Agenda
3M/EPA Science Seminar
October 28, 2015

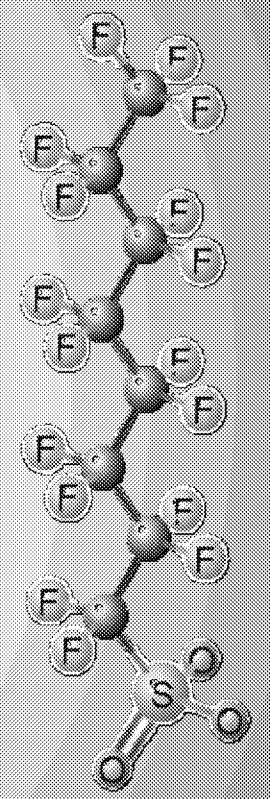
- **Introductions (All)**
- **Introductory Remarks (Carol Ley)**
- **PFOS monkey study update (Sue Chang)**
- **PFAS Biomonitoring and Epidemiology Research Update (Geary Olsen)**
- **General Discussion (All)**
- **Adjourn**

PFOS Monkey Study Update

Sue Chang, PhD
Medical Department, 3M Company
October 28, 2015

PFOS Toxicology

- Toxicological database for PFOS is extensive:
  - Acute, systemic, developmental/reproductive, 2-generation, immuotoxicity, DNT, genotoxicity, 2-year bioassay
  - Toxicity data available in rodents and nonhuman primates
  - Comparative pharmacokinetics are reasonably well-established (mice, rats, monkeys, humans)
- Human biomonitoring data are available.



Current PFOS Reference Doses

Agency	USEPA	MN DoH	UK FSA COT
Document	PHA[1]	HRL[2]	TDI[3]
Reference Study	Monkey 6-month (Seacat et al., 2002)		
Effects	↓HDL (F) ↑TSH (M) ↓TT3 (M & F)	↑TSH, ↓TT3, ↓HDL	Several
Basis	NOAEL	$BMCL_{10}$ (serum)	NOAEL
External Dose (mg/kg/d)	0.03		0.03
Internal Dose (µg/mL serum)		35	
Reference Dose (mg/kg/d)	0.000077 (inferred)	0.00008	0.0003

1 http://water.epa.gov/action/advisories/drinking/upload/2009_01_15_criteria_drinking_pha-PFOA_PFOS.pdf
2 http://www.health.state.mn.us/divs/eh/risk/guidance/gw/pfos.pdf
3 http://cot.food.gov.uk/sites/default/files/cot/cotstatementpfos200609.pdf

TOXICOLOGICAL SCIENCES 68, 249–264 (2002)
Copyright © 2002 by the Society of Toxicology

Subchronic Toxicity Studies on Perfluorooctanesulfonate Potassium Salt in Cynomolgus Monkeys

Andrew M. Seacat,* Peter J. Thomford,† Kris J. Hansen,‡ Geary W. Olsen,* Marvin T. Case,* and John L. Butenhoff*,[1]

*3M Medical Department, Saint Paul, Minnesota 55133; †Covance, Madison, Wisconsin 53704; and ‡3M Environmental Laboratory, Saint Paul, Minnesota 55133

Received November 7, 2001; accepted February 12, 2002

This study was conducted to determine the earliest measurable response of primates to low-level perfluorooctanesulfonate (PFOS) exposure and to provide information to reduce uncertainty in human health risk assessment. Groups of male and female monkeys received 0, 0.03, 0.15, or 0.75 mg/kg/day potassium PFOS orally for 182 days. Recovery animals from each group, except the 0.03 mg/kg/day dose group, were monitored for one year after treatment. Significant adverse effects occurred only in the 0.75 mg/kg/day dose group and included compound-related mortality in 2 of 6 male monkeys, decreased body weights, increased liver weights, lowered serum total cholesterol, lowered triiodothyronine concentrations (without evidence of hypothyroidism), and lowered estradiol levels. Decreased serum total cholesterol occurred in the 0.75 mg/kg/day dose group at serum PFOS levels > 100 ppm. Hepatocellular hypertrophy and lipid vacuolation were present at

products contain chemistries that can degrade or metabolize to PFOS; however, no evidence has been found for metabolic or environmental degradation of PFOS. In May 2000, 3M announced that it would voluntarily cease producing PFOS due to concerns about its biopersistence and its widespread exposure to human populations and wildlife (Giesy and Kannan, 2001; Hansen *et al.*, 2001; Kannan *et al.*, 2001). Nonoccupational exposures to PFOS or precursors are not well understood at this time, but could include environmental sources, consumer products, or as indirect food additives. Following 3M's announcement to cease production of PFOS, the U.S. EPA proposed a Significant New Use Regulation (SNUR) that would regulate new uses of PFOS and related chemicals (EPA, 2000).

Analysis of serum samples from the general population

Seacat et al. 2002 - Lipid Data (Males)

	Time (days)	-27	37	62	91	153	182	217	245	274	322	364	456	546
	Dose (mg/kg/d)		Daily PFOS Dose					Recovery						
Cholesterol (mg/dL)	0	138	140	153	154	154	152	132	135	131	134	127	132	135
	0.03	110	118	*114	126	120	*110							
	0.15	151	146	144	150	149	147	158	161	168	163	167	178	166
	0.75	138	130	125	*112	*65	48*	137	136	139	137	119	118	139
HDL (mg/dL)	0	Did Not Measure				69	63	58	77	65	69	61	59	70
	0.03					*46	*42							
	0.15					55	48	61	84	76	73	74	81	92
	0.75					*19	*13	28	53	40	39	38	35	57

Serum [PFOS] ~ 100 ug/mL

Seacat et al. 2002 - Lipid Data (Females)

	Time (days)	-27	37	62	91	153	182	217	245	274	322	364	456	546
	Dose (mg/kg/d)		Daily PFOS Dose					Recovery						
Cholesterol (mg/dL)	0	149	147	155	*166	163	160	119	131	129	119	137	121	124
	0.03	130	*124	127	134	*110	122							
	0.15	144	133	137	140	130	129	145	151	144	148	137	144	138
	0.75	154	130	*127	*111	*91	*82	133	149	145	129	142	138	146
HDL (mg/dL)	0	Did Not Measure				59	56	54	70	62	58	60	51	64
	0.03					47	42							
	0.15					*41	*36	44	72	52	60	54	47	62
	0.75					*23	*21	34	64	56	60	61	64	74

Serum [PFOS] ~ 100 ug/mL

Seacat et al. 2002 thyroid hormone data (Males)

Dose group (mg/kg/day)	Day –27	Day 37	Day 62	Day 91	Day 182	Day 184	Day 184[a]
Males							
TSH (μU/ml)							
0	0.00 ± 0.00	0.34 ± 0.39	0.57 ± 0.79	0.00 ± 0.00	0.43 ± 0.52	0.37 ± 0.07	0.55 ± 0.44
0.03	0.00 ± 0.00	0.35 ± 0.27	0.42 ± 0.21	0.00 ± 0.00	0.34 ± 0.30	0.56 ± 0.13	0.56 ± 0.10
0.15	0.05 ± 0.13	0.33 ± 0.39	0.98 ± 1.12	0.03 ± 0.07	0.74 ± 0.75	0.70 ± 0.15**	1.38 ± 0.78
0.75	0.00 ± 0.00	0.21 ± 0.26	0.22 ± 0.39	0.00 ± 0.00	0.93 ± 0.57	0.93 ± 0.57**	1.43 ± 0.25
Total thyroxine (T_4) (μg/dl)							
0	3.49 ± 0.64	4.06 ± 0.65	2.27 ± 0.67	3.89 ± 0.55	4.38 ± 0.61*	3.25 ± 0.45	3.24 ± 0.35
0.03	4.46 ± 1.48	5.11 ± 0.95	3.91 ± 0.62**	5.30 ± 0.73**	4.72 ± 0.68	3.85 ± 0.58	3.68 ± 0.5
0.15	4.63 ± 1.16	4.00 ± 0.84	3.08 ± 0.71*	4.47 ± 0.87	3.99 ± 0.62	2.71 ± 0.32	3.00 ± 0.18
0.75	4.88 ± 1.24	3.61 ± 0.55*	2.59 ± 0.59*	4.61 ± 0.57	5.34 ± 1.57	3.30 ± 1.54	3.77 ± 1.65
Total triiodothyronine (T_3) (ng/dl)							
0	110 ± 12	273 ± 30*	145 ± 17	153 ± 10	160 ± 7	115 ± 10	146 ± 19.8
0.03	113 ± 13	273 ± 32*	139 ± 14	153 ± 9*	119 ± 31**	110 ± 7	145 ± 18.0
0.15	118 ± 24	255 ± 25*	142 ± 21	147 ± 18*	125 ± 15**	94 ± 6**	129 ± 4.8
0.75	133 ± 11	239 ± 25*	121 ± 16**	118 ± 22**	66 ± 27*,**	43 ± 25*,**	76 ± 22*,**
Free T_4 (ng/dL)							
0	ND[b]	ND	ND	ND	ND	1.01 ± 0.15	1.4 ± 0.07
0.03	ND	ND	ND	ND	ND	1.21 ± 0.20	1.53 ± 0.19
0.15	ND	ND	ND	ND	ND	0.94 ± 0.11	1.47 ± 0.15
0.75	ND	ND	ND	ND	ND	1.12 ± 0.25	1.50 ± 0.10
Free T_3 (pg/ml)							
0	ND	ND	ND	ND	ND	4.21 ± 0.85	ND
0.03	ND	ND	ND	ND	ND	5.13 ± 0.39	ND
0.15	ND	ND	ND	ND	ND	4.33 ± 0.41	ND
0.75	ND	ND	ND	ND	ND	2.45 ± 0.80**	ND

