

Toxicological Profile of Perfluoroalkanesulfonates

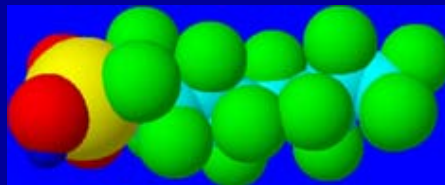
John L. Butenhoff, Ph.D.

3M Company

Presented to US EPA

October 15th, 2009

Structures and Molecular Weights



		<u>MW</u>
PFBS	$\text{F}_3\text{C}(\text{CF}_2)_3\text{SO}_3^-$	299
PFHxS	$\text{F}_3\text{C}(\text{CF}_2)_5\text{SO}_3^-$	399
PFOS	$\text{F}_3\text{C}(\text{CF}_2)_7\text{SO}_3^-$	499

Acute Toxicity

- Oral (LD_{50})
 - PFOS: 233 to 271 mg/kg (rat)
 - PFBS: > 2000 mg/kg (rats, no effects at 2000)
- Dermal (LD_{50})
 - PFOS: > 5,000 mg/kg (rabbit)
 - PFBS: > 2,000 mg/kg (rats)
- Inhalation (LC_{50})
 - PFOS: 5.2 mg/L (1 hr, rat)

Repeat Dose

- 28-Day (rats and monkeys)
 - PFBS
 - PFOS
- 90-Day (rats and rhesus monkeys)
- Six-month (monkeys)
- One-year interim (rats from two-year bioassay)
- Two-year bioassay (rats)

Repeat-Dose Toxicity - Rats

	PFBS	PFHxS	PFOS
Duration	90-Days	≥ 42 Days (M) ~ 60 Days (F)	90-Days
Doses (mg/kg)	60, 200, 600	0.3, 1, 3, 10	<ul style="list-style-type: none"> • 0.03, 0.13, 0.34, 1.33 (M) • 0.04, 0.15, 0.40, 1.56 (F)
NOAEL (mg/kg)	60 (M) >600 (F)	<0.3 (M) >10 (F)	0.34 (M) 0.40 (F)
Basis for NOAEL (effects at higher doses)	<ul style="list-style-type: none"> • ↓ RBC, HGB, HCT 	<ul style="list-style-type: none"> • ↓ BWG, CHOL, PT • At higher doses: ↓ RBC, HGB, HCT, liver, thyroid, BW 	<ul style="list-style-type: none"> • ↓ BWG, CHOL, ↑ ALT (M) • ↑ Liver wgt, liver cell hypertrophy and vacuolation (M & F)

28-Day Dietary Study in Rats

Seacat et al. (2003) Toxicology 183, 117-131

Erratum Seacat et al. (2008) Toxicology 194, 263-264

Table 1

Summary of selected clinical measurements after 4 and 14 weeks of dietary dosing of Sprague Dawley rats with potassium PFOS

Measured parameter ^a	Nominal dietary dose level (ppm)				
	0 (control) ^b	0.5	2	5	20
<i>4 weeks—males</i>					
Body weight (g)	323 ± 34	315 ± 16	303 ± 25	309 ± 19	296 ± 21
Liver/body weight (%)	3.6 ± 0.2	4.1 ± 0.4	3.9 ± 0.2	3.5 ± 0.3	4.4 ± 0.3*
PCNA LI (%) ^c	0.042 ± 0.024	0.038 ± 0.014	0.069 ± 0.028	0.043 ± 0.025	0.065 ± 0.029
Glucose (mg/dl)	97 ± 11	97 ± 5	91 ± 11	94 ± 9	84 ± 5*
AST (IU/l) ^d	122 ± 26	146 ± 29	104 ± 23	114 ± 17	131 ± 20
PCoAO (IU/g) ^e	9.0 ± 2.2	9.0 ± 2.3	7.0 ± 4.0	8.0 ± 0.8	6.0 ± 1.4
<i>4 weeks—females</i>					
Body weight (g)	213 ± 21	192 ± 11	202 ± 15	206 ± 29	193 ± 17
Liver/body weight (%)	3.8 ± 0.2	3.7 ± 0.2	3.8 ± 0.2	3.7 ± 0.4	4.1 ± 0.3
PCNA LI (%)	0.53 ± 0.032	0.055 ± 0.015	0.059 ± 0.013	0.097 ± 0.036	0.183 ± 0.085
Glucose (mg/dl)	114 ± 7	11 ± 7	113 ± 18	109 ± 11	107 ± 8
AST (IU/l)	123 ± 28	120 ± 37	101 ± 12	112 ± 24	92 ± 16*
PCoAO (IU/g)	5.0 ± 1.5	6.0 ± 1.1	3.0 ± 1.7	2.0 ± 1.1*	4.0 ± 1.1

