Meeting Between KEMI and 3M

Human Risk Characterization for PFOS

Tuesday, June 29, 2004

Areas of Agreement

- Comparisons of serum PFOS concentrations can be used for risk characterization in a margin-of-safety approach
  - Pharmacokinetics properties of PFOS
    - good absorption, protein binding, no metabolism, and poor elimination are ideal for using serum PFOS concentration as an index of exposure.
  - Biological effects in toxicology studies correlate strongly with dose and serum PFOS concentration

Areas of Agreement

- Characterization of risk based on more than one study and endpoint (e.g., chronic effects and reproductive effects) reduces uncertainty
- Interspecies comparisons can reduce uncertainty and add insight

Note: PFOS effect levels are remarkably consistent across species and endpoints

- Reasoned approach to uncertainty factors
- Phase-out of "PFOS-related" chemistry

Areas of Concern

- 3M does not believe that the conclusion of unacceptable risk for humans is supported by current data. However, 3M supports KEMI's recommendation for the phase-out of PFOS-related chemistry.

Areas of Concern

- 3M does not agree that workers are at serious risk.
  - 3M has conducted medical surveillance and epidemiology of all 3M fluorochemical production workers for several decades.
  - No effects have been attributed to PFOS exposure.

Areas of Concern

The NOAELs used overstate the actual risk:

1. *Systemic toxicity risk characterization*
   a. Hepatocellular or liver hypertrophy
   b. Serum data from 2-year-old rats
2. *Developmental/reproductive risk characterization*
   a. Feed consumption data (0.1 mg/kg F1 males)
   b. Serum data from lactating rats

Benchmark-Dose Method

- 3M believes that use of the benchmark dose and benchmark internal concentration, where possible, provides the a better basis for risk characterization than LOAELs and NOAELs
- Uses all study data
- Rewards good experimental design
- Allows for more rationale estimation of demarcation between LOEL and NOEL
- Can be used with external dose (eg., mg/kg) or internal dose (eg., concentration in serum)

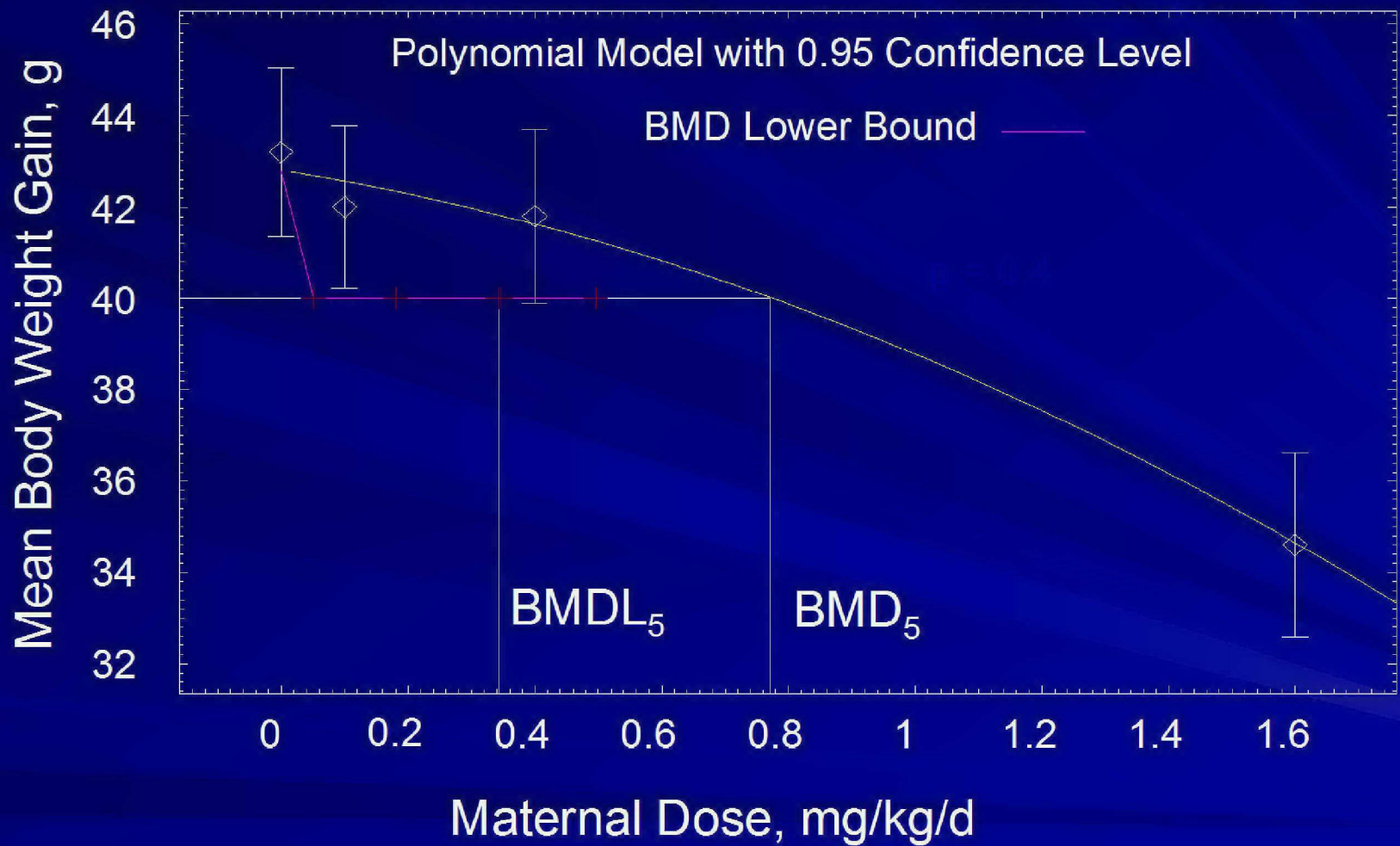
Impact on Margins of Safety

Sampled Group	NOAEL (ng/mL)	LBMIC (ng/mL)	Max [PFOS] (ng/mL)	Mean [PFOS] (ng/mL)	NOAEL MOS Max	NOAEL MOS Mean	LBMIC MOS Max	LBMIC MOS Mean	MOSref
Systemic									
Swedish Public	44,000	44,000	91	33.4	484	1317	484	1317	25
Fish-Eating Females	44,000	44,000	134	55.4	328	794	328	794	25
Workers	44,000	44,000	10,060	1,320	4	33	4	33	12.5
Repro/Devel									
Female Swedish Public	7,500	31,000	66	29.1	114	258	470	1065	100
Fish-Eating Females	7,500	31,000	134	54.4	56	138	231	570	100
Female Workers	7,500	31,000	3,620	930	2	8	9	33	50