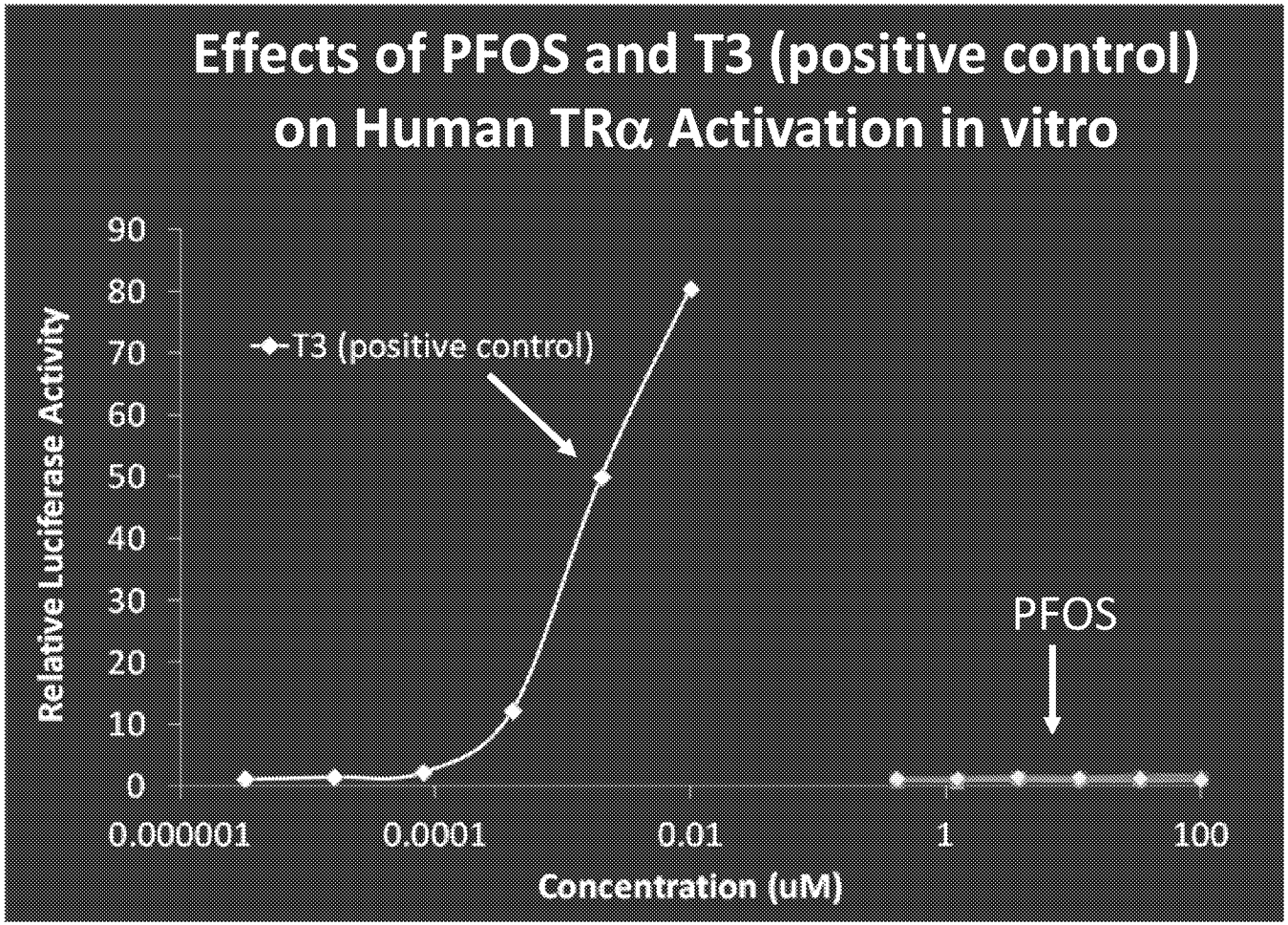
Seacat et al. 2002 thyroid hormone data (Females)

Dose group (mg/kg/day)	Day −27	Day 37	Day 62	Day 91	Day 182	Day 184	Day 184*
Female							
TSH (μU/ml)							
0	0.21 ± 0.51	0.73 ± 0.94	1.19 ± 1.72	0.00 ± 0.00	0.73 ± 1.12	0.53 ± 0.31	1.02 ± 0.69
0.03	0.00 ± 0.00	0.24 ± 0.32	0.46 ± 0.86	0.00 ± 0.00	0.68 ± 0.82	0.43 ± 0.09	2.01 ± 2.09
0.15	0.34 ± 0.80	0.61 ± 0.70	0.82 ± 1.18	0.02 ± 0.04	1.27 ± 1.52	0.47 ± 0.20	1.33 ± 1.13
0.75	0.01 ± 0.02	0.59 ± 0.62	0.74 ± 0.85	0.00 ± 0.00	0.84 ± 0.79	1.03 ± 0.50**	1.86 ± 1.29
Total thyroxine (T_4) (μg/dl)							
0	6.46 ± 1.71	5.82 ± 1.22	3.53 ± 0.86*	4.77 ± 0.75	5.66 ± 0.89	4.14 ± 1.31	3.78 ± 1.07
0.03	7.06 ± 1.79	5.06 ± 1.18	4.07 ± 1.08*	6.00 ± 0.72	4.33 ± 1.46	3.48 ± 0.72	2.80 ± 1.9
0.15	7.13 ± 1.17	3.68 ± 0.65*,**	2.77 ± 0.88*	3.77 ± 0.70*	3.91 ± 0.62*,**	2.88 ± 0.82	3.23 ± 0.50
0.75	7.10 ± 1.30	4.23 ± 0.90*,**	3.08 ± 1.05*	4.92 ± 0.81*	5.61 ± 1.00	3.43 ± 1.05	3.80 ± 0.67
Total triiodothyronine (T_3) (ng/dl)							
0	119 ± 39	230 ± 30*	115 ± 28	143 ± 36	135 ± 31	106 ± 19	148 ± 21.6
0.03	171 ± 80	244 ± 24	136 ± 29	147 ± 19	120 ± 24	92 ± 15	139 ± 11.5
0.15	138 ± 42	214 ± 21*	114 ± 19	110 ± 10**	97 ± 8*,**	80 ± 10*,**	116 ± 16.8
0.75	155 ± 74	196 ± 6	96 ± 9	88 ± 6*,**	85 ± 12*,**	58 ± 5*,**	99 ± 16.8*
Free T_4 (ng/dL)							
0	ND[b]	ND	ND	ND	ND	1.06 ± 0.30	1.53 ± 0.28
0.03	ND	ND	ND	ND	ND	1.01 ± 0.27	1.70 ± 0.26
0.15	ND	ND	ND	ND	ND	0.90 ± 0.22	1.35 ± 0.21
0.75	ND	ND	ND	ND	ND	1.08 ± 0.30	1.57 ± 0.31
Free T_3 (pg/mL)							
0	ND	ND	ND	ND	ND	4.05 ± 0.98	ND
0.03	ND	ND	ND	ND	ND	3.59 ± 0.50	ND
0.15	ND	ND	ND	ND	ND	3.27 ± 0.42	ND
0.75	ND	ND	ND	ND	ND	2.82 ± 0.29**	ND