28-Day Dietary Study in Rats

Seacat et al. (2003) Toxicology 183, 117-131

Table 2

The relationship of concentrations of PFOS in rat serum and liver to external dose after sub-chronic dietary dosing for 4 and 14 weeks: estimated daily dose in mg/kg/day; measured concentrations of PFOS in serum and liver; liver-to-serum PFOS concentration ratios; and, estimated percent of 14-week cumulative PFOS dose present in serum and liver

Parameter	Nominal dietary dose of potassium PFOS (ppm)				
	0 (control)	0.5	2	5	20
<i>4 weeks—males</i>					
Dose (mg/kg/day) ^a	0	0.05±0.00	0.18±0.01	0.37±0.03	1.51±0.07
[PFOS] _{serum} (µg/ml)	< LOQ ^b	0.91±0.06	4.33±1.16	7.57±2.17	41.8±7.9
[PFOS] _{liver} (µg/g)	0.10±0.07	11.0±2.3	31.3±5.8	47.6±12.5	282±45
[PFOS] _{liver:serum} ^c	NA ^d	12.2±3.1	7.6±2.0	6.3±0.2	7.2±1.0
<i>4 weeks—females</i>					
Dose (mg/kg/day)	0	0.05±0.00	0.22±0.02	0.47±0.05	1.77±0.10
[PFOS] _{serum} (µg/ml)	0.03±0.01	1.61±0.21	6.62±0.50	12.6±1.7	54.0±7.3
[PFOS] _{liver} (µg/g)	0.11±0.05	8.71±0.55	25.0±6.1	83.0±14.1	373±44
[PFOS] _{liver:serum}	4.1±1.5	5.6±0.6	3.7±0.7	6.6±0.3	6.9±0.4

28-Day Dietary Study in Rats

Curran et al. (2008) J Tox Environ Health A 71, 1526-1541

TABLE 9

Summary of Lowest-Observed-Effect Levels (LOELs; mg PFOS/kg diet) and Corresponding Serum PFOS Levels (μg PFOS/g Serum) for Selected Statistically Significant Changes in Rats Exposed to Dietary PFOS for 28 d

Parameter	Males		Females	
	LOEL	Serum PFOS	LOEL	Serum PFOS
Final liver/body weight	20	13.45	2	1.50
Serum thyroxine (T4)	20	13.45	20	15.40
Liver ACOX1 expression	50	20.93	20	15.40
Liver CYP4A22 expression	20	13.45	50	31.93
Serum cholesterol	50	20.93	50	31.93
Serum triglycerides	50	20.93	50	31.93
Final body weight	50	20.93	50	31.93
Serum lipase	50	20.93	100	43.20
Serum triiodothyronine (T3)	100	29.88	50	31.93
Serum conjugated bilirubin	100	29.88	50	31.93
Serum total bilirubin	100	29.88	100	43.20
Final thyroid/body weight	100	29.88	100	43.20
Circulating red blood cells	>100	>29.88	100	43.20
Final spleen/body weight	>100	>29.88	100	43.20
Serum unconjugated bilirubin	>100	>29.88	100	43.20

90-Day Dietary Study in Rats

3M (2003) EHAD (1978 Study)

30 ppm	↓ body weight; ↑ ALT, AST; liver discoloration
100 ppm	3 pre-term deaths; ↓ food consumption, hemoglobin, hematocrit, erythrocyte count, reticulocyte count (females), leukocyte count; ↑ CK, AP, Glucose, BUN, sensitivity to external stimuli; liver enlargement, hepatocellular hypertrophy & necrosis; stomach discoloration & hemorrhage
300 ppm	Fatal pre-term; symptoms of emaciation, convulsions, stomach mucosal hyperkeratosis, bone marrow hypocellularity, thymic follicular atrophy, atrophy of mesenteric lymph nodes, atrophy of villi in small intestines, skeletal muscle atrophy, & dermal acanthosis
1000 ppm	Fatal early pre-term; hunched posture
3000 ppm	Fatal early pre-term; hypoactivity
NOAEL	None - the lowest dose tested (30 ppm) was an effect dose