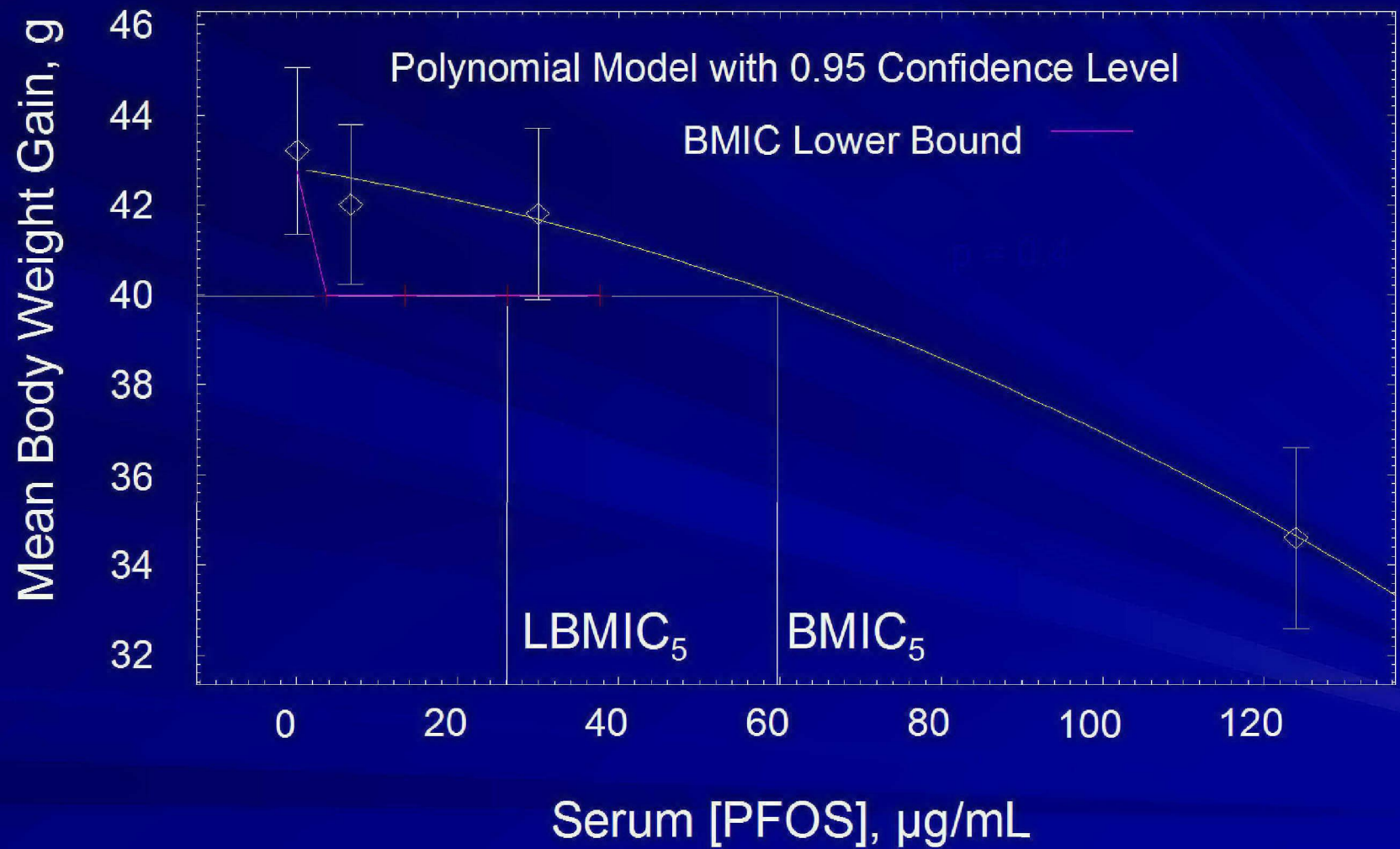
Upper-Bound Estimates versus Maximum Values

- To represent public health risk, 3M supports use of an upper-bound estimate of exposure (e.g., estimated 95th percentile) as opposed to the maximum exposure.
- Upper-bound estimates are based on the distribution characteristics of all the data, and are less likely to be influenced by an outlier.
- For US population, based on ~2,000 samples, 95th %-tile = 100 ng/mL and 99th %-tile = 200 ng/mL.

Rat Pup Body-Weight Gain During Lactation vs. Maternal Dose (mg/kg/day)



Rat Pup Body-Weight Gain During Lactation vs. Maternal Serum [PFOS] at Gestation Day 21



Concerns

Concerns:
1. Systemic Toxicity

a. 3M does not agree that hepatocellular or liver hypertrophy is an adverse effect in the case of PFOS

b. Serum PFOS concentrations from two-year-old rats introduce a negative bias

Note: Survival to two years was more than 2x control for male rats consuming 5 and 20 ppm PFOS in diet

1.a. Hepatocellular Hypertrophy

- Liver hypertrophy in 2 ppm dose-group male rats from 2-year study is adaptive and not an adverse effect

  – Hypertrophy, absent clinical evidence of altered liver function or liver damage, is a reversible, adaptive effect (Robbins Pathology Text)

  – Liver hypertrophy in the case of PFOS is not associated with manifestations of liver toxicity in 2 ppm dose-group males

1.a. Hepatocellular Hypertrophy

- Microscopic hepatocellular hypertrophy was minimal to mild, and was reversible on cessation of dosing
- Serious liver pathology representing possible liver damage was not a treatment-related finding in the 104-week dietary study
  - Hyperplasia of liver cells has not been observed in sub-chronic studies with PFOS
  - Hepatocellular necrosis was observed only in one sub-chronic study at doses that produced lethality.

1.a. Hepatocellular Hypertrophy

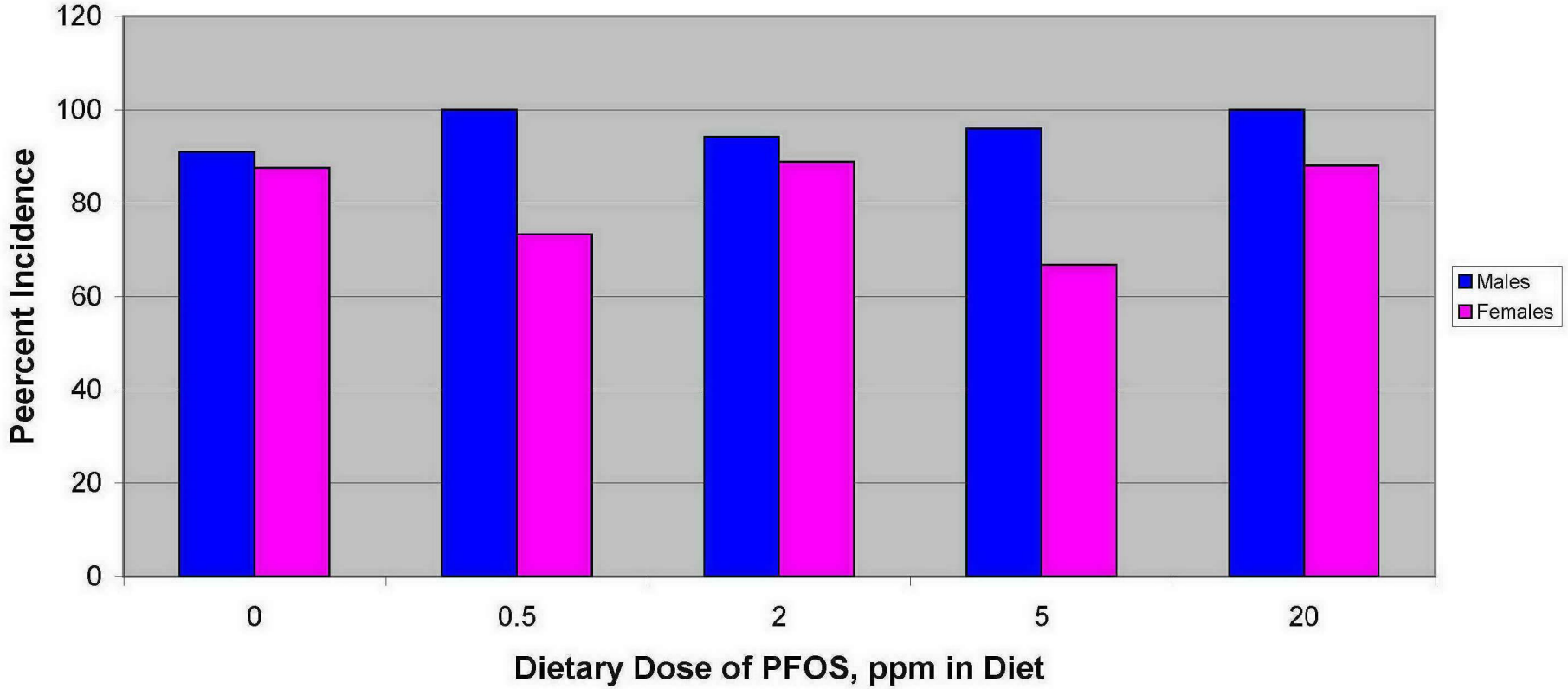
- Clinical chemistry results from studies in rats, monkeys, and human workers do not indicate liver disease
- Male rats with hypertrophy had a statistically significant increase in life span over controls
- Thus, hypertrophy was likely an adaptive response, and does not represent liver toxicity.