Clinical Diagnosis

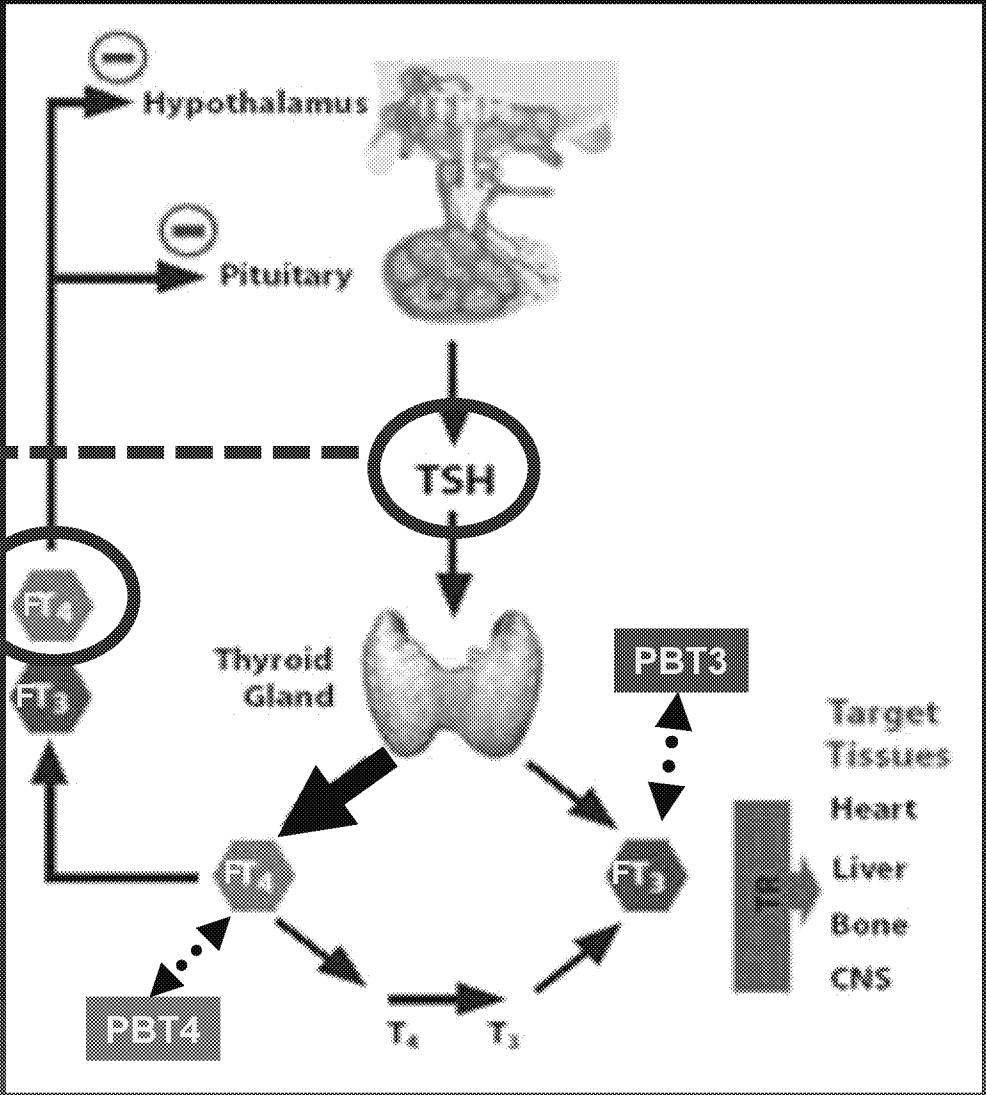
✓ Normal histological findings: thyroid and pituitary

✓ PFOS does not activate human thyroid receptors



Thyroid Hormones and H-P-T Axis At-A-Glance

Clinical Diagnostic Index for Thyroid Hormones



New Monkey Study with PFOS

- OBJECTIVE -

To rigorously determine serum PFOS concentrations that are potentially associated with a change (from baseline) in selected clinical chemistries in cynomolgus monkeys

	Seacat et al., 2002	Current study
Dose route	Daily oral capsule	Bolus oral dose (periodic)
Exposure Length	Daily for 182 days	DG 1: Control (sham-dosed) DG 2: D43, 288, 358 DG 3: D106
Recovery	One year post dose	Up to 1 year
Blood sampling for serum PFOS determination	Days -27, 7, 14, 28, 42, 56, 84, 112, 140, 168, 182, 187, 196, 203, 210, 217, 245, 273, 301, 329, 357, 371, 399, 427, 455, 483, 511, 539, and 553	Days -7, 1, 8, 22, 43, 50, 64, 85, 106, 113, 127, 148, 169, 176, 190, 211, 232, 253, 274, 288, 295, 309, 330, 358, 365, 379, and 400
Blood sampling for clinical chemistry	Days -27, 37, 62, 91, 153, 182, 217, 245, 274, 322, 364, 456, and 546	Days -7, 1, 8, 22, 43, 50, 64, 85, 106, 113, 127, 148, 169, 176, 190, 211, 232, 253, 274, 288, 295, 309, 330, 358, 365, 379, and 400

Key Clinical Chemistry Parameters

Group	Parameters
Lipid Panel	CHOL, HDL, LDL, TRIG
Thyroid Hormone Panel	TT3, TT4, dFT4, TSH
Liver Function Panel	CK, AST, ALT, ALP, GGT, TBIL, PT
Renal Function Panel	UREAN, CREAT, GLU, ALB, GLOB
Electrolytes	CA, PHOS, Na, K, Cl
Coagulation	PT, APTT

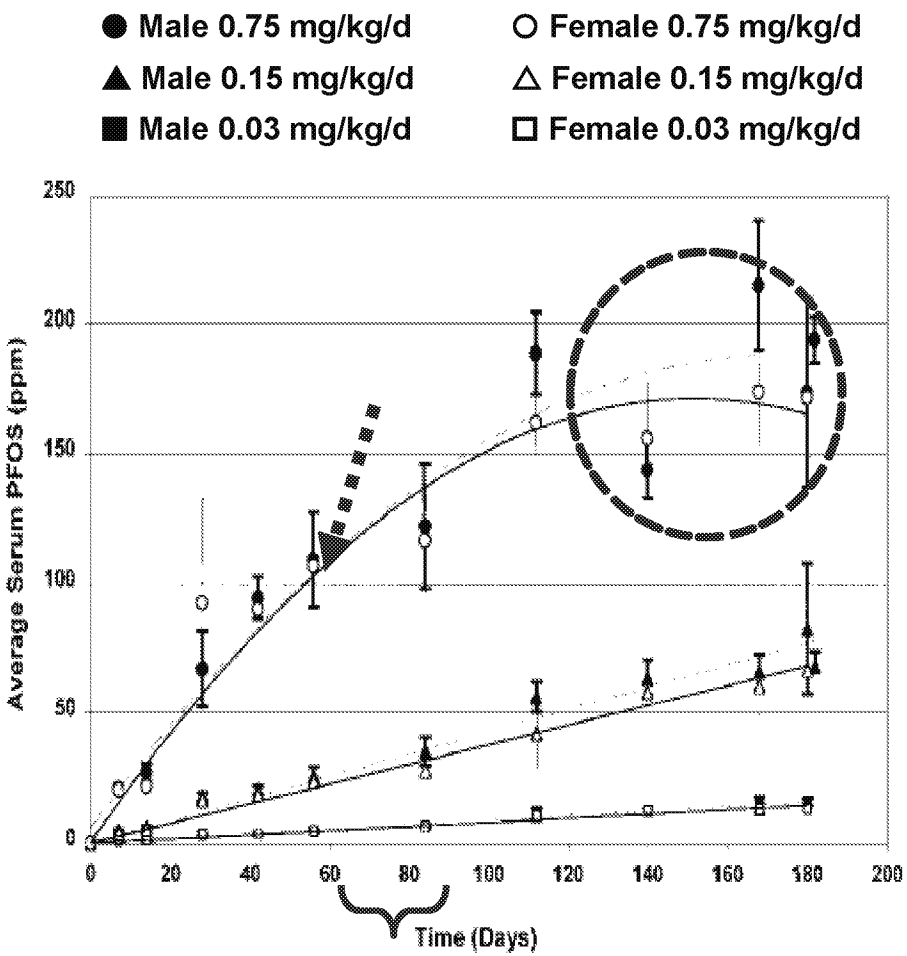
Data Interpretations

#	Tasks
1	Statistical analyses
2	Clinical pathology review (board-certified clinical pathologists)
3	Benchmark Modelling

Serum PFOS Concentrations (µg/mL, ppm)

