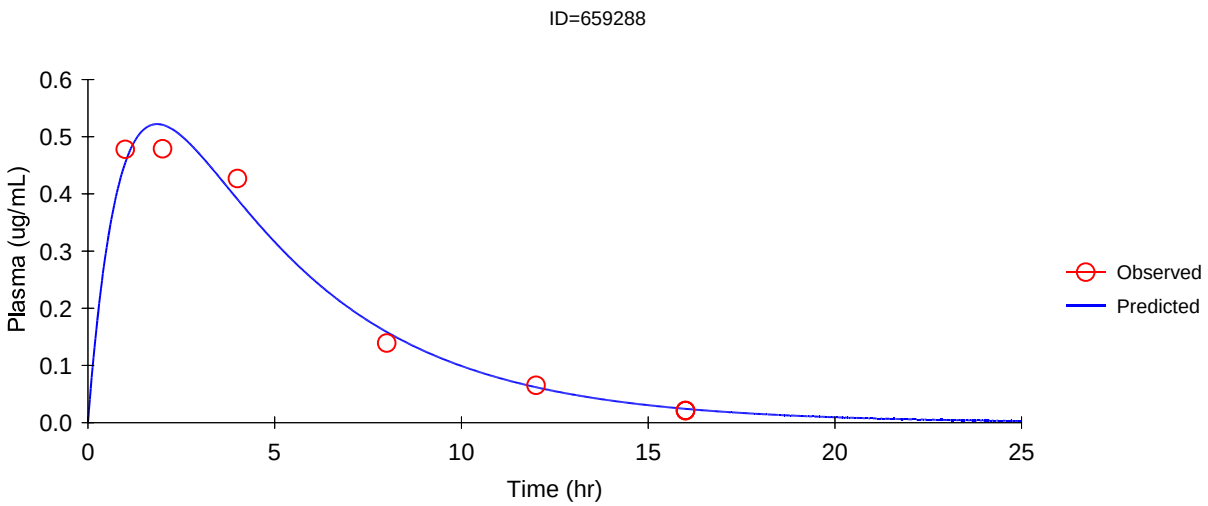
Css = DR /(V × ke)

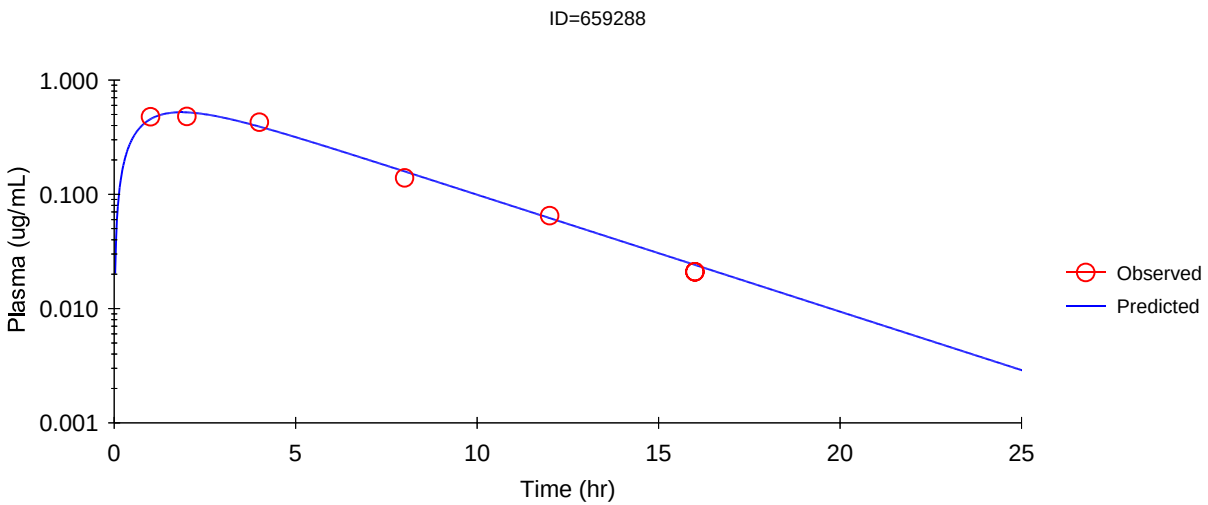
For 100% absorbed

Compartmental Modeling

- 1 compartment model
  - Generally fitted rat PK data well, though there were indications of poorer fitting at late times at higher doses for females, some doses for males, and intravenous dosing
  - Values for volume of distribution, absorption rate, and elimination rate used to predict dose metrics for adults
- 2 compartment model
  - Improved some fits, but parameters not consistent across datasets