1.b. Serum [PFOS] in 2-Year-Old Rats

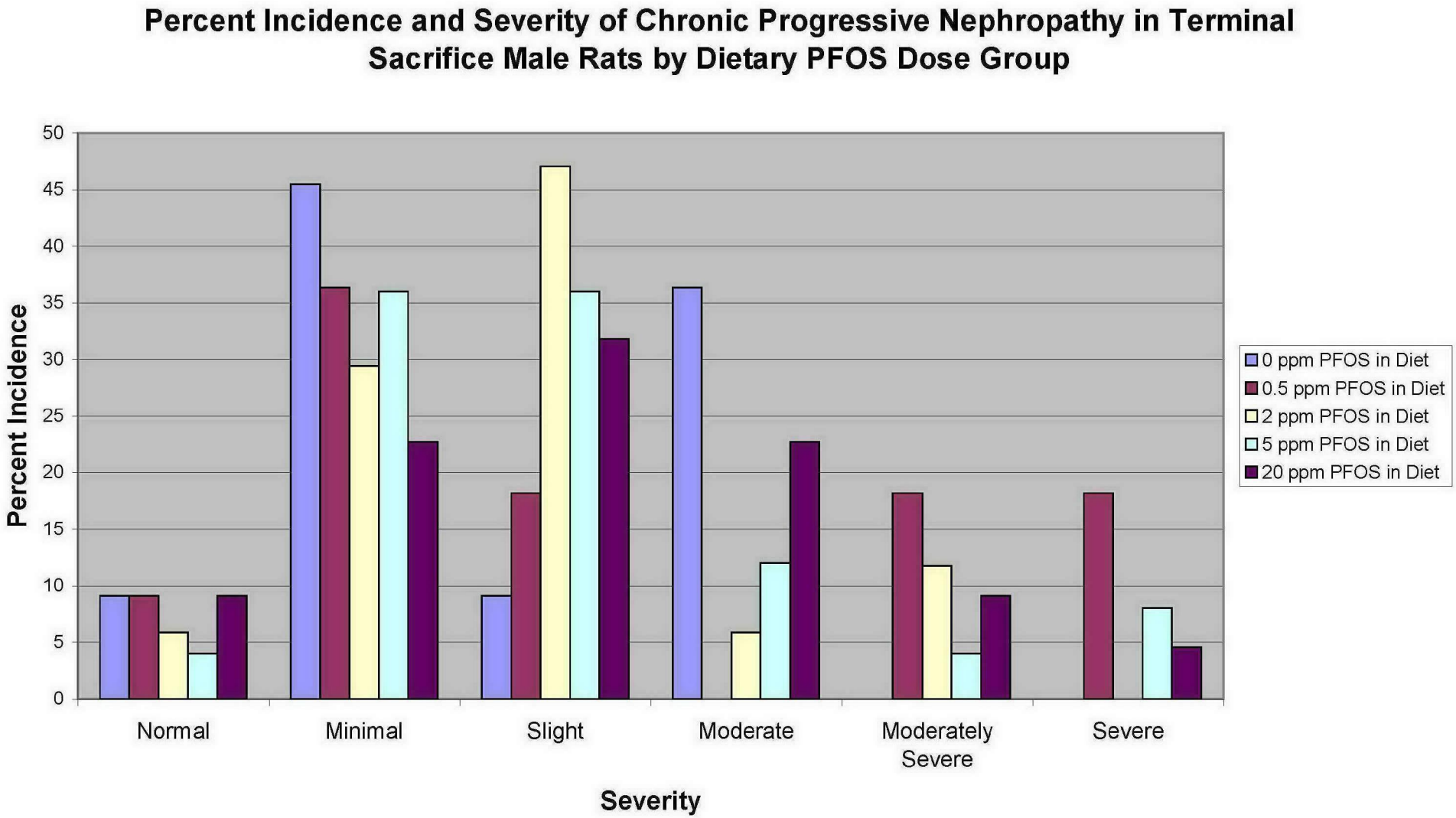
- Serum PFOS Concentrations in 2-Year Old SD Rats are Negatively Biased due to Chronic Progressive Nephropathy
- >90% of 2-year-old SD rats excrete more than 20 mg/day protein in their urine due to chronic progressive nephropathy (Couser and Stilmant, 1975)
- This is consistent with terminal findings in the 2-year dietary study of PFOS

1.b. Chronic Progressive Nephropathy in Study Rats at Two Years

Percent Incidence of Chronic Progressive Nephropathy in Male and Female Sprague Dawley Rats at Terminal Sacrifice in a Two-Year Chronic Dietary Study with PFOS



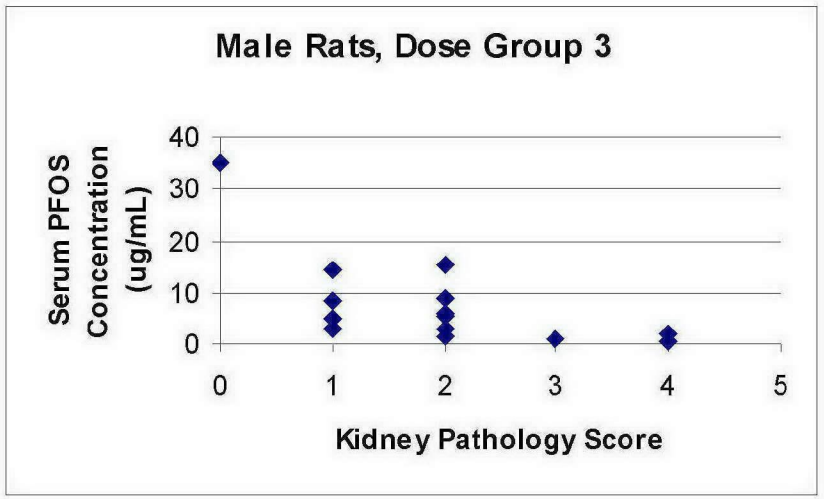
1.b. Incidence and Severity of CPN in Male Study Rats

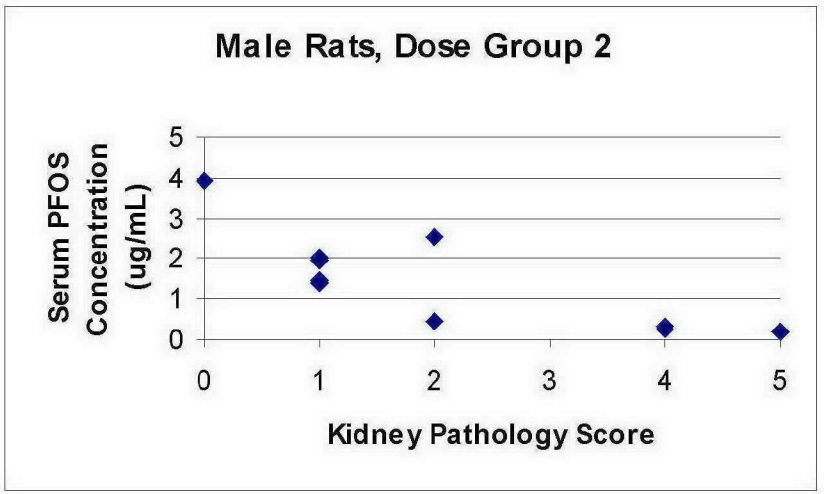


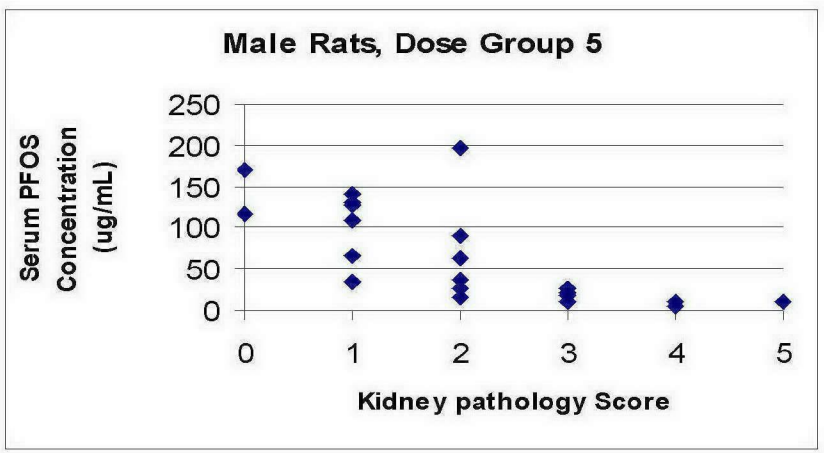
1.b. Proteinuria from CPN: Loss of PFOS in Urine

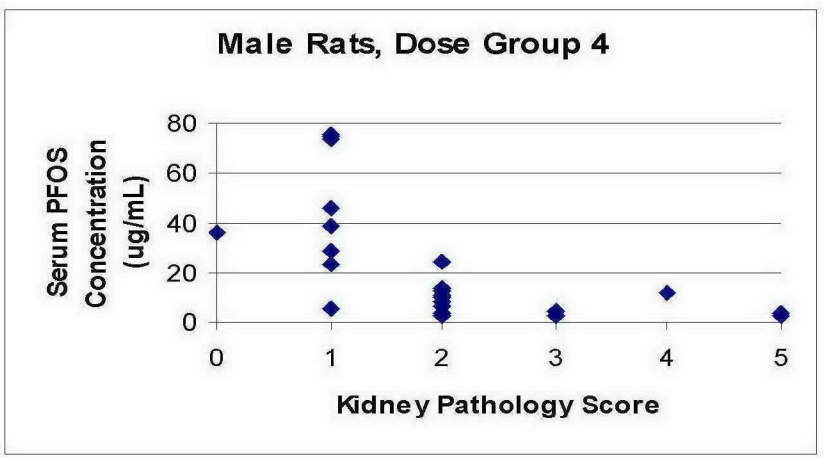
- PFOS is highly protein bound (Luebker et al., 2002; Kerstner-Wood et al., 2004; others)
- The result is lowering of serum PFOS concentration due to protein excretion in urine
- Thus, terminal serum values are not representative of exposure levels