90-Day Dietary Study in Rats

Seacat et al. (2003) Toxicology 183, 117-131

Erratum Seacat et al. (2008) Toxicology 194, 263-264

Table 1

Summary of selected clinical measurements after 4 and 14 weeks of dietary dosing of Sprague Dawley rats with potassium PFOS

Measured parameter ^a	Nominal dietary dose level (ppm)				
	0 (control) ^b	0.5	2	5	20
<i>14 weeks—males</i>					
Body weight (g)	496 ± 56	481 ± 51	434 ± 31	424 ± 44	470 ± 40
Liver weight (g)	15.5 ± 1.1	15.5 ± 2.7	14.0 ± 1.4	18.8 ± 3.0	20.3 ± 2.2*
Liver/body weight (%)	3.2 ± 0.3	3.2 ± 0.2	3.2 ± 0.2	3.6 ± 0.3	4.3 ± 0.4*
N-SEG (10 ³ /μl) ^f	1.1 ± 0.4	1.3 ± 0.3	1.2 ± 0.3	1.2 ± 0.4	1.6 ± 0.4*
Glucose (mg/dl)	102 ± 6.2	106 ± 11	91 ± 14	99 ± 9	95 ± 10
Cholesterol (mg/dl)	63 ± 13	53 ± 17	51 ± 15	57 ± 7	37 ± 13*
ALT (IU/l) ^g	36 ± 7	41 ± 6	41 ± 5	44 ± 14	65 ± 53*
UN (mg/dl) ^h	13 ± 2	14 ± 2	13 ± 2	14 ± 1	16 ± 2*
PCoAO (IU/g)	4.6 ± 1.3	4.8 ± 3.3	5.4 ± 3.0	1.8 ± 1.8	5.4 ± 1.9
<i>14 weeks—females</i>					
Body weight (g)	284 ± 39	298 ± 41	266 ± 16	247 ± 18	249 ± 26
Liver weight (g)	9.3 ± 1.6	9.2 ± 1.3	8.4 ± 0.7	8.7 ± 1.0	10.6 ± 0.7
Liver/body weight (%)	3.3 ± 0.2	3.1 ± 0.1	3.2 ± 0.3	3.5 ± 0.3	4.3 ± 0.4*
N-SEG (10 ³ /μl)	1.0 ± 0.5	1.0 ± 0.5	0.7 ± 0.2	0.9 ± 0.6	1.0 ± 0.6
Glucose (mg/dl)	106 ± 12	106 ± 9	108 ± 6	95 ± 8*	99 ± 7
Cholesterol (mg/dl)	75 ± 15	88 ± 27	87 ± 24	70 ± 13	66 ± 14
ALT (IU/l)	34 ± 2.4	36 ± 9	37 ± 18	34 ± 5	39 ± 18
UN (mg/dl)	12 ± 2	13 ± 2	13 ± 2	14 ± 3	17 ± 2*
PCoAO (IU/g)	1.8 ± 1.6	3.0 ± 2.6	1.0 ± 0.8	1.6 ± 26	5.0 ± 2.9

90-Day Dietary Study in Rats

Seacat et al. (2003) Toxicology 183, 117-131

Table 2

The relationship of concentrations of PFOS in rat serum and liver to external dose after sub-chronic dietary dosing for 4 and 14 weeks: estimated daily dose in mg/kg/day; measured concentrations of PFOS in serum and liver; liver-to-serum PFOS concentration ratios; and, estimated percent of 14-week cumulative PFOS dose present in serum and liver