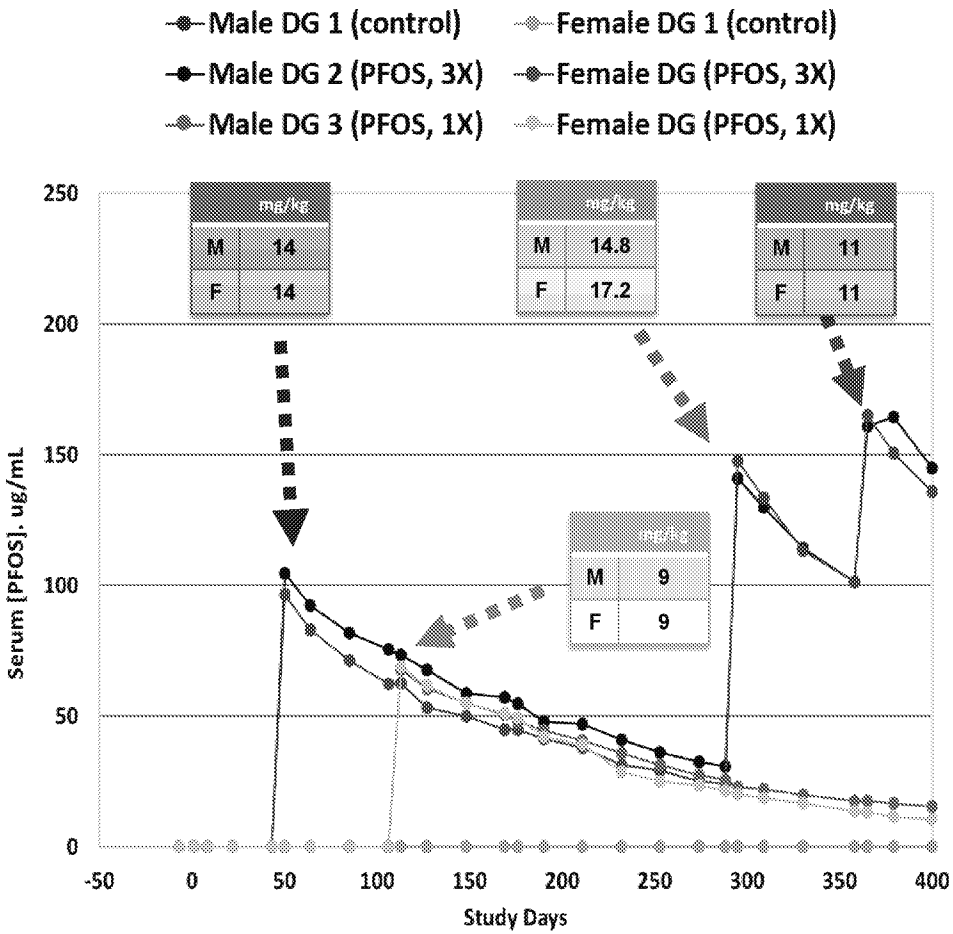
Seacat et al. Study

(Daily oral capsule)



Current Study

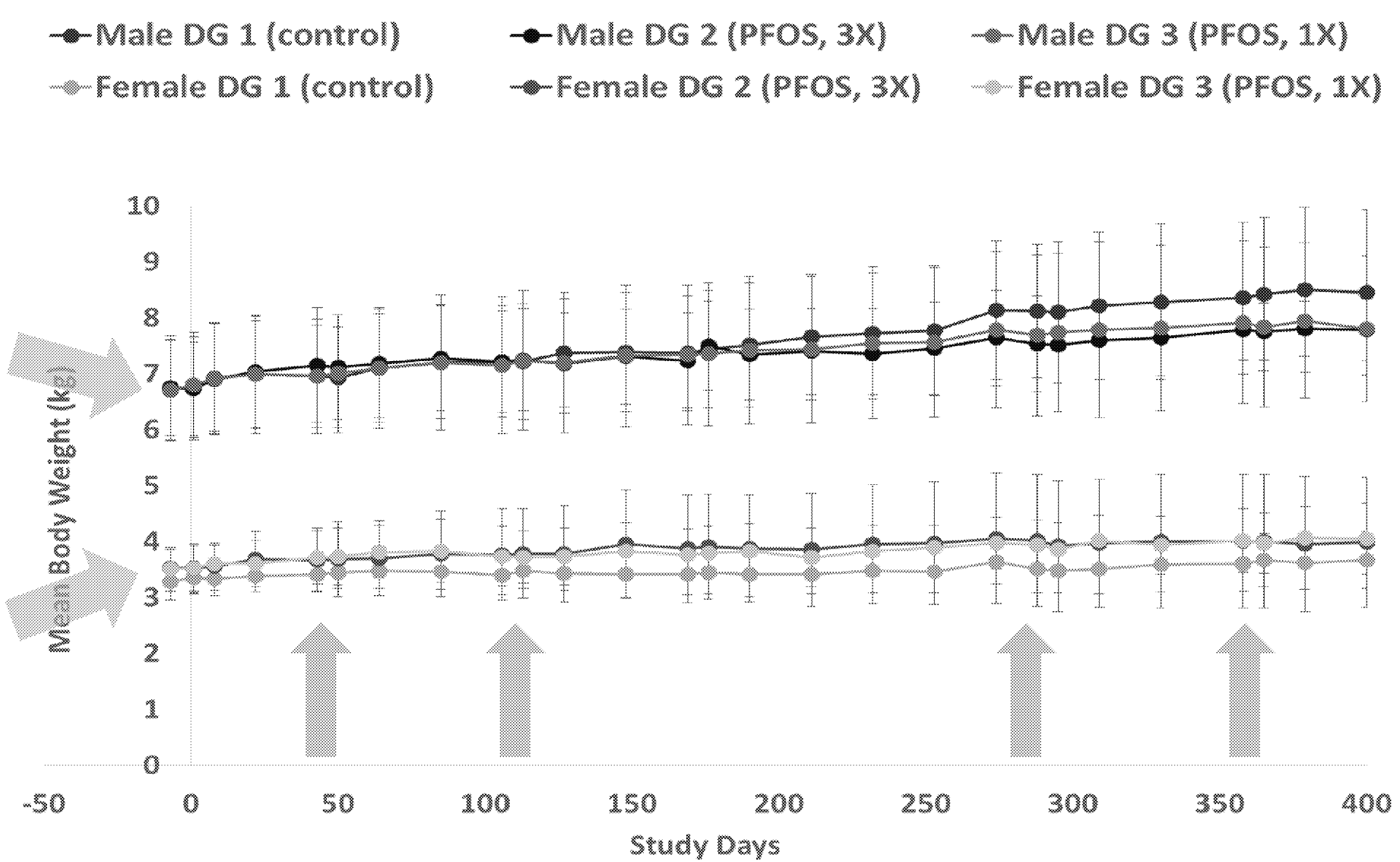
(Periodic bolus oral dose)