1.b. Serum PFOS Concentration is Negatively Correlated with Severity of Chronic Progressive Nephropathy in 2-Year Old Male Sprague Dawley Rats









1.b. Use of Representative PFOS Serum Concentration Data

- 14-week serum PFOS concentration data from the 2-year study is more representative of internal dose in the rats over time

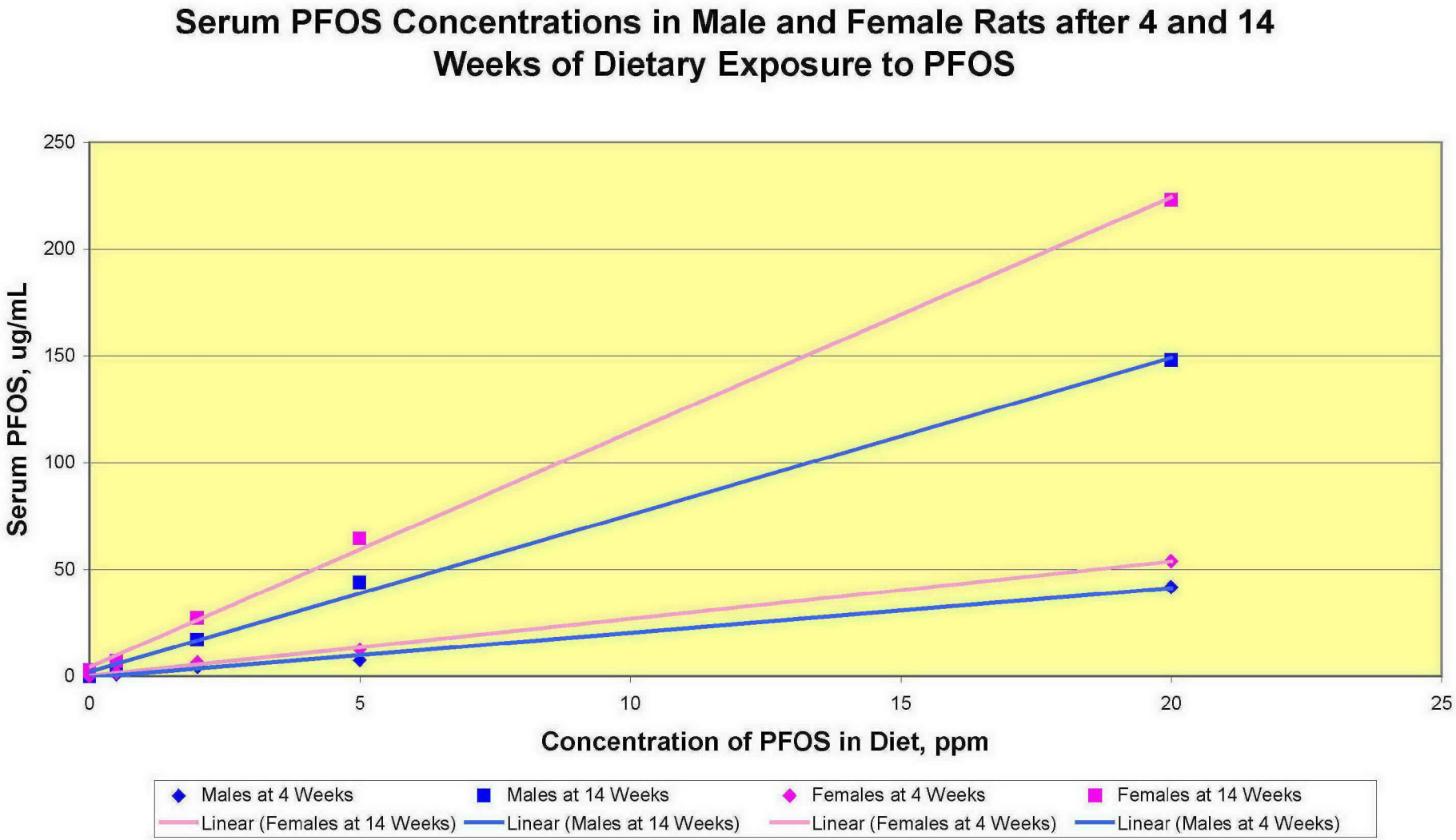
Mean Serum PFOS Concentrations

Table 7. FACT TOX-002 Data Summary of PFOS Concentration—Serum (µg/mL)

Timepoint	Sex	Group 1 Control Average ±SD	Group 2 Low Average ±SD	Group 3 Mid Average ±SD	Group 4 Mid-High Average ±SD	Group 5 High Average ±SD	Group 6 High Recovery Average ±SD
Week 4[a]	Male	<LOQ[b] (n = 5)	0.907 ±0.0619 (n = 5)	4.33 ±1.16 (n = 5)	7.57 ±2.17 (n = 5)	41.8 ±7.92 (n = 5)	
	Female	0.0259 ±0.00663 (n = 5)	1.61 ±0.207 (n = 5)	6.62 ±0.499 (n = 5)	12.6 ±1.73 (n = 5)	54.0 ±7.34 (n = 5)	
Week 14[a]	Male	<LOQ[c] (n = 5)	4.04 ±0.801 (n = 5)	17.1 ±1.22 (n = 5)	43.9 ±4.90 (n = 5)	148 ±13.8 (n = 5)	
	Female	2.67 ±4.58 (n = 5)	6.96 ±0.993 (n = 4[d])	27.3 ±2.34 (n = 5)	64.4 ±5.48 (n = 5)	223 ±22.4 (n = 5)	
Week 53	Male	0.0249 ±0.0182 (n = 5)				146 ±33.5 (n = 4)	
	Female	0.395 ±0.777 (n = 5)				220 ±44.0 (n = 5)	
Day 719	Male						
	Female			20.2 ±13.3 (n = 9)			
Week 105	Male	0.0118 ±0.0104 (n = 11)	1.31 ±1.30 (n = 10)	7.60 ±8.60 (n = 17)	22.5 ±23.5 (n = 25)	69.3 ±57.9 (n = 22)	
	Female	0.0836 ±0.134 (n = 24)	4.35 ±2.78 (n = 15)		75.0 ±45.7 (n = 15)	233 ±124 (n = 25)	
Week 106	Male						2.42 ±5.09 (n = 10)
	Female						9.51 ±8.70 (n = 17)