Parameter	Nominal dietary dose of potassium PFOS (ppm)				
	0 (control)	0.5	2	5	20
<i>14 weeks—males</i>					
Dose (mg/kg/day)	0	0.03±0.01	0.13±0.04	0.34±0.09	1.33±0.38
Cum. dose (mg/kg) ^e	0	3.3±0.2	13±1	33±2	130±6
[PFOS] _{serum} (µg/ml)	< LOQ ^f	4.04±0.80	17.1±1.22	43.9±4.9	148±14
[PFOS] _{liver} (µg/g)	0.46±0.06	23.8±3.5	74.0±6.2	358±29	568±107
[PFOS] _{liver:serum}	NA	6.2±2.2	4.4±0.5	8.2±1.2	3.9±0.9
% in serum ^g	NA	4.4	4.5	5.5	4.3
% in liver ^g	NA	31	21	57	24
<i>14 weeks—females</i>					
Dose (mg/kg/day)	0	0.04±0.01	0.15±0.04	0.40±0.08	1.56±0.35
Cum. Dose (mg/kg)	0	3.6±0.1	15±0	39±2	148±8
[PFOS] _{serum} (µg/ml)	2.67±4.58	6.96±0.99 ^h	27.3±2.3	64.4±5.5	223±22
[PFOS] _{liver} (µg/g)	12.0±22.4	19.2±3.8	69.2±3.5	370±22	635±49
[PFOS] _{liver:serum}	3.5±0.8	2.8±0.7	2.5±0.1	5.8±0.5	2.9±0.3
% in serum	NA	6.8	5.4	5.2	4.9
% in liver	NA	18	15	33	19

PFOS Repeat-Dose Toxicity - Monkeys

	Rhesus	Cynomolgus
Duration	90 Days Oral Gavage	182 Days Oral Gavage
Doses (mg/kg)	0.5, 1.5, 4.5	0.03, 0.15, 0.75
NOAEL	0.5 (M & F)	0.15 (M & F)
Basis for NOAEL (effects at higher doses)	<ul style="list-style-type: none"> • GI effects, dehydration, tremors, ↓BW, ↓CHOL, ↓activity • 4.5 mg/kg fatal within 7 wks 	<ul style="list-style-type: none"> • 2 M pre-term deaths • ↓BW, ↑liver wgt, ↓CHOL, ↓HDL, ↓ T3, ↓E2, ↑liver cell hypertrophy & vacuoles

Six-Month Study in Cynomolgus Monkeys

Seacat et al. (2002) Toxicol Sci 68, 249-264

Dose (mg/kg/d)	Sex	Serum PFOS (µg/mL)	Liver PFOS (µg/g)	Effects
0.03	M	16	17	NOAEL
	F	13	23	
0.15	M	83	59	LOEL/NOAEL; Slightly but statistically-significantly lowered HDL cholesterol in females was of questionable clinical relevance and baseline data were not available; Total T3 was reduced somewhat with statistical significance in females, but no change in TSH or free T3 and free T4.
	F	67	70	
0.75	M	173	395	1 pre-term death & 1 pre-term moribund sacrifice (males); decreased body weight; increased liver weight; decreased total cholesterol, HDL, T3, E2; mottled liver (2 males, 1 female); centrilobular or diffuse hepatocellular hypertrophy and vacuolation.
	F	171	273	

Two-Year Bioassay

Dose, ppm: 0 0.5 2 5 20 20 S.D.

Hepatocellular adenoma

Males 0/60 3/50 3/50 1/50 7/50* 0/40**

Females 0/60 1/50 1/49 1/50 5/60* 2/40

Hepatocellular carcinoma

Females 0/60 0/50 0/49 0/50 1/60 0/40

Combined hepatocellular adenoma & carcinoma

Females 0/60 1/50 1/49 1/50 6/60* 2/40

* Significantly different than control ($p < 0.05$)

** Significantly different than 20 ppm dose group ($p < 0.05$)

PFOS Genotoxicity Negative

- Point mutation
 - Salmonella typhimurium
 - Escherichia coli
- Chromosomal aberration
 - Mouse micronucleus
 - Human lymphocyte
- Unscheduled DNA synthesis
 - Rat liver

PFOS Liver Tumor Mode of Action

- PPAR α mode of action
 - Receptor binding and activation
 - Induction of key target genes
 - Increased cell proliferation and inhibition of apoptosis
 - Clonal expansion of activated cells
- Evidence exists to support PPAR α mode of action

PFOS Mode of Action

- Study conducted by Dr. Cliff Elcombe (CXR Biosciences)
- Male rats feed for 1, 7, or 28 d
 - PFOS (20 and 100 ppm)
 - Phenobarbital (500 ppm)
 - WY 14643 (50 ppm)
- Endpoints
 - Liver weights and histology
 - Expression of CYP4A, CYP2B, CYP3A, CYP2E
 - Cell proliferation (BrDU staining)
 - Apoptotic index
 - Clinical chemistry