Compartmental Modeling
Female CD Rats, 0.1 mg/kg, 1 comp



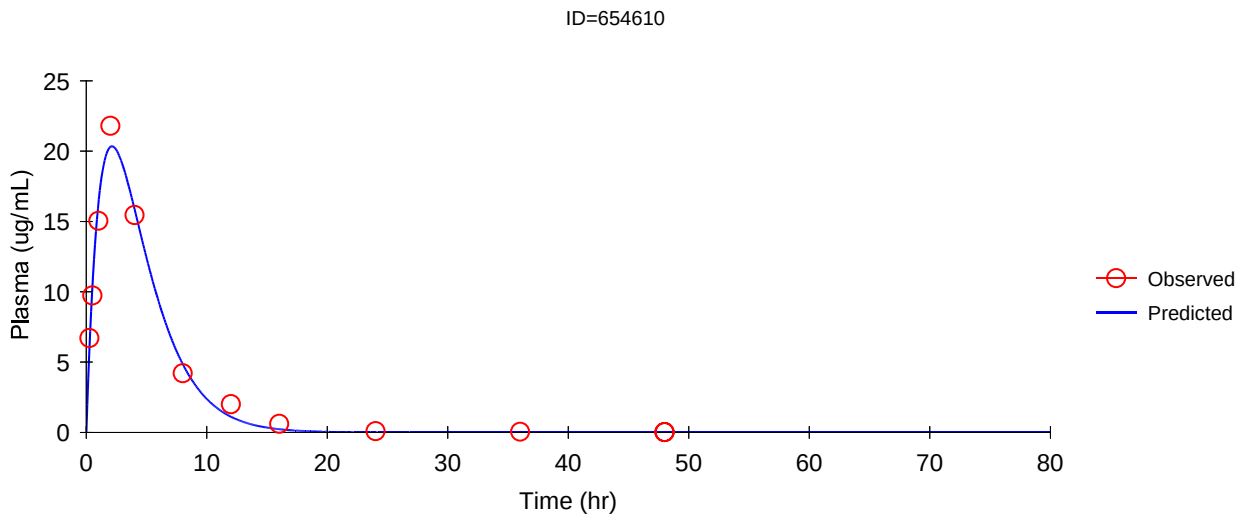


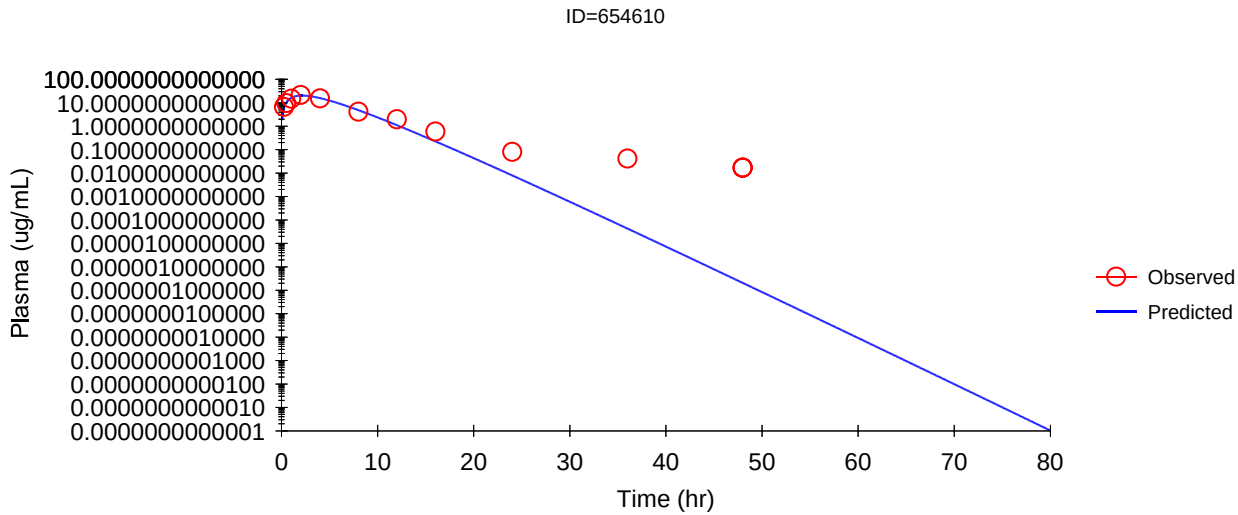
Data:
Kemper 2003

Analysis:

EPA 2005

Compartmental Modeling
Female CD Rats, 5 mg/kg, 1 comp



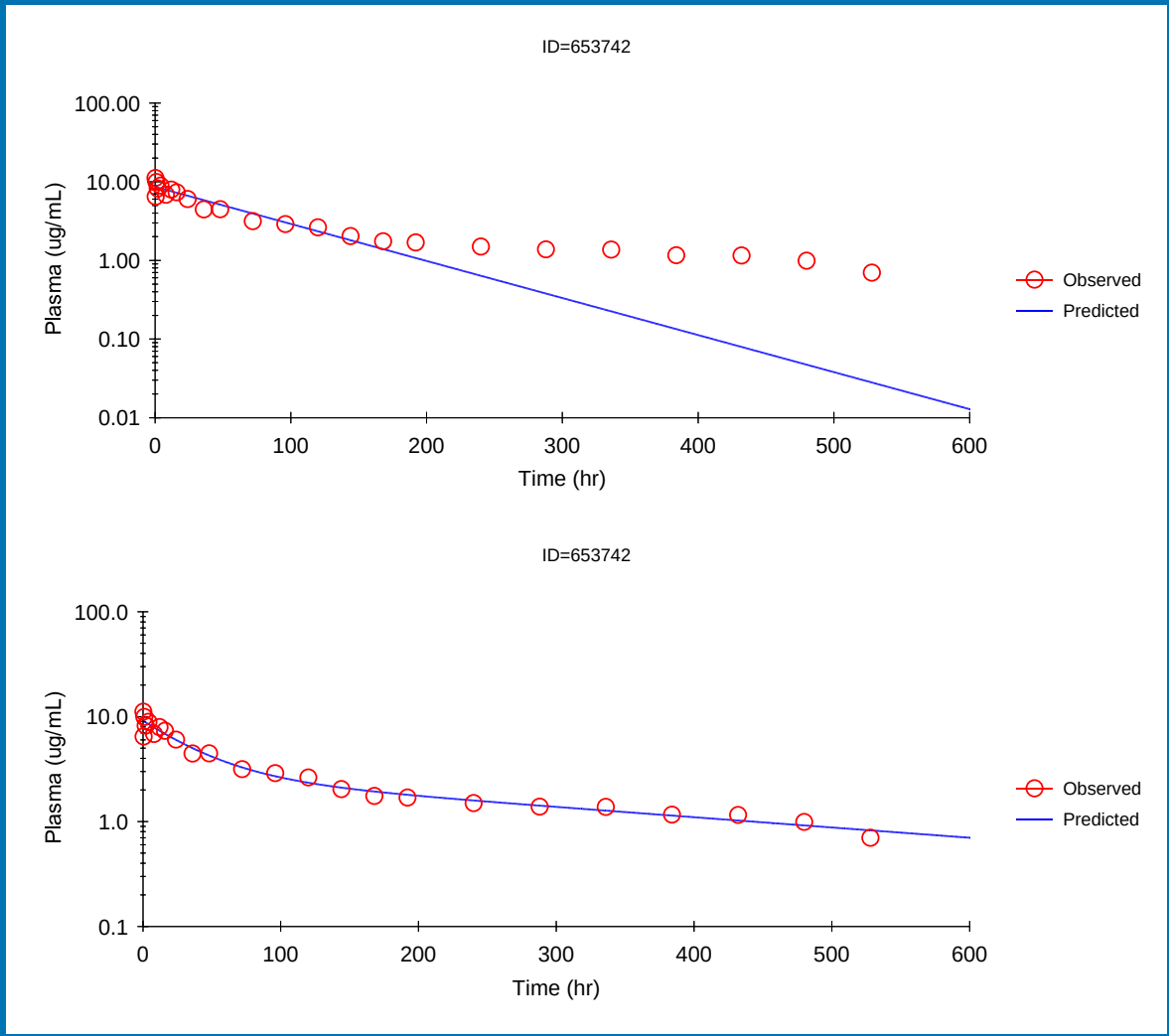


Data:
Kemper 2003

Analysis:

EPA 2005

Compartmental Modeling
Male CD Rats, 1 mg/kg intravenous



Data:
Kemper 2003

Analysis:

EPA 2005

Non- & Compartmental Modeling
AUC_{INF}/D (hr·ug/mL/mg/kg)

	Male	Female
0.1 mg/kg oral*	1097 ± 310	31.7 ± 5.9
0.1x mg/kg oral*	2111 ± 587	34.4 ± 3.3
1 mg/kg oral*	1194 ± 216	39.1 ± 10.2
1 mg/kg iv*	1123 ± 100	30.7 ± 6.8
1 mg/kg **	**1011**	**27.6**
5 mg/kg oral*	1222 ± 250	20.8 ± 2.0
25 mg/kg oral*	942 ± 285	29.5 ± 7.0

*Kemper 2003 **Predicted with 1 Compartment Model

Predicting Chronic Steady State

Diet * (ppm)	Dose Rate (mg/kg/day)	Predicted C_{ss} (µg/mL)**	Measured* Avg 5, 8, 14 wks (µg/mL)
1	0.06	3	7.0
10	0.64	27	47.4
30	1.94	82	87.0
100	6.5	274	148.7

*Palazzolo 1993 **1 Compartment Model

Predicting Female Rat Plasma

Time	Dose Rate (mg/kg/day)	Predicted C (µg/mL)*	Measured (µg/mL)
2 hr	3	12	11±3**
2 hr	10	41	27±4**
24 hr	10	0.35	0.37±0.08 #
2 hr	30	123	67±10**
24 hr	30	1.06	1.0 ±0.4#