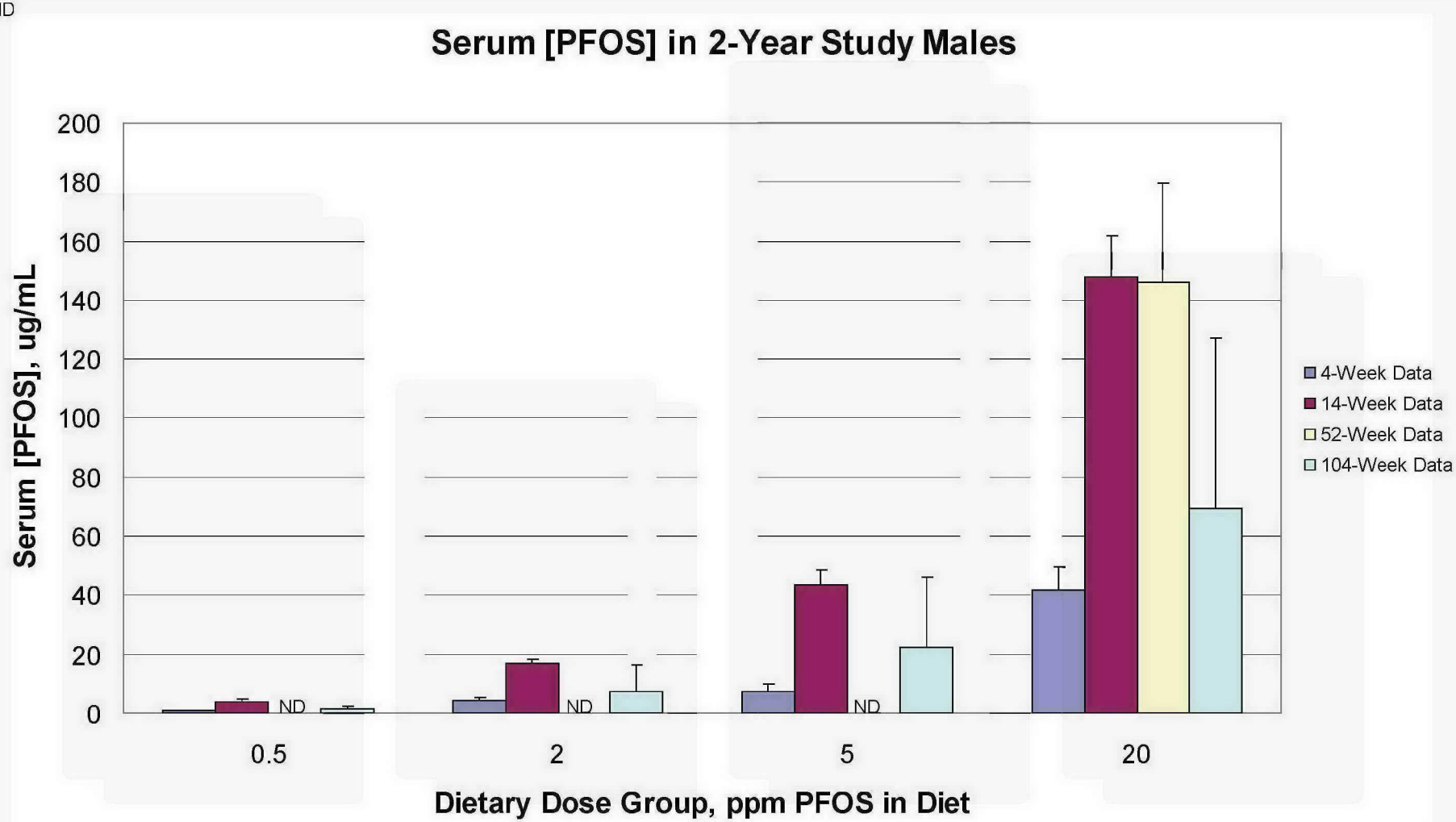
[a] Not corrected for purity of the standard material.
[b] LOQ—Limit of Quantitation = 0.00910 µg/mL
[c] LOQ—Limit of Quantitation = 0.0457 µg/mL
[d] C92987F sample spilled during extraction, no sample remaining for analysis.
It is not possible to verify true recovery of endogenous analyte from tissues without radio-labeled reference material. The only measurement of accuracy available at this time, matrix spike studies, indicated that the sera data are accurate to ±30%; liver data are accurate to ±50%.

1.b. [PFOS] in Serum of Male and Female Rats is Linearly Proportional to Dietary PFOS Dose at 4 and 14 Weeks



1.b. Serum [PFOS] in Males

ND



NOAELs: 1. Systemic Toxicity

Species (Sex)	NOAEL (mg/kg)	Serum [PFOS] (ug/mL)
Monkey (M/F) [a]	0.15	83 (M)/67 (F)
Rat (M/F) [b]	0.34 (M)/0.40 (F) [c]	44 (M)/64 (F)

[a] Seacat et al., 2002

[b] Seacat et al., 2003

[c] Estimated from intake of diet containing 5 ppm PFOS

Note: 3M believes that use of the benchmark dose and benchmark internal concentration, where possible, provides a better basis for risk characterization than LOAELs and NOAELs

3M Approach to Repeat-Dose Data

- Liver weight is preferable to microscopic hypertrophy as a more objective measure, although still not an adverse effect
- Either liver weight or tumor incidence give points of departure far in excess of values used by KEMI
- 3M used modeled “benchmark dose” rather than NOEL

Table. Lower 95% CL of the Benchmark Dose and Benchmark Internal Concentration for Liver/Lipid Effects at 10% Benchmark Response Level

Species/Sex	Study	Endpoint	LBMD (mg/kg)	LBMIC (ppm)
Rat - male	14-Week Dietary	Liver Weight	0.40	44
Rat - male	14-Week Dietary	Serum CHOL Decrease	0.40	44
Monkey - male	6-Month Oral	Serum HDL Decrease	0.14	37
Monkey - male	6-Month Oral	Serum CHOL Decrease	0.16	48
Monkey - female	6-Month Oral	Serum HDL Decrease	0.22	45
Monkey - female	6-Month Oral	Serum CHOL Decrease	0.29	64
Monkey-female	6-Month Oral	Liver Weight	0.22	49
Rat - male	104-Week Bioassay	Liver Tumors	~0.5 [a]	62
Rat - female	104-Week Bioassay	Liver Tumors	~0.5 [a]	92

[a] Based on 7.9 ppm PFOS in diet

Summary:
1. Systemic Toxicity

a. Microscopic incidence of hepatocellular hypertrophy in 2 ppm PFOS dietary dose-group males does not represent an adverse effect

b. Serum PFOS concentration data from two-year-old male rats is negatively biased, and 14-week data should be used.

Note: Benchmark-dose methodology provides better points of departure for risk assessment

Concerns:
2. Developmental Effects

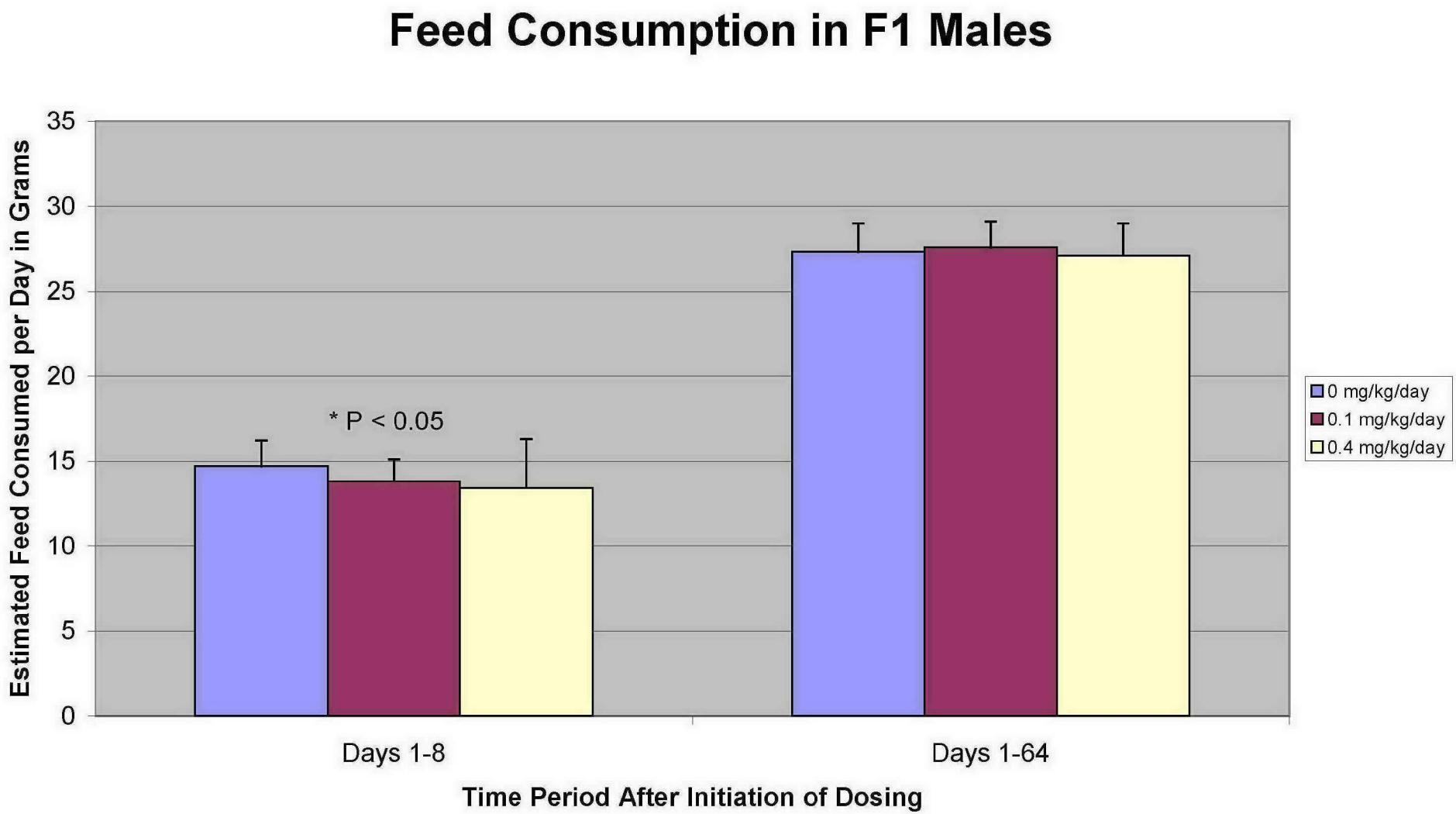
a. Consideration of apparent reduced feed consumption in F1 0.1 mg/kg males during first week post-weaning as an adverse effect

b. Parental generation maternal serum [PFOS] from the end of lactation (at weaning) were used to estimate a serum [PFOS] NOAEL for the feed consumption effect

