

Risk Assessment Approaches

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Risk Assessment Approaches for PFOS/PFOA Should Be Based On:

- Internal dose as represented by serum PFOA & PFOS concentrations
- Multiple health endpoints that consider human relevance
- Benchmark-dose methodology where possible
- Appropriate Uncertainty Factors for assessment based on internal dose
- Appropriate Relative Source Contribution based on available data

Why Use Internal Dose?

- Robust data set exist from human and experimental studies
- Includes serum concentration data
- Integrates all routes of exposure
- Bridges PK differences
- NOAEL/BMD have been established based on serum concentration

Internal Dose in RiskAssessment (Butenhoff et al. 2004)

J.L. Butenhoff et al. / Regulatory Toxicology and Pharmacology 39 (2004) 363–380

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Table 10

Margin of exposure values based on various LBMIC₁₀ points of departure and highest upper bound 95th percentile estimate of general population serum PFOA concentrations

Response (species)	Source table	Point of departure LBMIC ₁₀ ($\mu\text{g}/\text{mL}$)	Margin of exposure ^a
Post-natal effects (rats)	Table 8	29 ^b	2100
Liver-weight-to-brain-weight ratio ^c (monkeys)	Table 9	23	1600
Body-weight change (monkeys)	Table 9	60	4300
Leydig cell tumors (rats)	Table 6	125	8900

^a The margin of exposure is calculated by dividing the LBMIC₁₀ ($\mu\text{g}/\text{mL}$) by the general population serum [PFOA] representing the upper 95% confidence limit of the estimate of the 95th percentile general population serum [PFOA] (0.014 $\mu\text{g}/\text{mL}$). Margins of exposure based on the upper bound of the geometric mean general population serum [PFOA] (0.005 $\mu\text{g}/\text{mL}$) are approximately three times higher.

^b The serum [PFOA] in post-weaning rat pups was estimated conservatively based on adult-female rat AUC at the LBMD₁₀ value of 22 mg/kg/day for post-natal effects using the relationship of AUC to administered oral dose from Fig. 1. Results from studies currently in progress support the premise that this is a conservative estimate for weanling rat pups (Han, 2003; Mylchreest, 2003). Availability of data in the future may require adjustment of this estimate of the MOE.

^c Liver-weight increase is not necessarily reflective of an adverse effect, as this is a normal adaptive response. This endpoint was used as a sensitive indication of biological response.

Internal-Dose Risk Assessment 3M EHAD (2003)

**Table 4-26. Human-Health Risk Assessment for PFOS Body Burden:
Margin-of-Exposure Analysis based on Human Serum and
Estimated Human Liver PFOS Concentrations**

PFOS Concentration in Humans (C), ppm	Point-of-Departure (POD), ppm	Endpoint	Margin of Exposure (Ratio POD:C)
Serum:			
0.040 (mean)	31 ^a	Pup weight gain	775
0.040 (mean)	44 ^b	Liver effects, rats	1100
0.040 (mean)	62 ^c	Liver tumors, rats	1550
0.100 (upper bound) ^d	31	Pup weight gain	310
0.100 (upper bound)	44	Liver effects, rats	440
0.100 (upper bound)	62	Liver tumors, rats	620
Liver: Human liver concentrations estimated from serum assuming a liver-to-serum ratio of 1.7:1.			
0.068 (mean)	59 ^e	Liver effects, monkeys	868
0.17 (upper bound) ^f	59	Liver effects, monkeys	347

^a LBMIC at 5% response level, using mean of gestation day 21 and pre-gestational serum levels in dams.

^b NOAEL for liver toxicity (LBMIC could not be calculated for male rats and is higher than the male NOAEL for female rats). It should be noted that the LBMIC (10% response level) for increased liver weight in male rats is also 44 ppm.

^c LBMIC at 10% response level.

^d Upper 95% confidence limit at 95% tolerance limit.

^e NOAEL (as liver-tissue [PFOS]) for liver toxicity (LBMIC could not be calculated for male monkeys and is higher than the male NOAEL for female monkeys).