*1 Compartment Model

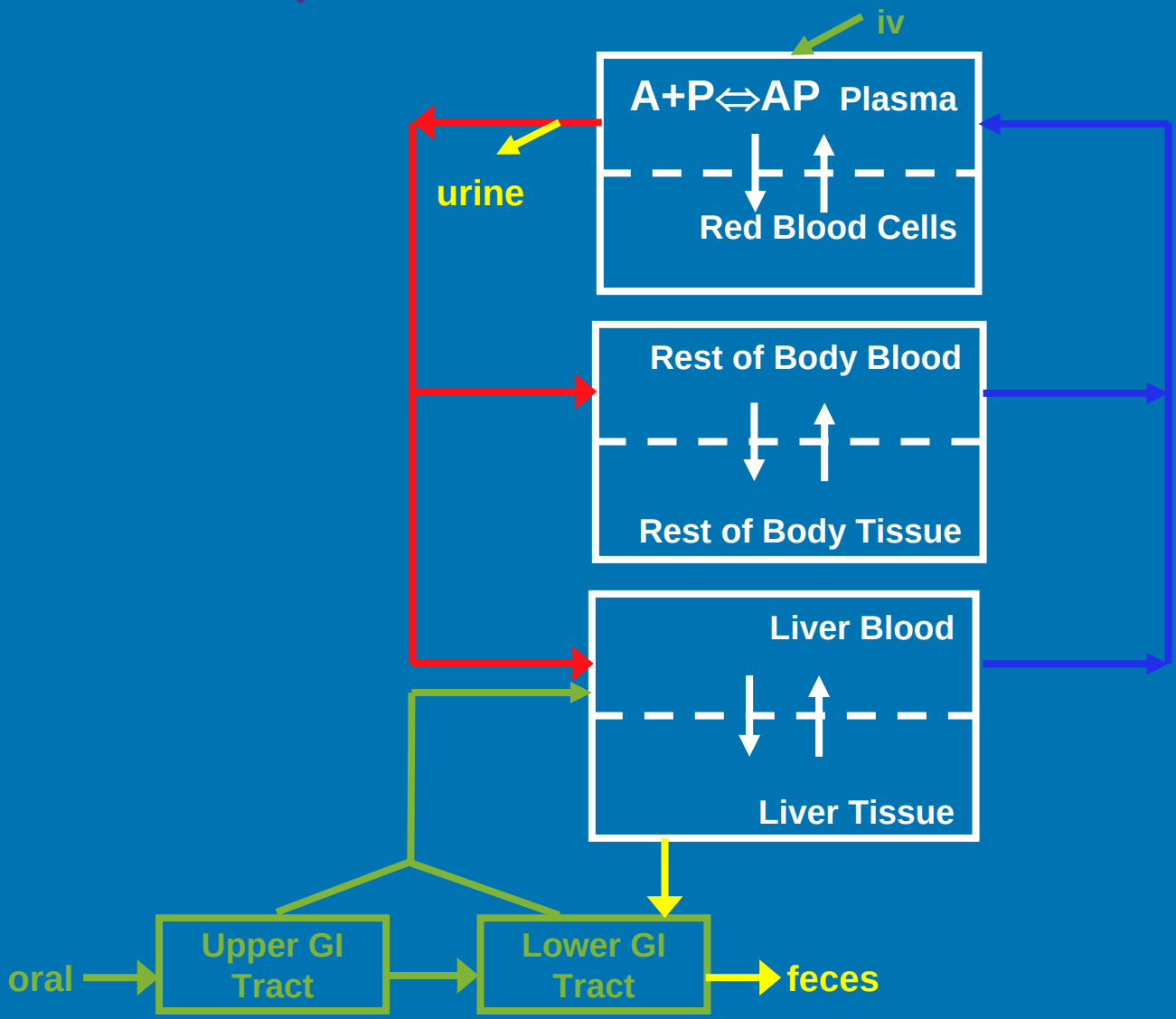
**Mylchreest (2003) pregnant rats

#York (2002) lactating rats

Predicting Rat Dose Metrics

- Have adequate data and satisfactory model (1 compartment) to predict Cmax and AUC for adult male & female rats at NOAEL/LOAEL in toxicity studies to evaluate MOE
- Limited predictions made for weanling pups, but not lactational period, for MOE evaluation