2.a. Feed Consumption

- Feed consumption of F1 males in the 0.1 mg/kg/day dose group were reduced in the first week with statistical significance ($p < 0.05$)
- **However, 0.4 mg/kg/day males were comparable to controls in same period**
- There were no other time periods with statistically-significant decreases in feed consumption in 0.1 and 0.4 mg/kg/day F1 dose-group males

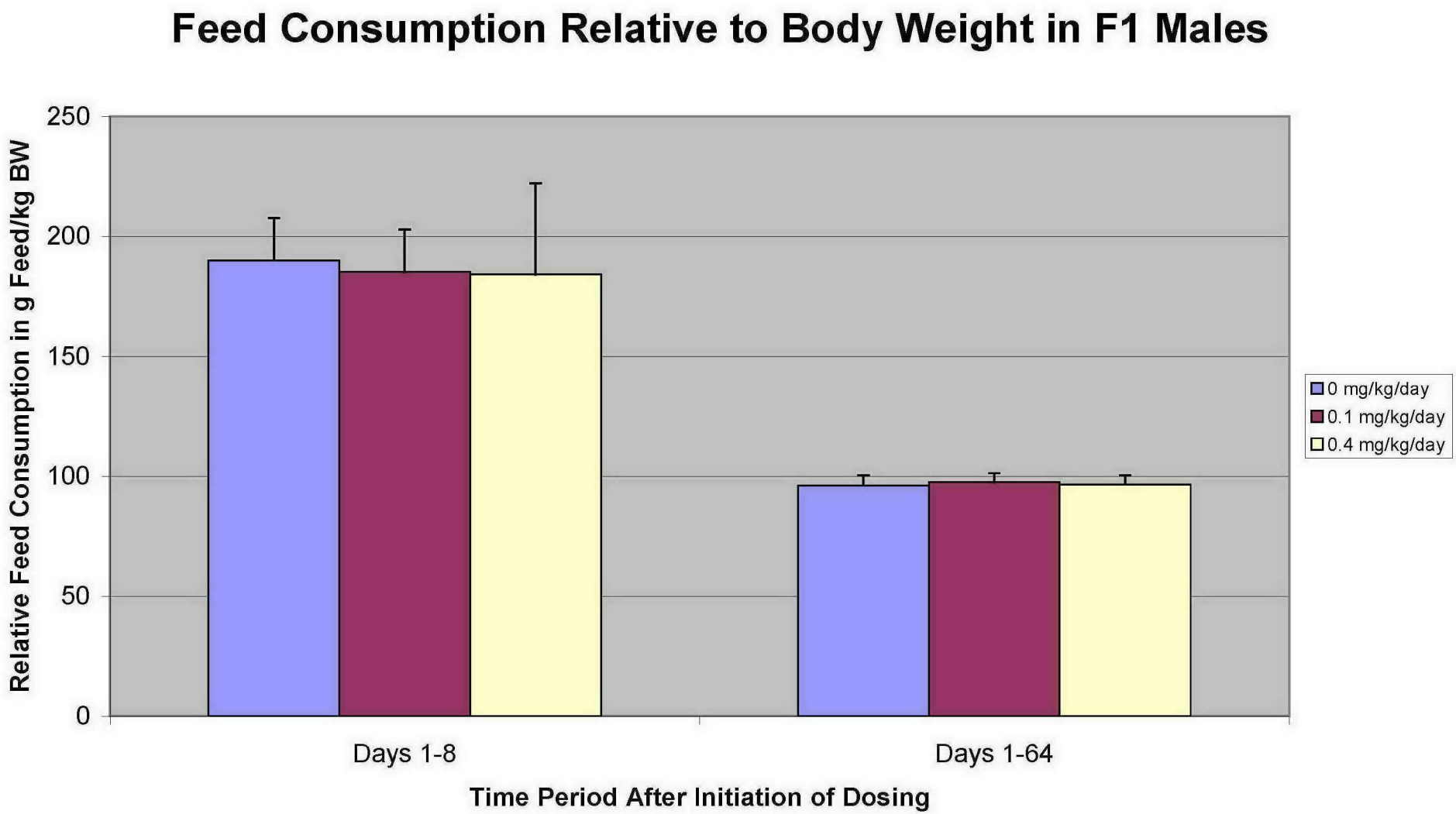
2.a. Feed Consumption Data in F1 Males is Comparable to Controls



2.a. Feed Consumption and Body Weight Comparable to Controls

- Feed consumption relative to body weight was comparable to controls in 0.1 and 0.4 mg/kg/day dose-group F1 males
- Body weight and body-weight gain were also comparable to controls
- The single-week occurrence of statistically-significant reduction in feed consumption in 0.1 mg/kg/day dose-group F1 males has no toxicological significance