PFOS Liver Evaluations

	PFOS	PB	Wy14.643
DNA content	↑	↑	↑
P450 content	↑	↑	↔
β-oxidation	↑	↔	↑
Cyp 4A	↑	↔	↑
Cyp 3A	↑	↑	↔
Cyp 2B	↑	↑	↔
Cyp 2E	↑	↑	↔
Histology	↓ glycogen, vacuolation, centrilobular hypertrophy	↓ glycogen, vacuolation, centrilobular hypertrophy	↓ glycogen, vacuolation, diffuse hypertrophy
Apoptotic index	↓	↓	↓
S-phase labelling	↑	↑	↑

Thyroid Cell Proliferation

- Thyroid endpoints
 - Histology
 - BrDU proliferation assay

	PFOS	PB	Wy14.643
Histology	↔	↔	↔
S-phase labelling	↔	↑	↑

PFOS Liver Evaluation

Recovery Following 7 d Treatment

	Weeks follow-up			
	0	4	8	12
DNA content	↓	↓	↓	↔
P450 content	↑	↑	↑	↑
β-oxidation	↑	↑	↑	↑
Cyp 4A	↑	↑	↑	↔
Cyp 3A	↑	↑	↑	↑
Cyp 2B	↑	↑	↓	↓
Histology	↓ glycogen, centrilobular hypertrophy			
Apoptotic index	↓	↓	↓	↓
S-phase labelling	↑	↔	↔	↔

PFOS Thyroid Evaluation

Recovery Following 7 d Treatment

	Weeks follow-up			
	0	4	8	12
Histology	Normal			
Apoptotic index	Minimal			
S-phase labelling	Normal			

PFOS Cholesterol Effect

- PFOS reduces serum cholesterol and triglycerides by increased lipolysis and clearance of VLDL-TG, and strongly reduced VLDL-TG/particle production
- PFOS reduces HDL-cholesterol and apoA1 by reducing HDL synthesis (apoA1), maturation (LCAT) and uptake (SR-B1)
- PFOS increases hepatosteatosis and liver cholesterol accumulation
- Based on mRNA signals PFOS has strong PPAR α - and PXR-agonistic activity (lipolysis \uparrow , β -oxidation \uparrow , FA uptake \uparrow , FA synthesis \uparrow ; HDL metabolism)

Reproductive Function

- PFOS^a and PFBS^b – two generations (Rat)
- PFHxS^c – one generation (rat, OECD 422)
- Studied parameters
 - Fertility
 - Estrous Cycling
 - Natural Delivery
 - Sperm (number, morphology, motility)
 - Sexual organ (weight, histology)
- No effects on reproductive function (rat)

^a Luebker et al (2005) Toxicology 215, 126-148

^b Lieder et al. (2009) Toxicology 259, 33-45

^c Butenhoff et al. (2009) Repro Toxicol 27, 331-341

Pre-Natal Development

- PFBS, PFHxS, and PFOS studied
- Not selective teratogens

Pre-Natal Development - PFOS

Species	Doses	NOAEL	LOAEL	Effects at LOAEL
Rabbit	0.1 – 3.75 (mg/kg, oral)	Doe, 0.1 Fetus, 1	Doe, 1 Fetus, 2.5	↓ Body wgt ^a ↓ Body wgt ^b
Rat	1 – 10 (mg/kg, oral)	Dam, 1 Fetus, 1	Dam, 5 Fetus, 5	↓ Body wgt ^c ↑ Skel. vari.
Rat	1 - 10	Dam, 1 Fetus, 5	Dam, 2 Fetus, 10	↓ Wgt gain ^d ↑ Sternal defects, etc ^e
Mouse	1 - 20	Dam, 1 Fetus, 1	Dam, 5 Fetus, 5	↓ Wgt gain ^d ↑ Sternal defects ^f

^a Increased abortions at higher doses; ^b Delayed ossifications at higher doses; ^c Two dam deaths at 10 mg/kg; ^d Severe at higher doses; ^e ↑ cleft palate, ↑ liver weight, ↑ ansarca; ^f enlarged right atrium, ventri. septal defects, ↑ cleft palate, ↑ liver weight at higher doses.