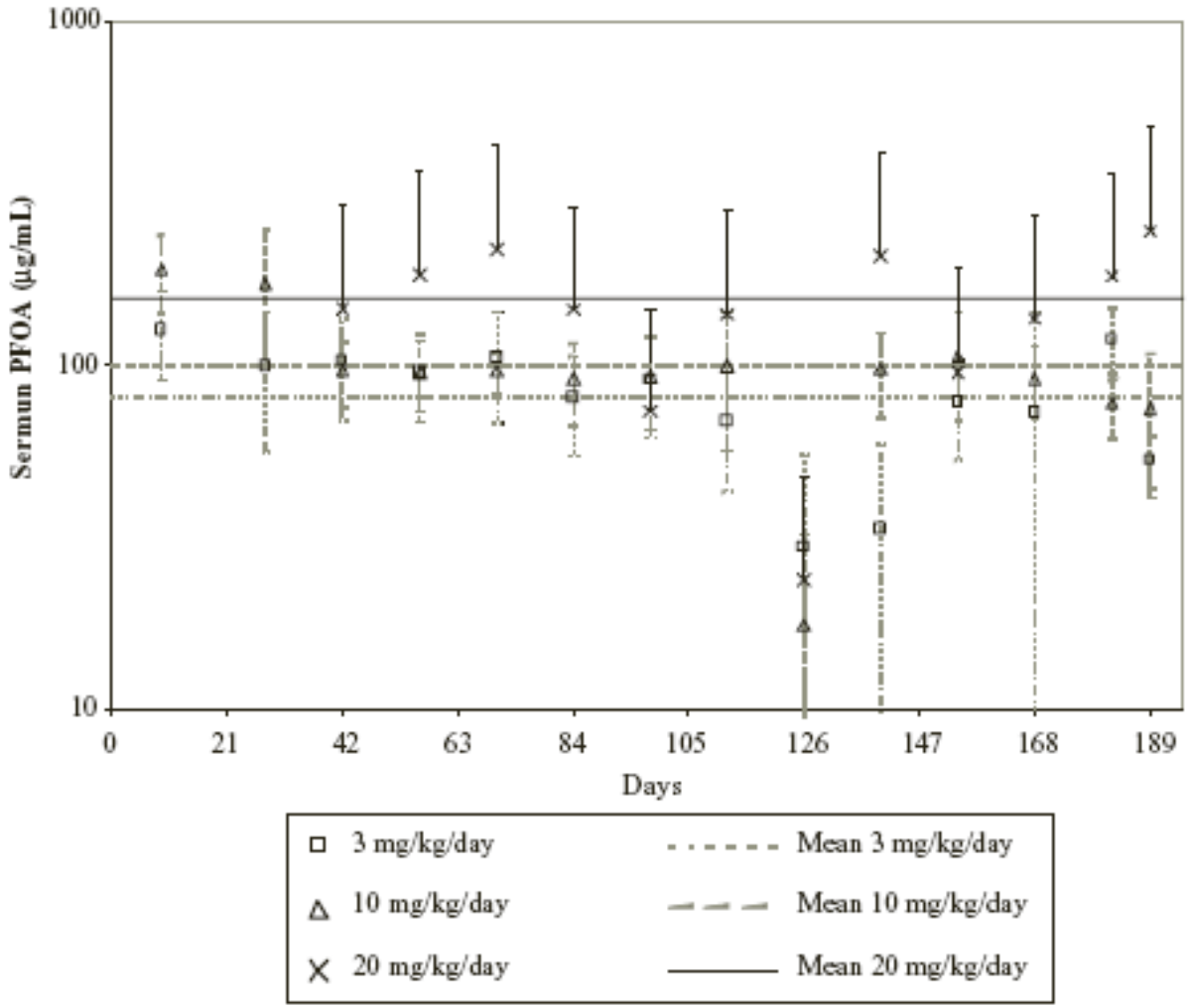
Conceptual PBPK Model for Adult



Proposed PBPK Model

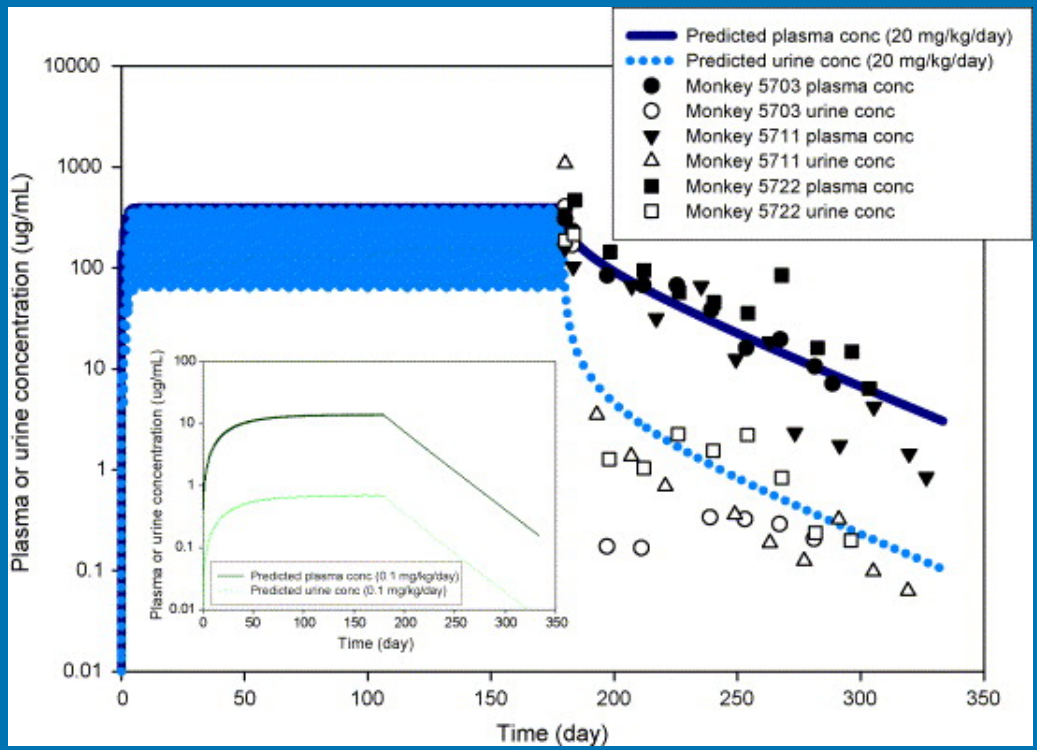
- Andersen ME, Clewell HJ 3rd, Tan YM, Butenhoff JL, Olsen GW. Pharmacokinetic modeling of saturable, renal resorption of perfluoroalkylacids in monkeys-Probing the determinants of long plasma half-lives.Toxicology. 2006 Oct 3;227(1-2):156-64.
- Motivation: Kinetics of single and repeated dose studies were possibly inconsistent or unknown indicated dose-dependencies
- Model
  - Two compartment (essentially classical compartmental model)
  - Kidney filtration of free plasma PFOA
  - Dose-dependent kidney resorption transporter