2.a. Relative Feed Consumption Comparable to Controls



2.a. Body Weights Comparable to Controls

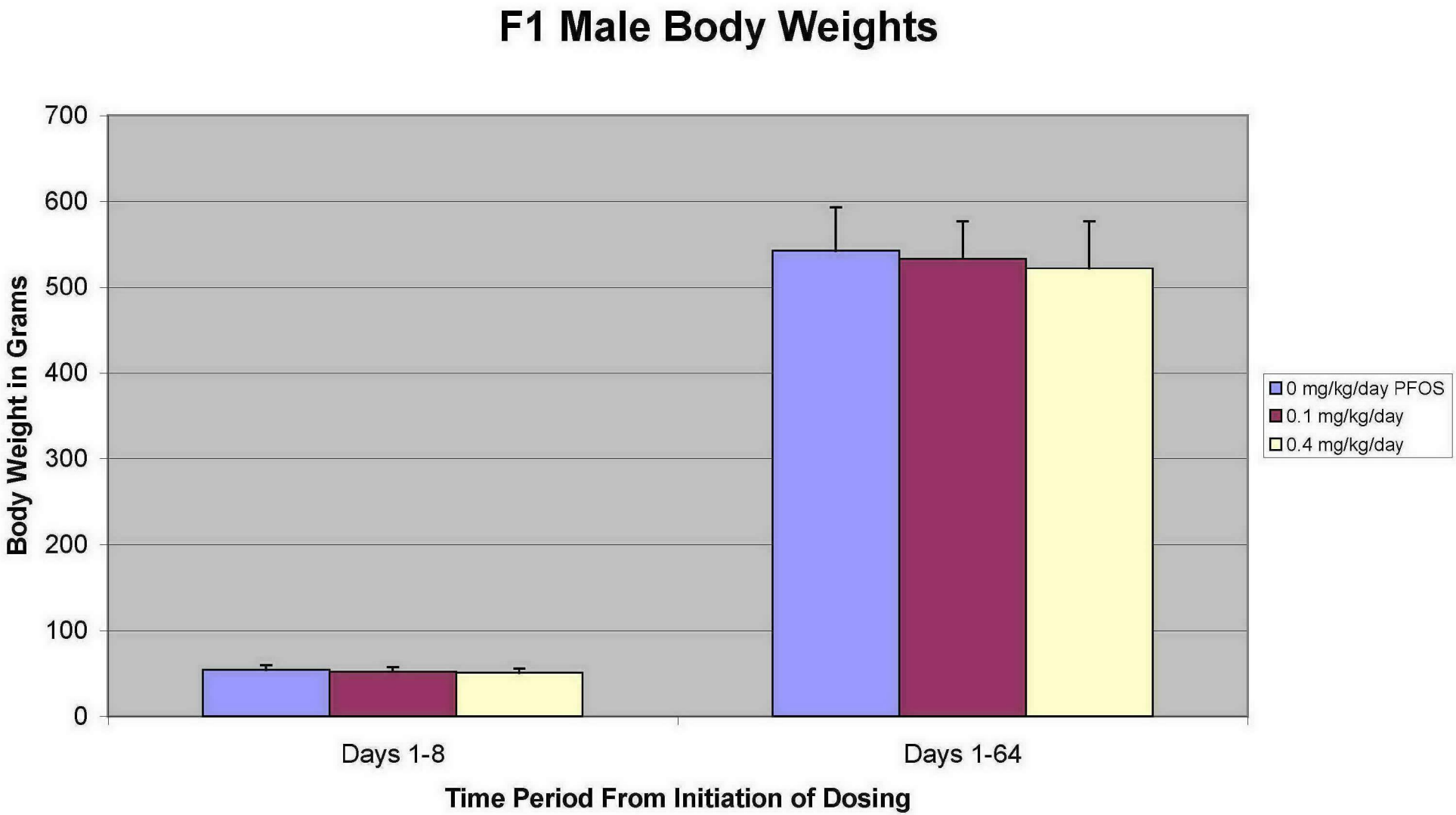
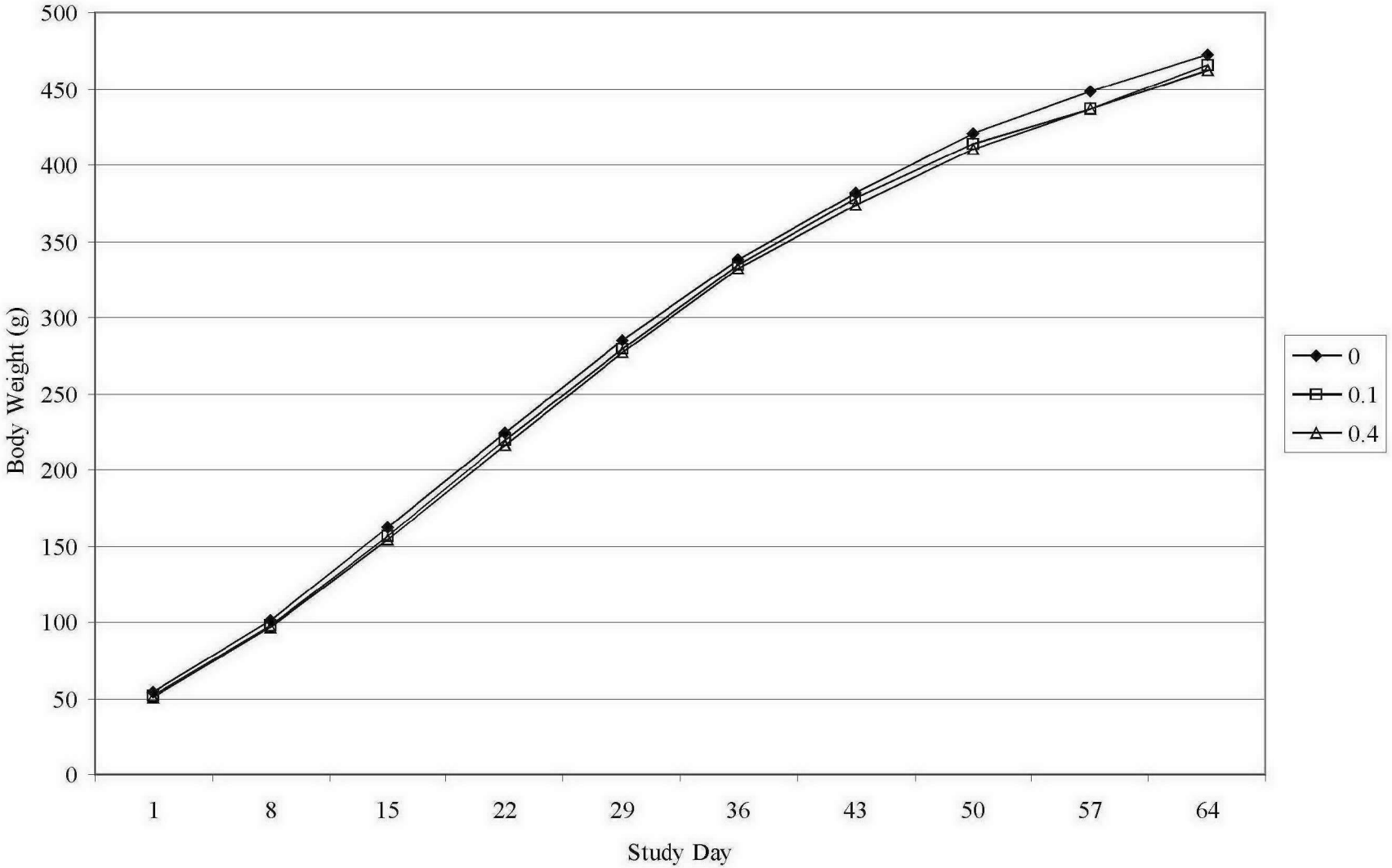
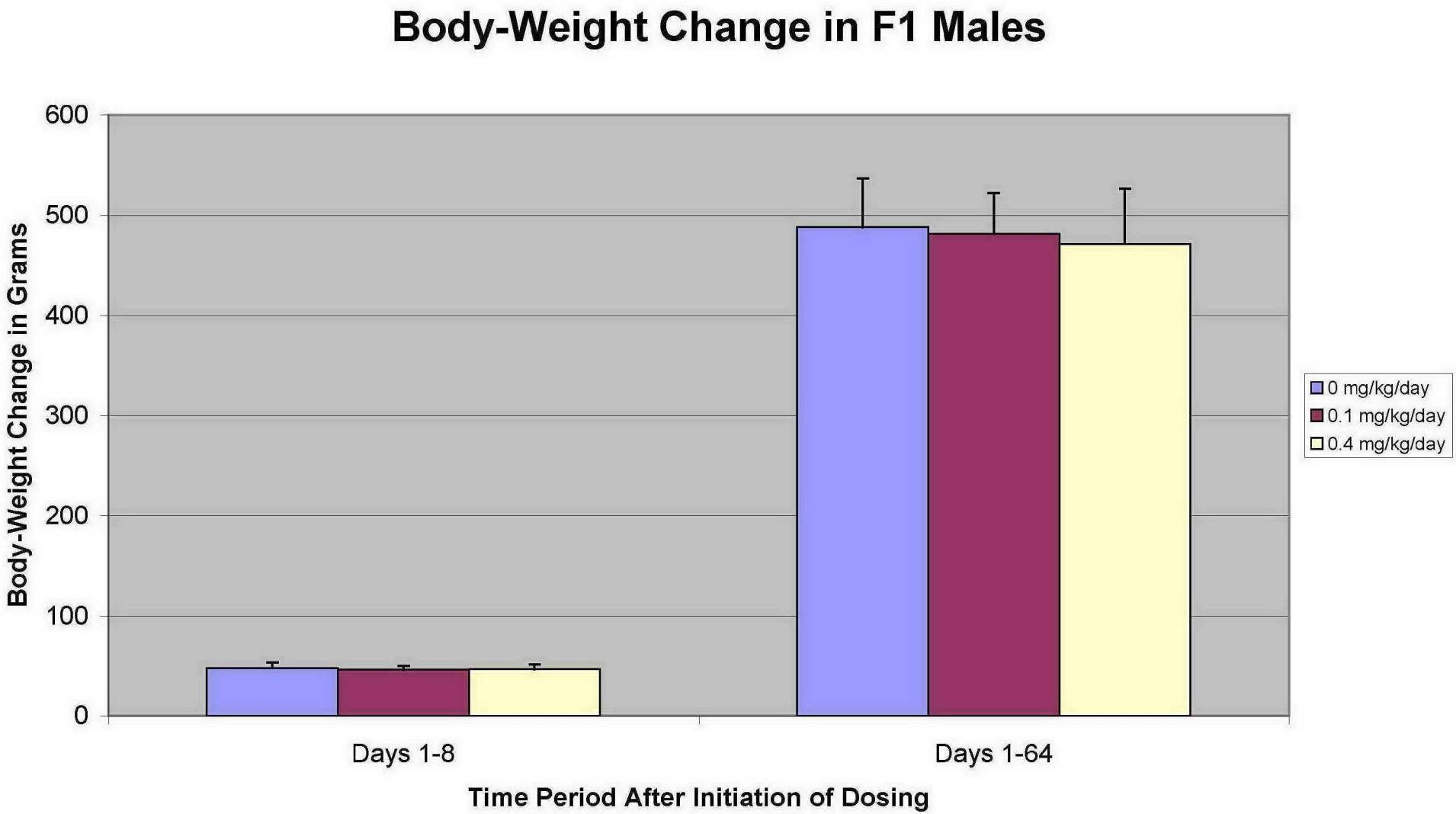


FIGURE 3: Mean Body Weights F_1 Males



2.a. Body-Weight Change Comparable to Controls



2.b. Maternal Rat Serum [PFOS] at End-of-Lactation

- Transfer of PFOS across placenta and into milk reduces maternal body burden and serum PFOS concentration

- Maternal rat serum concentrations at the end of lactation are not appropriate for comparison to general human population values

2.b. Serum Samples from Maternal Rats Were Taken At End of Lactation

"At scheduled sacrifice after completion of the cohabitation period (male rats that sired litters of dams allowed to naturally deliver a litter) and on DL 21 (female rats allowed to naturally deliver a litter), blood samples (approximately 4 mL per rat) were collected from the inferior vena cava from five male and five female rats per dosage group and shipped to the Sponsor for pharmacokinetic analysis."