^f Upper 95% confidence limit at 95% tolerance limit based on assumed liver-to-serum PFOS concentration ratio of 1.7:1.

Examples of Internal-Dose Risk Assessments

- EPA Draft PFOA Risk Assessment
- German/EU “CSR” Biological DNEL
- Minnesota HRLs
- Butenhoff et al. (2004)
- 3M PFOS “EHAD” (2003)
- Tardiff et al. (2009)
- Standard approach for pharmaceuticals

Human Experience

- Numerous human studies are available.
- Results can be associated with known serum PFOS & PFOA concentrations.
- No causal associations have been observed.
- Likely human “no-effect levels” based on studied endpoints in occupational cohorts are >5,000 ng/mL (ppb) for both PFOA and PFOS.

Human Relevance

- Rodent data must be interpreted based on human relevance of modes of action.
- Non-human primate is best laboratory model.

Benchmark Dose

- Uses all study data
- Normalizes species differences to a specific, defined level of response
- Recommended in EPA's Draft Benchmark Dose Technical Guidance document

Benchmark Dose

US EPA Science Advisory Expert Panel
on EPA PFOA Draft Risk Assessment

“The Panel likewise stressed that benchmark dose methodologies would be preferable to the reliance in the draft document on LOAEL-driven MOE calculations.”

Considerations for Uncertainty

- Lack of metabolism, use of internal-dose metric, and understanding of pharmacokinetics reduces pharmacokinetic component of uncertainty.
- Six-month studies in an appropriate model (monkey) combined with decades of occupational studies lessen uncertainty related to chronic exposure.
- Adaptive versus adverse effects should be considered.

Approaches to Establishing Risk Levels

- Evolution of approaches
 - Traditional: based on external dose
 - Hybrid: based on external dose with correction for PK differences
 - Internal-Dose: based on internal dose with adjustment for uncertainty followed by PBPK-based derivation of external dose equivalent.
- Internal-Dose approach accounts for PK differences up front.

Values – PFOA & PFOS

Traditional Approach

	PFOA		PFOS
	North Carolina	UK Drinking Water Inspectorate	UK Drinking Water Inspectorate
Study	Rat 2-gen.	Several	Monkey 6-mo.
Effect	Liver weight	Liver weight	Several
Basis	LOAEL	BMDL10	NOAEL
Dose (mg/kg/d)	1	0.3	0.03
Dose (µg/mL)			
Human Eq. Dose (mg/kg/d)			
UF - Intraspecies	10	10	10
UF - Interpecies	10	10	10
UF - Interspecies TD			
UF - LOAEL to NOAEL	10		
UF - Database	3		
UF - PK adjustment			
UF - Total	3,000	100	100
RfD (mg/kg/d)	0.0003	0.003	0.0003
RfD Serum (µg/mL)			
LADD (µg/person/d)			
Intake Rate (L/kg/d)	0.029		
DW Guidance Level (µg/L)	2	10	1

Values – PFOA & PFOS

Hybrid Approach

	PFOA		PFOS
	EPA Region 5 (PFOA)	EPA OW PHA (PFOA)	EPA OW PHA (PFOS)
Study	Monkey 6-mo.	Mouse dev.	Monkey 6-mo.
Effect	Liver weight	Maternal liver weight	TSH, T3, HDL
Basis	LOAEL	BMDL10	NOAEL
Dose (mg/kg/d)	3	0.46	0.03
Dose (µg/mL)			
Human Eq. Dose (mg/kg/d)			
UF - Intraspecies	10	10	10
UF - Interpecies		3	3
UF - Interspecies TD	3		
UF - LOAEL to NOAEL	10		
UF - Database			
UF - PK adjustment	T1/2 ratio = 45	CL ratio = 81	CL ratio = 13
UF - Total	13,500	2,430	390
RfD (mg/kg/d)	0.0002	inferred = 0.00019	inferred = 0.000077
RfD Serum (µg/mL)			
LADD (µg/person/d)			
Intake Rate (L/kg/d)	0.085	10 kg child = 0.1	10 kg child = 0.1
DW Guidance Level (µg/L)	0.5	0.4	0.2