Pre-Natal Development - PFBS

Species	Doses	NOAEL	LOAEL	Effects at LOAEL
Rat	100 – 1000 (mg/kg, oral)	Dam, 300 Fetus, 300	Dam, 1000 Fetus, 1000	↓ Body wgt ↓ Body wgt

Pre-Natal Development - PFHxS

Species	Doses	NOAEL	LOAEL	Effects at LOAEL
Rat	0.3 – 10 (mg/kg, oral)	Dam, 10 Fetus, 10	Dam, >10 Fetus, >10	--- ---

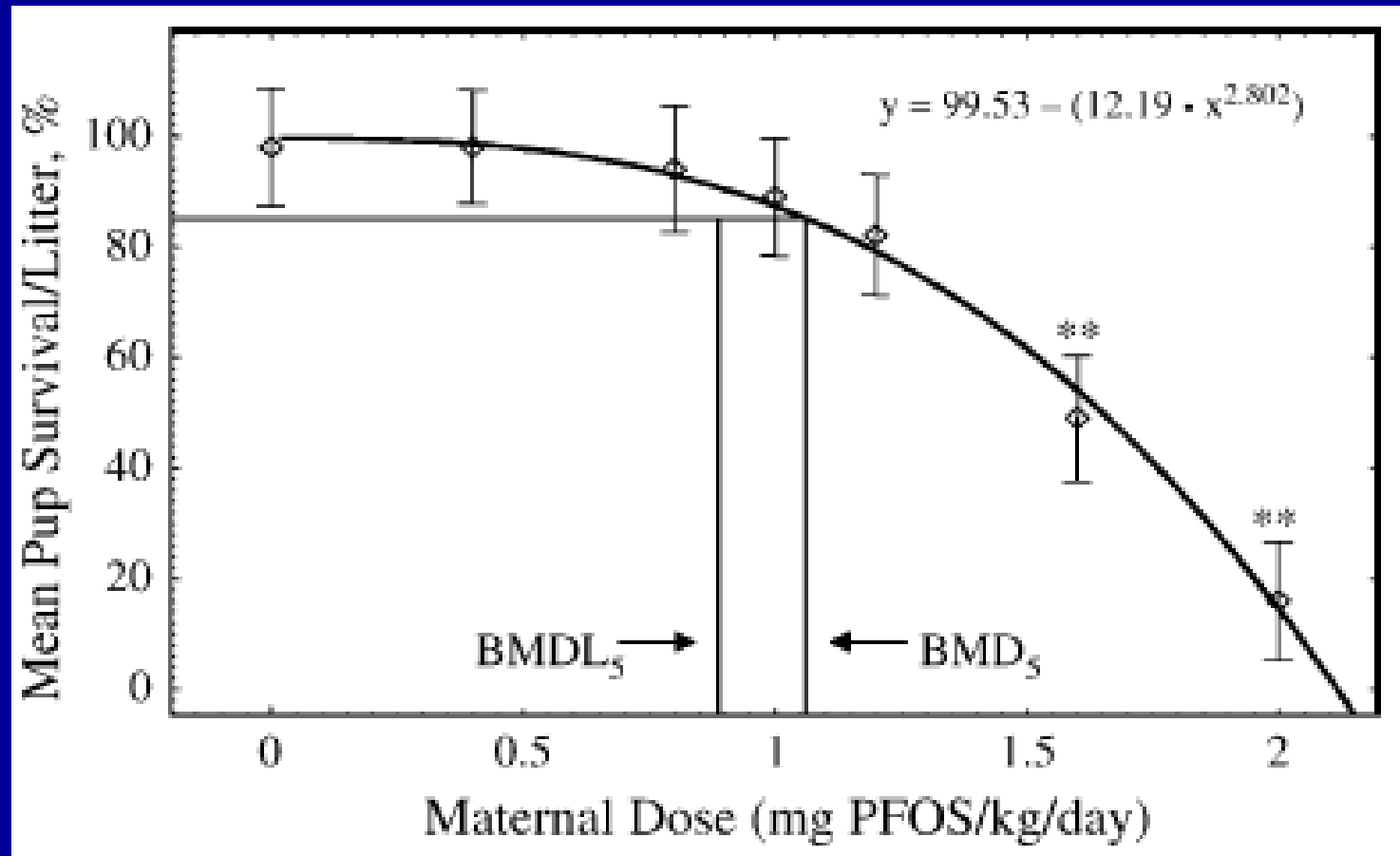
Post-Natal Developmental Studies

- Two-generation reproduction studies (rats)
 - PFBS, PFOS
- One-generation reproduction studies (rats)
 - PFOS, PFHxS
- Gestational-dosing studies (rats)
 - PFOS
- Gestational-dosing studies (mice)
 - PFOS