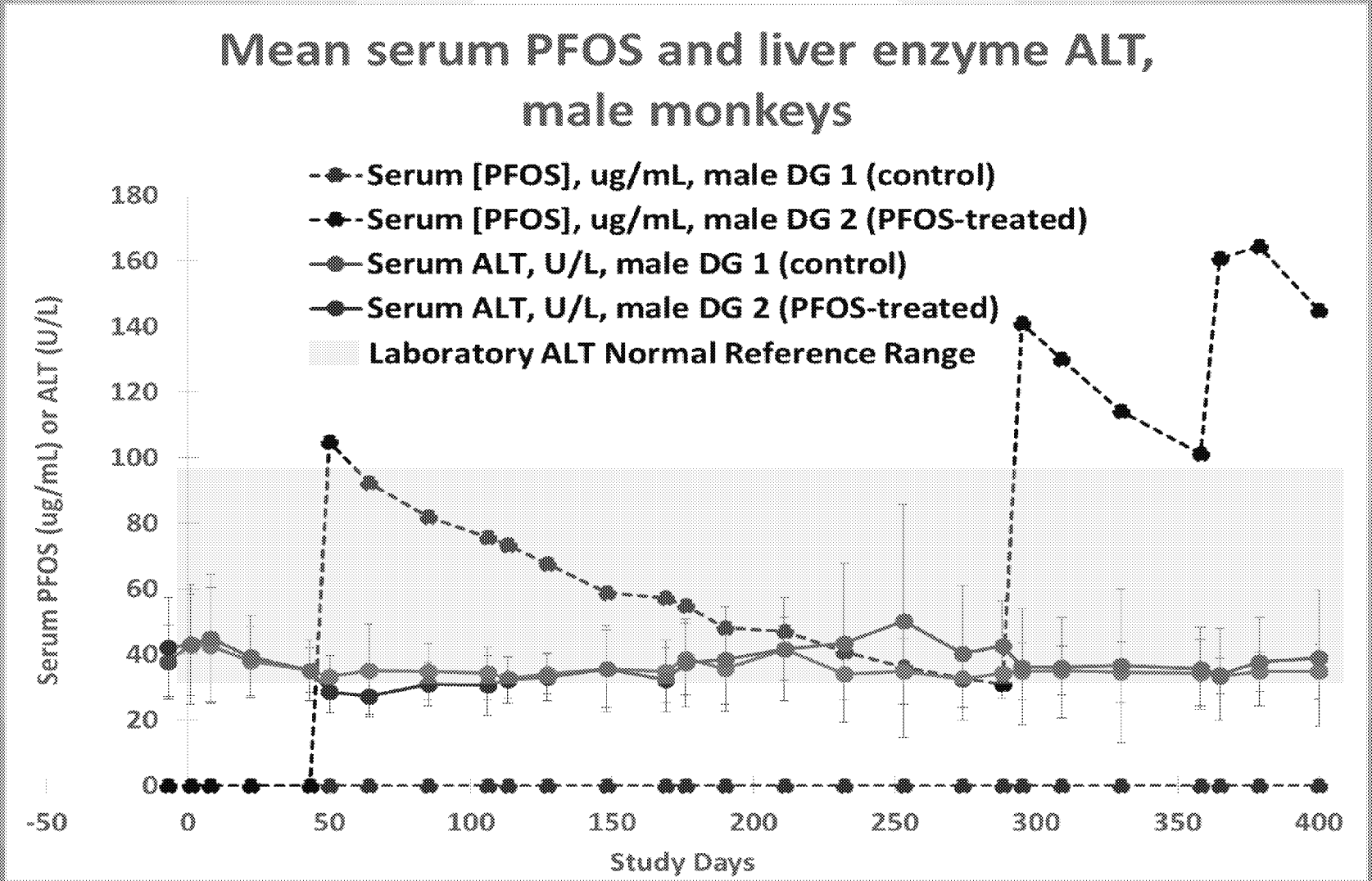
In-life Observations

- No mortality
- All monkeys appeared normal and healthy throughout the study
- All monkeys gained weight during the study
- All monkeys were released back to the colony right after the end of in-life

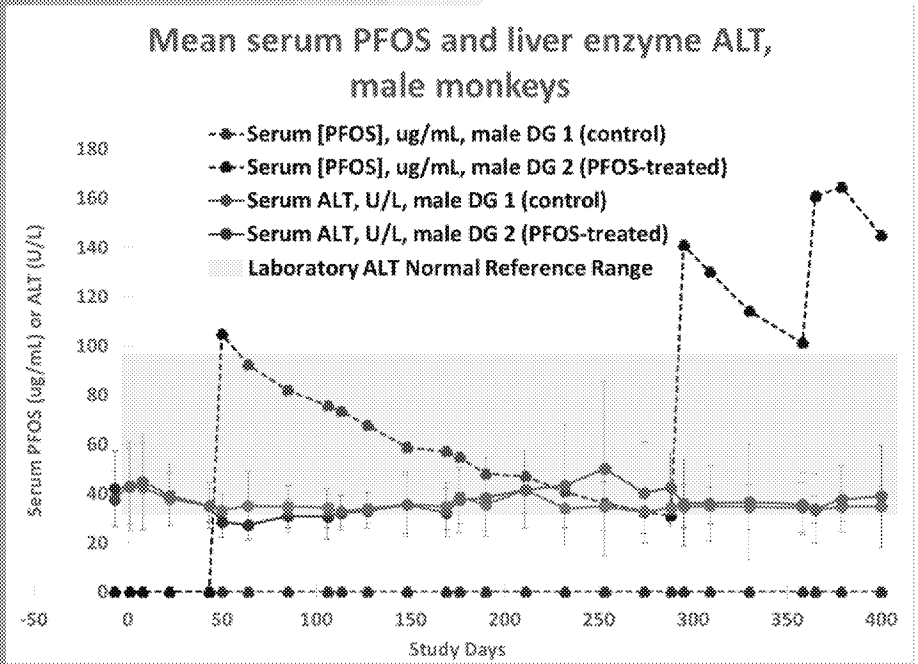
Body Weight Data

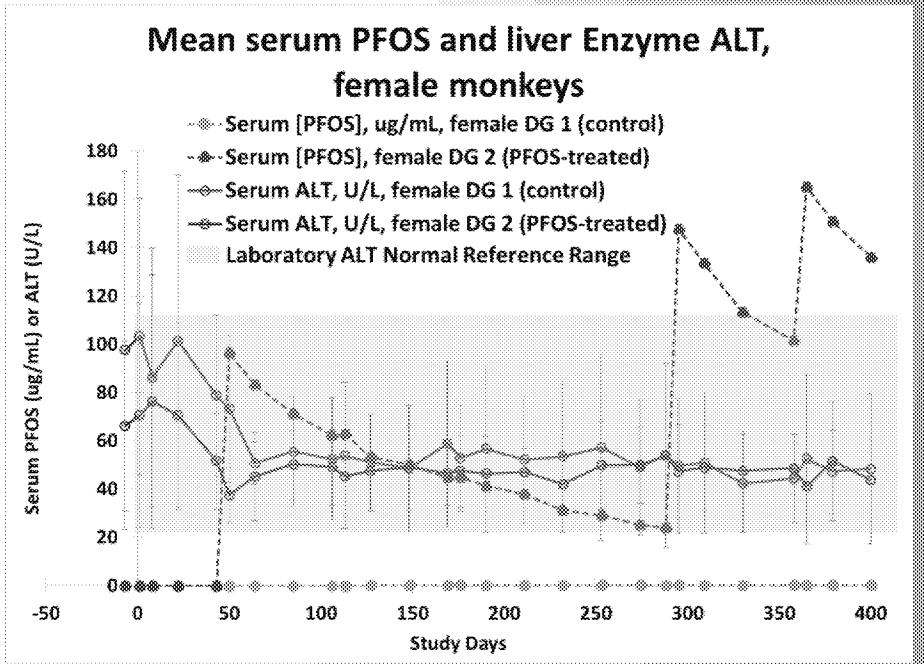


Explanation of Graph Legends



Current Study:
ALT Enzyme (Liver Function)