Values – PFOA & PFOS

Internal-Dose Approach

	PFOA		PFOS
	Minnesota (PFOA)	Tardiff et al. (PFOA)	Minnesota (PFOS)
Study	Monkey 6-mo.	Monkey 6-mo.	Monkey 6-mo.
Effect	Liver weight	Liver wgt:brain wgt ratio	TSH, T3, HDL
Basis	LBMIC10	LBMIC10	LBMIC10
Dose (mg/kg/d)			
Dose (µg/mL)	23	23	35
Human Eq. Dose (mg/kg/d)	0.0023		0.0025
UF - Intraspecies	10	10	10
UF - Interpecies			
UF - Interspecies TD	3	2.5	3
UF - LOAEL to NOAEL			
UF - Database			
UF - PK adjustment			
UF - Total	30	25	30
RfD (mg/kg/d)	0.000077		0.00008
RfD Serum (µg/mL)		0.92	
LADD (µg/person/d)		8.8	
Intake Rate (L/kg/d)	0.053	0.029	0.053
DW Guidance Level (µg/L)	0.3	0.88	0.3

Internal Dose and Pharmacokinetic Component of Uncertainty

- EPA PFOA Draft Risk Assessment Science Advisory panel:

“While the pharmacokinetic modeling that is presented in the PFOA risk assessment is useful, a more comprehensive way to account for biological processes that determine internal dose is with the development of a physiologically based toxicokinetic model. The Panel encourages EPA to continue to develop toxicokinetic models as they can improve dose-response assessment by revealing and describing nonlinear relationships between applied and internal dose.”

Example PBPK Risk Assessment for PFOA

- Serum Concentrations Associated with Toxicity Endpoints in Animals:

<u>Endpoint (MDH 2009)</u>	<u>BMDL_{IC}*</u> <u>(ug/ml)</u>
• 6-month monkey liver weight	23

* Lower bound benchmark plasma concentration (from Butenhoff et al., 2004)

- Uncertainty factor: 30
 - 3 for animal-to-human pharmacodynamics
 - 10 for human variability
- Target blood concentration: $23/30 = 0.77 \text{ ug/ml} = 770 \text{ ng/ml}$
- Resulting RfD: 90 ng/kg/day
 - Exposure predicted to produce a blood concentration of 770 ng/ml

Example PBPK Risk Assessment for PFOS

- Serum Concentrations Associated with Toxicity Endpoints in Animals:

Endpoint (MDH 2009)

BMDL_{IC}*

(ug/ml)

- 6-month monkey TSH, T3, HDL

35

* Lower bound benchmark plasma concentration (from Seacat et al., 2002)

- Uncertainty factor: 30

- 3 for animal-to-human pharmacodynamics
- 10 for human variability

- Target blood concentration: $35/30 = 1.17 \text{ ug/ml} = 1170 \text{ ng/ml}$

- Resulting RfD: 120 ng/kg/day

- Exposure predicted to produce a blood concentration of 1170 ng/ml

Post et al. (2009)

TABLE 4. Derivation of Health-Based Drinking Water Concentrations for PFDA from End Points in Animal Studies (29)