Postnatal Development

- PFOS (F_0 doses of 0.1 – 3.2 mg/kg/d)
 - Reduced birth weight and weight gain
 - Delayed eye opening
 - Reduced survival
- PFHxS (F_0 doses of 0.3 – 10.0 mg/kg/d)
 - No F_1 effects
 - Mean F_1 serum PFHxS 44,000 $\mu\text{g/mL}$ on GD 21
 - Mean F_1 serum PFHxS 94,000 $\mu\text{g/mL}$ on PND 22
- PFBS (F_0 doses of 30 – 1000 mg/kg/d)
 - Male F_1 pup body weight at 1000 mg/kg/d was slightly lower and correlated with slight delay (1.6 d) in sexual maturation.

Neonatal Survival Through PND 5



Luebker et al. (2005) Toxicology 215, 126-148

PFOS and Neonatal Toxicity

- PPAR α independent (unlike PFOA)
 - Abbott et al. (2009) *Repro Toxicol* 27, 258-265
- Survival affected shortly after birth
- Enlarged right atrium
- Effect manifested if dosed at end of gestation

PFOS and Neonatal Toxicity

- Direct interaction with pulmonary surfactant?
- No effect on surfactant production
- PFOS detected in amniotic fluid
- No mortality on gavage of newborn rats
- PFOS interacts with surfactant component, dipalmitoylphosphatidylcholine (DPPC)
- PFOS disrupts surface-tension reducing properties of pulmonary surfactant

Developmental BMDL₅ Values

Endpoint	BMDL5 (mg/kg/d)	Dam Mean Serum PFOS on GD21 (ng/mL)
↓ Pup survival (rat) ^a	0.58	16,000
↓ Pup body weight (rat) ^c	0.27	23,000
↓ Pup weight gain ^c	0.28	23,000
↓ Gestation length (rat) ^c	0.31	26,000
↓ Birth Weight (rat) ^c	0.39	33,000
↓ Pup survival (mice) ^a	3.88	56,000
↓ Pup survival (rat) ^c	0.89	75,000

^a Lau et al. (2003) Toxicol Sci 74, 382-392

^b Luebker et al. (2005) Toxicology 215, 149-169.

Developmental Neurotoxicity

Butenhoff et al. (2009) *Repro Toxicol* 27, 319-330

- Maternal doses of 0.1, 0.3, and 1.0 mg/kg/d
- ↓ maternal body weights LD 4 – 21 in the 1.0 mg/kg/day group
- No PFOS-related effects on male motor activity counts on PND 13, 21 and 61, but ↑ motor activity counts 1.0 mg/kg/d dose group males on PND 17 indicative of ↓ habituation on PND 17
- No effects at any age tested in the female pups
- mRNA RT-PCR: PND 21 1.0 mg/kg/d group male pups
 - ACoA (↑1.5 fold),
 - Cyp4a1 (↑2.1 fold)
 - Cyp7a1 (↓0.3 fold)
 - Cyp2b2 (↑1.8 fold)
 - indicating induction of PPARα and CAR nuclear receptors

Developmental Neurotoxicity

Butenhoff et al. (2009) *Repro Toxicol* 27, 319-330

- No significant change from controls for:
 - Live litter size, pup sex ratio, postnatal survival, pup weights, and ages at sexual maturation
 - Pup functional observational parameters, auditory startle response, learning and memory, and brain weights
 - Thyroid parameters (TSH, histopathology, morphometric analyses of follicle cell height and colloidal area) on PND 4 and 21

Developmental Neurotoxicity

Butenhoff et al. (2009) *Repro Toxicol* 27, 319-330

- Maternal NOAEL = 0.3 mg/kg/d (6,200 ng/mL – 9,000 ng/mL serum)
 - Slight body-weight decrease during lactation at 1.0 mg/kg/d
- Developmental NOAEL = 0.3 mg/kg/d
 - Increased motor activity with decreased habituation in males on PND 17 at 1.0 mg/kg/d

PFOS Immunotoxicity

- At least 8 studies available
- Suppressed adaptive immunity
- Enhanced innate immunity
- Large variation in effective doses
- Are effects secondary to liver changes?
 - Liver effects occur at lower doses than immune effects in most studies
- To what extent is PPAR α involved?

Thank You!