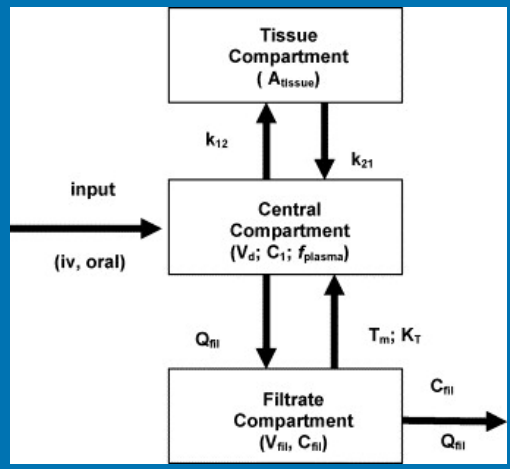
Monkey Repeated Dose Serum PFOA



Butenhoff JL et al. Pharmacokinetics of perfluorooctanoate in cynomolgus monkeys.Toxicol Sci. 2004 Dec;82(2):394-406.

Monkey Repeated Dose Serum PFOA





Andersen ME et al Pharmacokinetic modeling of saturable, renal resorption of perfluoroalkylacids in monkeys-Probing the determinants of long plasma half-lives.Toxicology. 2006 Oct 3;227(1-2):156-64.

Predicting Human Dose Metrics

- Measured PFOA blood concentrations in two population studies.
- Use directly for MOE comparisons based upon Cmax.
- Assume steady state to calculate AUC for MOE

Biomonitoring Data
U.S. General Population

- US Adults--645
- 332 males, 313 females
- age 20-69 yrs
- 6 ARC blood banks in various geographic locations (LA to Boston)
- Samples collected in 2000
- ~10 samples/10-yr age interval/ sex

- US Children--598
- 300 males, 298 females
- age 2-12 yrs
- Study of group A streptococcal infections
- Samples collected in 1994-1995 from 23 states and DC

Human Biomonitoring Data

Population	Arithmetic Mean (ppb)	90th Percentile (ppb)	Range (ppb)	Geometric Mean (ppb)
Adults (20 - 69 years, American Red Cross blood banks, 2000, n=645)	5.6	9.4	1.9 – 52.3	4.6
Children (2-12 years, 1995, n=598)	5.6	8.5	1.9 – 56.1	4.9

Draft Risk Assessment MOEs

Monkey	16,739 GM (8191 90th percentile)
Adult Female	398 GM (195 90th percentile)
Adult Male	9158 GM (4481 90th percentile)
Pregnant female	C_{max} 3095 GM (1548 90th percentile) AUC 823 GM (412 90th percentile)
Young (F1 mortality)	Male: 17,194 GM (9912 90th percentile) Female: 11760 GM (6779 90th percentile)
Young (delayed sexual maturation)	Male: 78,546 GM (45,279 90th percentile) Female: 10,485 GM (6,044 90th percentile)

Advantages of Blood Dosimetry-Based Assessment

- Reflects aggregate (multi-route) historical environmental exposures
- Overcomes lack of adequate exposure pathway information
- Measure of internal dose reflects substantial pharmacokinetic differences across species and between rat sexes.

Challenges of Blood Dosimetry-Based Assessment

- Need data: pharmacokinetic studies, toxicity study dosimetry
- Total concentration, free concentration, other?
- Is there a consistent relationship between blood and target tissue concentrations (body burden)?
- MOE evaluates current status – future trends?
- Evaluating general population, lifestages, and subpopulations.

Acknowledgments

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