species	key study (28)	end point (28)	NOAEL or LOAEL (29)	animal serum level (µg/L) at LOAEL or NOAEL (29)	uncertainty factor	target human serum level ^a (µg/L)	target contribution to human serum from drinking water ^b (µg/L)	health-based drinking water concentration ^c (µg/L)
adult female rat	chronic diet	↓ body weight, hematology	NOAEL 1.6 mg/kg/day (30 ppm)	1800 (based on modeled AUC)	100 (10 intraspecies, 10 interspecies)	18	4	0.04
adult male rat	two-generation reproductive, gavage	↓ body weight, ↓ liver and kidney weight in F1 generation	LOAEL 1 mg/kg/day	40 000 (USEPA model)	1000 (10 intraspecies, 10 interspecies, 10 LOAEL to NOAEL)	40	8	0.08
nonhuman primate	subchronic male cynomolgus monkey, capsule	increased liver weight and possible mortality	LOAEL 3 mg/kg/day	77 000 (measured)	3000 (10 intraspecies, 3 interspecies, 10 subchronic to chronic, 10 LOAEL to NOAEL)	36	5	0.05
pregnant female rat	two-generation reproductive, gavage	↓ body weight in male F1 pups during postweaning	NOAEL 3 mg/kg/day	3500 (based on modeled AUC)	100 (10 intraspecies, 10 interspecies)	35	7	0.07
male rat pups, postweaning	two-generation reproductive, gavage	↓ body weight in male F1 pups during postweaning	NOAEL 3 mg/kg/day	8400 (based on modeled AUC at week 4)	100 (10 intraspecies, 10 interspecies)	84	17	0.17
female rat pups, postweaning	two-generation reproductive, gavage	↓ body weight in female F1 pups during postweaning	NOAEL 10 mg/kg/day	13 000 (based on modeled AUC at week 7)	100 (10 intraspecies, 10 interspecies)	130	26	0.26
male rats (tumor) (37)	chronic diet	Leydig cell, pancreatic, and liver tumors	13.6 mg/kg/day (360 ppm) (~10% tumor incidence) (LOAEL or NOAEL not applicable)	572 000 µg/L (USEPA model)	not applicable, target human serum level is based on linear extrapolation from 10 ⁻¹ tumor incidence to 10 ⁻⁶ incidence	5.7	5.7	0.06 ^d

^a Target human serum level is derived by application of uncertainty factors to animal serum level at NOAEL or LOAEL. ^b Target contribution to human serum from drinking water is derived by applying a relative source contribution factor of 20% (to account for nondrinking water sources of exposure) to target human serum level. ^c Health-based drinking water concentration assumes a 100:1 ratio between PFDA concentrations in serum and drinking water (16). ^d Note: 20% relative source contribution factor was not used for cancer endpoint.

Comments on Post et al. (2009)

- Use of questionable female body-weight and hematology endpoints from 2-yr study
- Use of “LOAEL” and “NOAEL” as opposed to BMD
- Use of interspecies UF of 10 when using PK adjustment
- Use of default RSC when using “Emmett Factor”
- Use of linear, low-dose extrapolation for tumor endpoints

Tardiff et al. (2009)

Table 10
DWEL calculations for PFOA related to noncancer and cancer data.

Endpoint	Internal dose selection	LBMIC ₁₀ (µg/mL)	UFs	RfD ^a (µg/mL)	LADD ^b (µg/person-day)	Adjusted by RSC [20%] (µg/person-day)	DWEL ^c (µg/L) for tap water
<i>Noncancer</i>							
Liver/brain weight ratio: F0 and F1 rats in 2 generation study (Butenhoff et al., 2004b)	LBMIC ₁₀ for internal dose	25	25	1	9.5	1.9	0.95
Liver/brain weight ratio in monkeys (Butenhoff et al., 2002, 2004c)	LBMIC ₁₀ for internal dose	23	25	0.92	8.8	1.8	0.88
Body weight change in monkeys (Butenhoff et al., 2002, 2004c)	LBMIC ₁₀ for internal dose	64	25	2.6	24.4	4.9	2.44
Delayed ossification in mice (Lau et al., 2006)	LBMIC ₁₀ for internal dose	23	25	0.92	9.5	1.9	0.95
<i>Cancer</i>							
Testicular adenoma in rats (Sibinski, 1987)	LBMIC ₁₀ for internal dose	203	25	8	77	15	7.7

NA, not applicable.

^a RfD = LBMIC₁₀/UF.