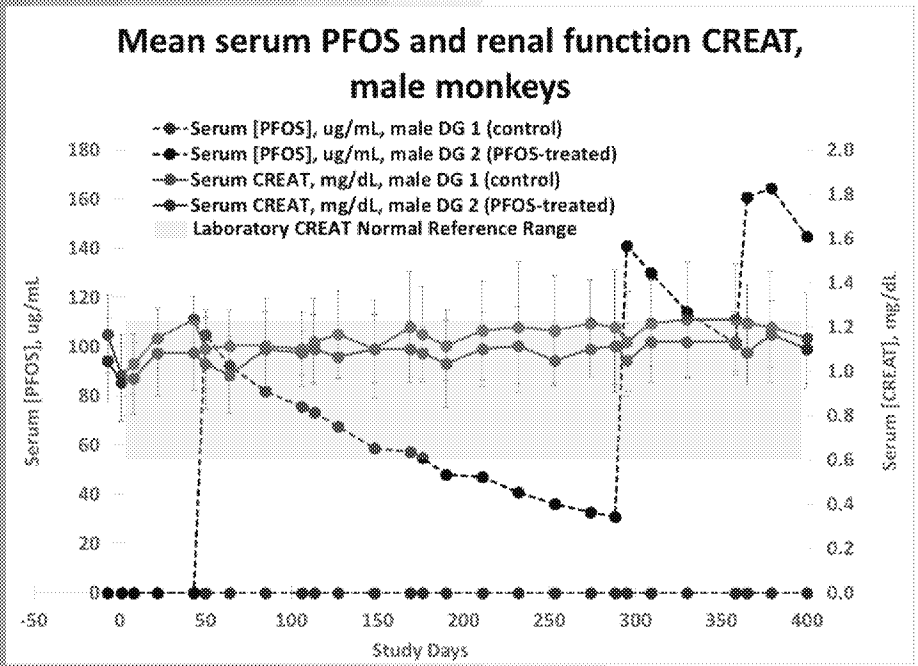


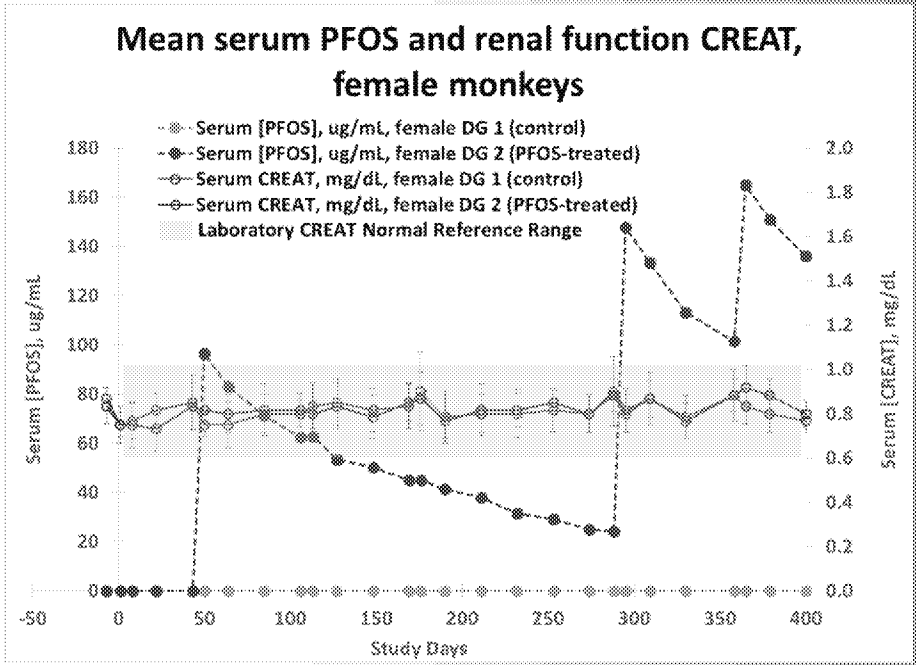


All other liver panel measurements were within normal ranges

AST, ALP, GGT, CK, BIL, PT

Current Study: CREATININE (Kidney Function)

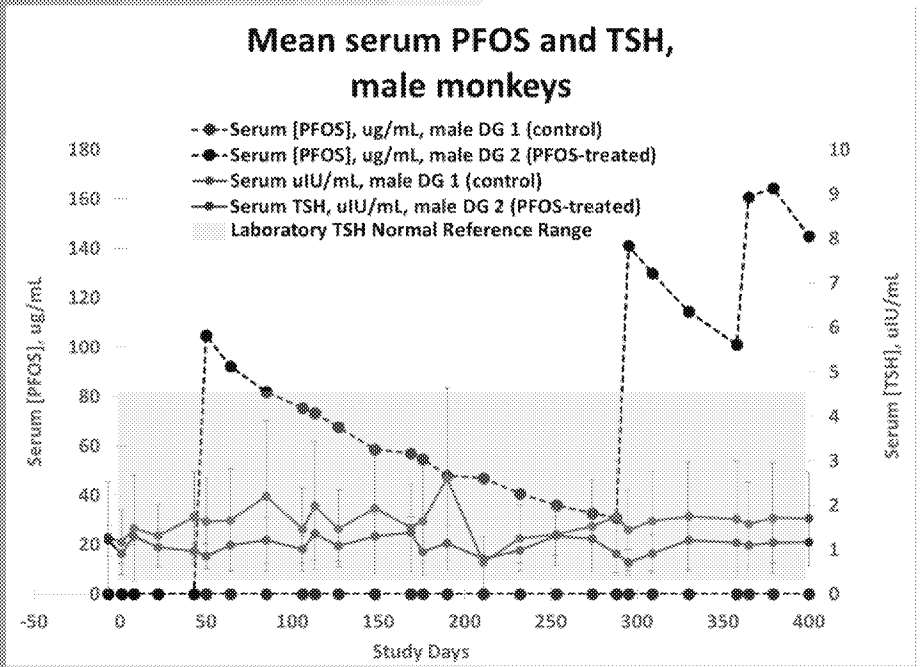


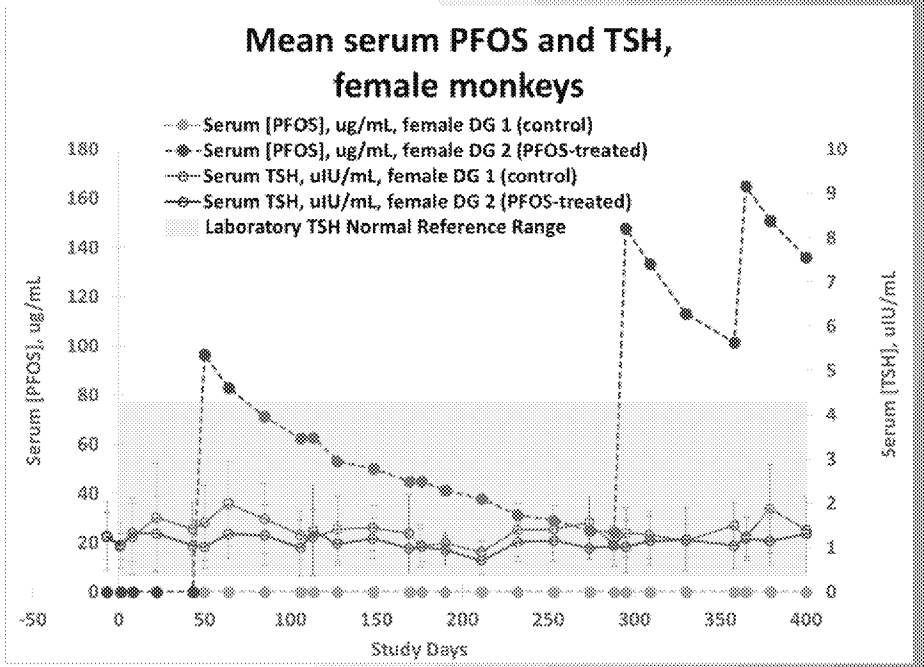


All other renal panel measurements were within normal ranges

UREAN, GLU, ALB, GLOB

Current Study:
TSH (Primary Thyroid Function Diagnosis)



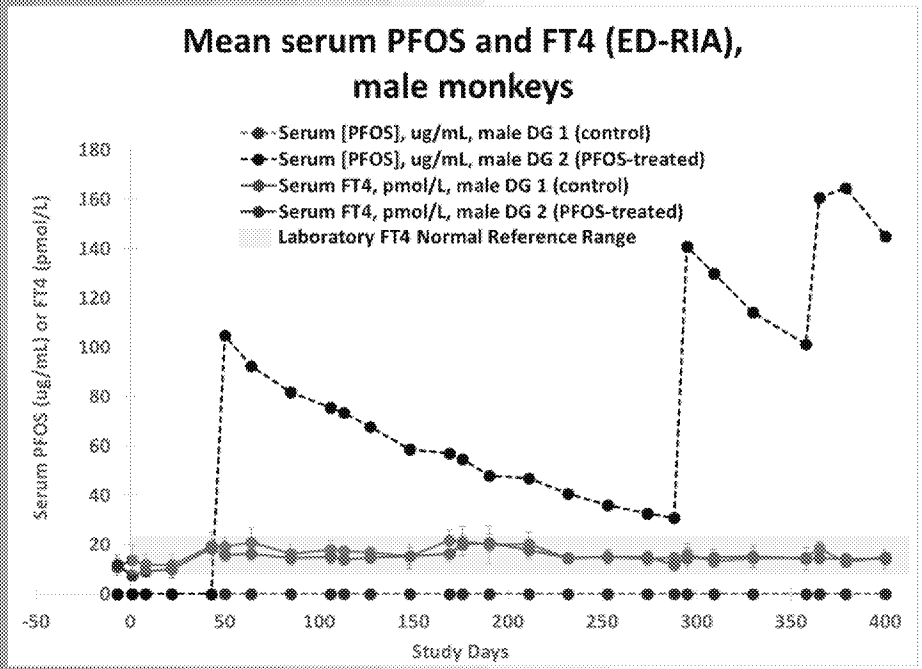


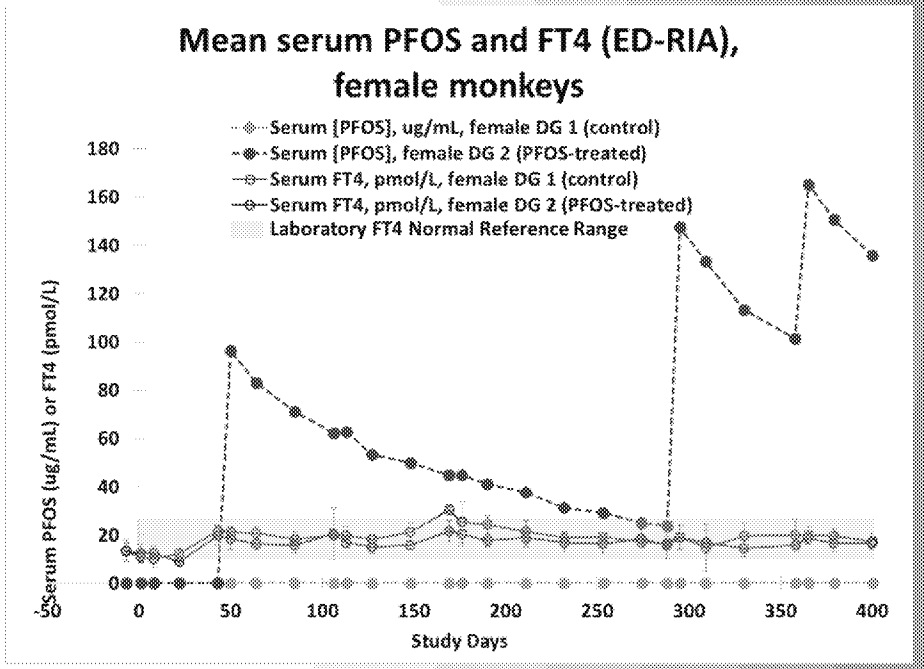
No effects on TSH

Current Study:

FT4 (Supplemental Thyroid Function Diagnosis)

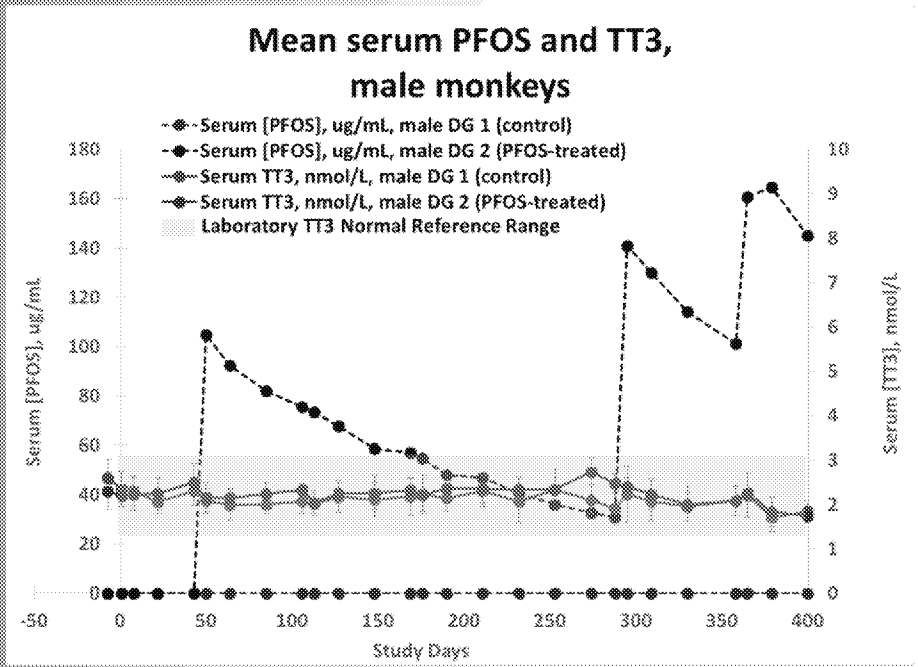
(should not be used stand alone)

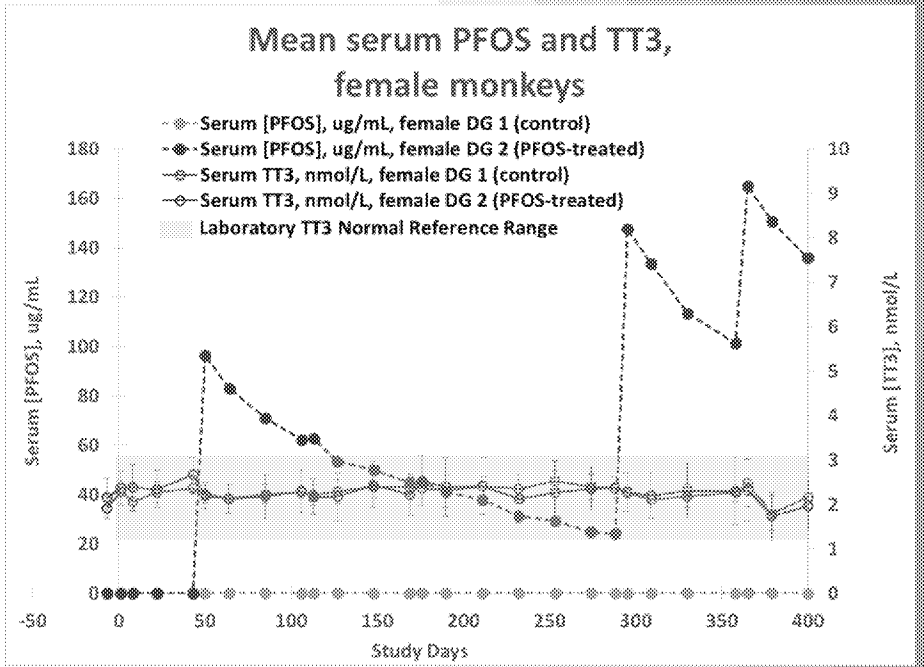




No effects on FT4

Current Study: TT3 (Thyroid)