Note: 3M has conducted several subsequent PK studies to understand maternal [PFOS] prior to mating, during gestation, and during lactation.

2.b. Serum [PFOS] ~50% Lower at End of Lactation

Table. Serum PFOS Concentrations in Rat Dams Treated Daily with PFOS 6-Weeks Prior to Mating and Through Mating, Gestation, and Lactation

	Serum PFOS Concentration, ug/mL, Mean (SD)		
Dose	GD0	GD21	LD22
0.1	10.3 (1.3)	4.91 (1.23)	5.28 (0.358)
0.4	47.1 (5.0)	30.3 (17.0)	18.9 (1.30)
1.6	185 (14)	158 (87)	82.0 (17.5)
3.2	367 (24)	180 (42)	ND

NOAELs: 2. Reproductive and Developmental Toxicity

Species (Sex)	NOAEL (mg/kg)	Serum [PFOS] (ug/mL)
Rat (F) [a]	0.1	10 (GD0) [b] 5 (GD21)

[a] Two-generation study data using PK data from PK studies

[b] GD = gestation day

Note: 3M believes that use of the benchmark dose and benchmark internal concentration, where possible, provides the a better basis for risk characterization than LOAELs and NOAELs

3M Approach to Developmental Data

- Benchmark-dose modeling of:
  - Pup weight gain during lactation
  - Litter size at culling
  - Perinatal pup mortality

- Average of maternal serum PFOS concentration going into gestation and at end of gestation

LBMIC5 Values for Benchmarked Developmental Effects in Rats

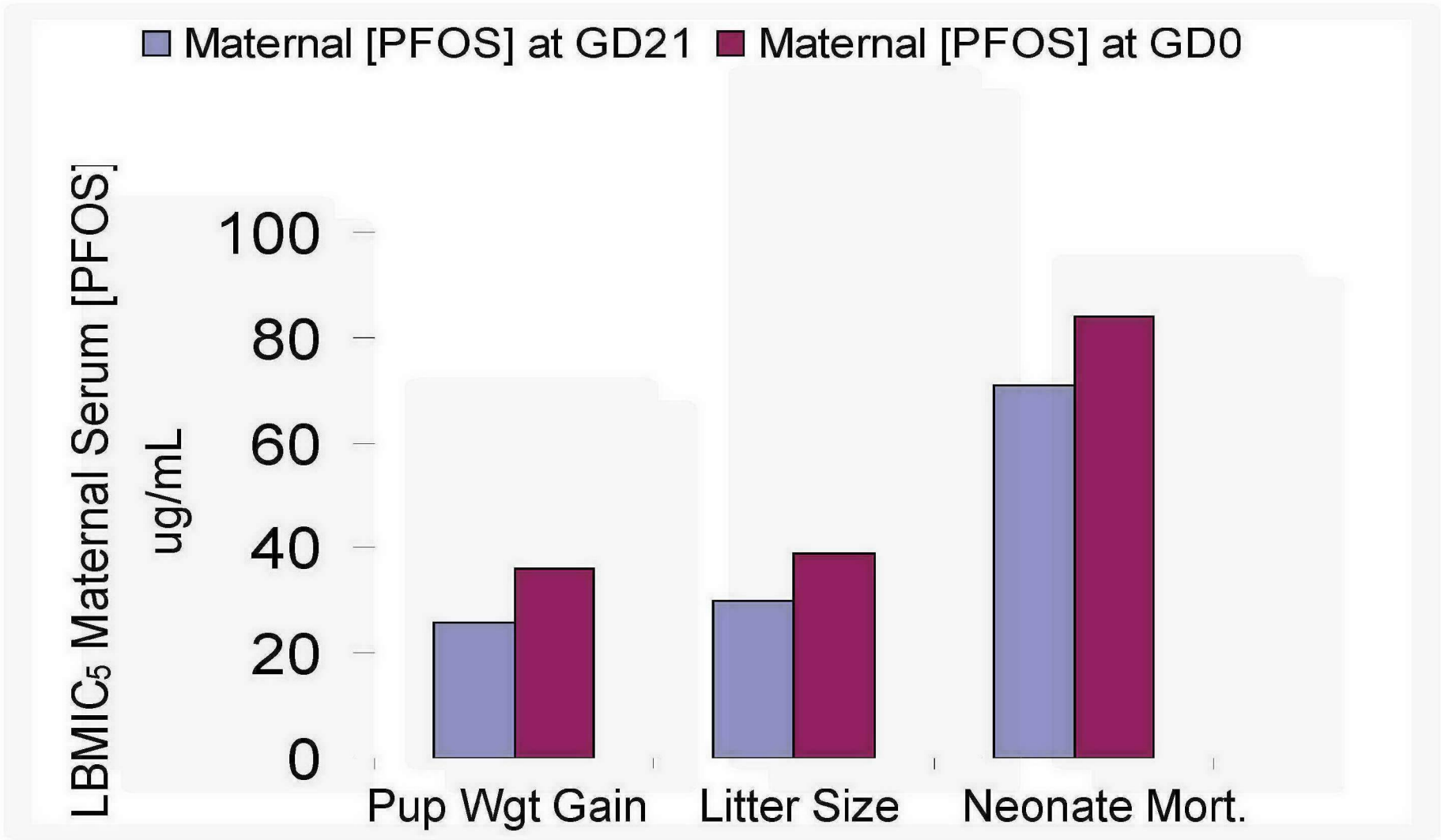


Table. Lower 95% CL of the Benchmark Dose and Benchmark Internal Concentration for Developmental Effects at 5% Benchmark Response Level

Study	Endpoint	LBMD (mg/kg)	LBMIC (ppm)
2-Gen Repro/Dev	F_1 Pup Weight Gain (LD21) [a]	0.34	26
2-Gen Repro/Dev	F_1 Pup Weight Gain (LD21) [b]	0.34	36
2-Gen Repro/Dev	F_1 Litter Size (LD4) [a]	0.39	30
2-Gen Repro/Dev	F_1 Litter Size (LD4) [b]	0.39	39
1-Gen Repro/Dev	F_1 Litter Size (LD5) [a]	0.83	71
2-Gen Repro/Dev	F_1 Pup Mortality (LD4) [a]	0.84	71
1-Gen Repro/Dev	F_1 Pup Mortality (LD5) [a]	0.83	83
2-Gen Repro/Dev	F_1 Pup Mortality (LD4) [b]	0.84	84

[a] **Based on serum samples taken on GD 21**

[b] **Based on serum samples taken on GD 0**

Summary:
2. Developmental Effects

a. A single-week incident of reduced feed consumption in 0.1 mg/kg/day F1 males is not toxicologically meaningful

b. Maternal serum PFOS concentration at the end of lactation is not appropriate for comparison with human population

Note: Benchmarking relevant endpoints provided sounder points of departure for risk assessment

Summary

1. *Systemic Toxicity*

a. Microscopic incidence of hepatocellular hypertrophy in 2 ppm PFOS dietary dose-group males does not represent an adverse effect

b. Serum PFOS concentration data from two-year-old male rats is negatively biased, and 14-week data should be used.

2. *Reproductive/Developmental*

a. A single-week incident of reduced feed consumption in 0.1 mg/kg/day F1 males is not toxicologically meaningful

b. Maternal serum PFOS concentration at the end of lactation is not appropriate for comparison with human population

Note: Benchmark-dose methodology provides better points of departure for risk assessment

Impact on Margins of Safety

Sampled Group	NOAEL (ng/mL)	LBMIC (ng/mL)	Max [PFOS] (ng/mL)	Mean [PFOS] (ng/mL)	NOAEL MOS Max	NOAEL MOS Mean	LBMIC MOS Max	LBMIC MOS Mean	MOSref
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Fish-Eating Females	7,500	31,000	134	54.4	56	138	231	570	100
Female Workers	7,500	31,000	3,620	930	2	8	9	33	50

Discussion

- 3M does not believe data supports conclusion of unacceptable risk to humans.
- 3M would like KEMI to consider these comments before finalizing the risk characterization.
- Is it possible to include 3M comments in record?
- When could KEMI respond to 3M's comments? Is it possible in one week?