^b LADD for internal dose = RfD µg/mL serum × 0.127 µg ingested/kg bw-day/µg/mL serum × 75 kg bw/person to get µg/person-day (Clewell et al., 2006; Clewell, 2006); when calculating the adjustment factor of 0.127 for humans, the following was taken into consideration: body weight, cardiac output, volume of renal filtrate, renal filtration rate, volume of distribution, half-life (3.5 years; Olsen et al., 2007), transport affinity, transfer rate constant, and free fraction in plasma. A RfD 'Z' µg/mL human plasma was determined for the endpoints and using the human PK model of Clewell et al. (2006) and Clewell (2006), 0.77 µg/mL human plasma was determined to be equivalent to a continuous exposure to 98 ng/kg/day. Therefore, assuming a linear relationship between human PFOA ingestion rate and plasma level, we estimate that the human RfD for the endpoints is 'Y' ng/kg/day [Y = Z × 98/0.77 = Z × 127].

^c DWEL = (LADD adjusted by RSC µg/person-day)/2 L/day.

Relative Source Contribution

- Exposure of general population is well-established and continues to be monitored.
- Drinking water exposure is the dominant exposure when PFOA and PFOS are present in drinking water.
- EPA guidance allows departure from default if adequate data are available.

Relative Source Contribution

2009 Minnesota Department of Health Biomonitoring

	PFOA			PFOS		
	Geometric Mean	Arithmetic Mean	Median	Geometric Mean	Arithmetic Mean	Median
Exposed through water (ng/mL)	15.4	22.5	16.0	35.9	47.7	41
Control: 2006 Red Cross (ng/mL)	3.4	3.9	3.6	14.5	16.9	14.2
RSC from water (%)	78	83	78	60	66	65

$$\text{RSC} = \left\{ \left[(\text{Sera conc exposed}) - (\text{Sera conc control}) \right] / \text{Sera conc exposed} \right\} * 100$$

Concurrent controls are best; however using 2006 values as controls probably makes the estimate RSC conservative; i.e. 2009 population averages are likely to be lower than 2006.

Data sources:

East Metro Perfluorochemical Biomonitoring Pilot Project. Minnesota Department of Health, July 2, 2009.

Olsen et al. (2008) Environ Sci Technol 42, 4989 – 4995.

Relative Source Contribution

West Virginia and Ohio Water Districts

Water District	Median Serum [PFOA] (ng/mL)	RSC (%)
Belpre	35.0	90
Tupper Plains	37.2	90
Little Hocking	224.1	98
Lubeck	66.9	95
Mason County	12.4	71
Pomeroy	12.1	70

Based on assumption that median blood sera concentrations would be at median concentration of 2006 Red Cross donors plus contribution from PFOA through water in their district.

$$\text{RSC} = \left\{ \left[\frac{\text{Median resident concentration} - \text{Median Red Cross donor concentration}}{\text{Median resident concentration}} \right] \right\} * 100$$

Median Red Cross donor level from Olsen et al. (2008) Environ. Sci. Technol. 42, 4989 – 4995.

Median sera concentration from residents in each water district from Steenland et al. (2009) EHP 117, 1083 – 1088.

PFOA Biological DNEL:

Internal Dose, REACH Methodology

- Developed for EU by German authorities and industry
- Considered human data

Endpoint	Species	Effect	Dose Descriptor	[PFOA] µg/mL	DNEL µg/mL
Human-health endpoints	Human	Examined effects	NOAEL	>5	≥0.8
Fertility impairment	Rat	Reproductive function	NOAEL	>39	≥4.9
Development	Mouse (pup)	Postnatal body weight	BMCL5	16	2.0
Repeat-dose toxicity	Monkey	Body-weight change	BMCL10	60	7.5
Carcinogenicity	Rat	Leydig-cell tumors	BMCL10	125	5.2

PFOA Biological DNEL (REACH Methodology)

- For Man via the Environment [i.e., general population], Biological DNEL = 800 ng/mL
- Approaches suggested for conversion of Biological DNEL to acceptable daily intake:
 - Simple first-order model (results in 0.08 $\mu\text{g}/\text{kg}/\text{d}$)
 - PBPK model (H. Clewell) (results in 0.096 $\mu\text{g}/\text{kg}/\text{d}$)

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Thank You!