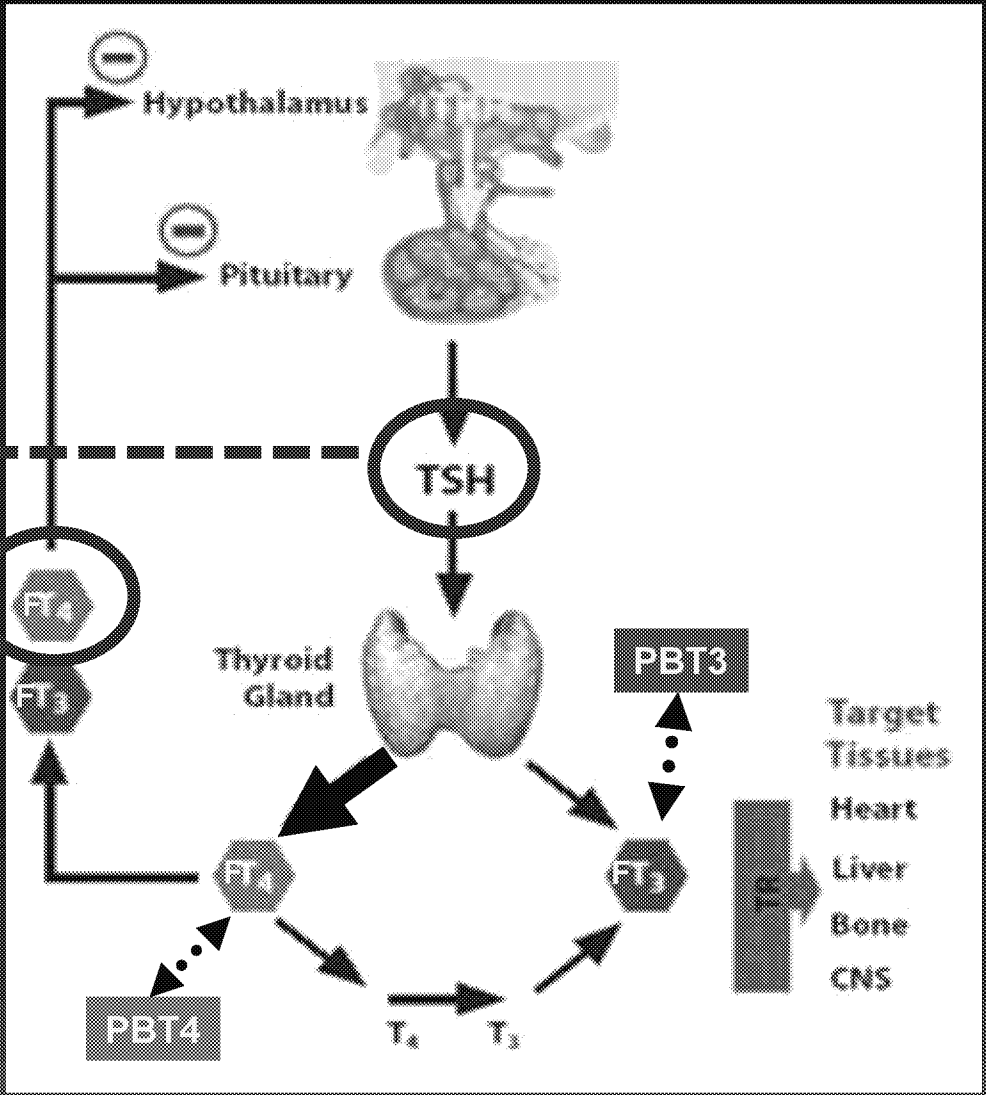




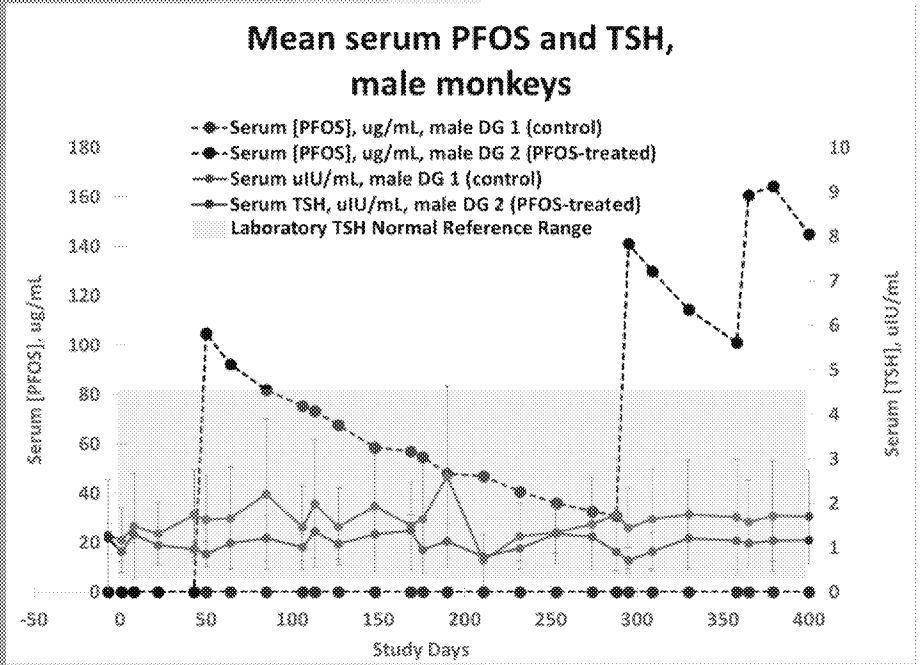
No effects on TT3

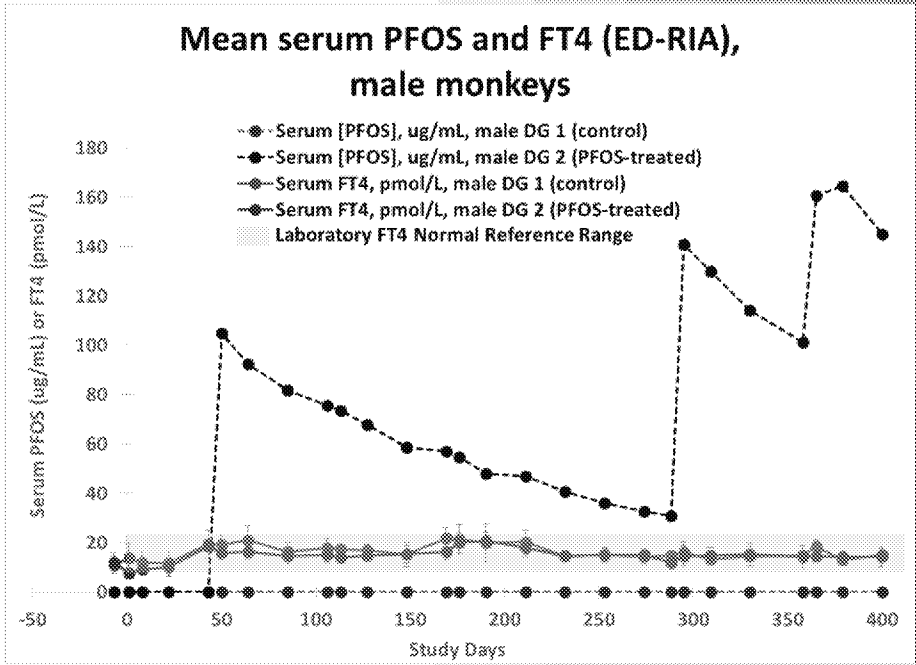
Thyroid Hormones and H-P-T Axis At-A-Glance

Clinical Diagnostic Index for Thyroid Hormones



Current Study: Male TSH & FT4 (Thyroid)

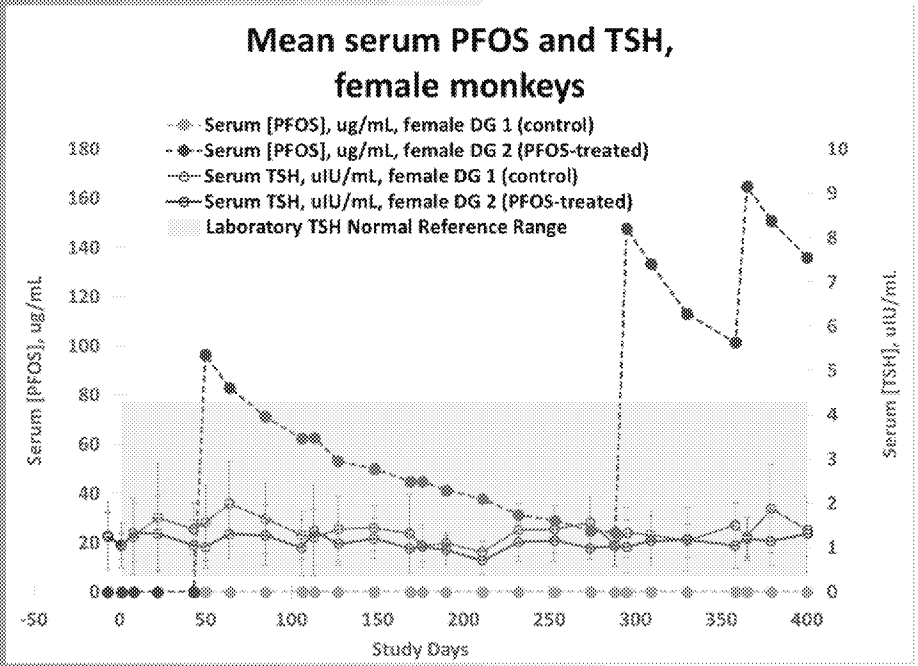


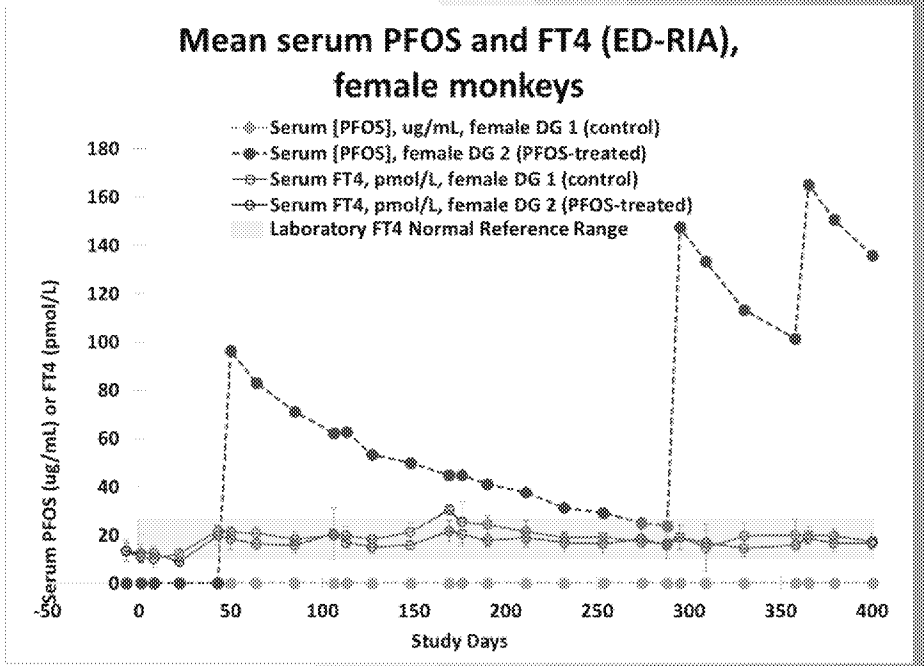


No evidence suggesting comprised thyroid function

No compensatory changes

Current Study: Female TSH & FT4 (Thyroid)





No evidence suggesting comprised thyroid function

No compensatory changes

Summary: PFOS and Thyroid Hormones

Seacat et al. 2002 Study

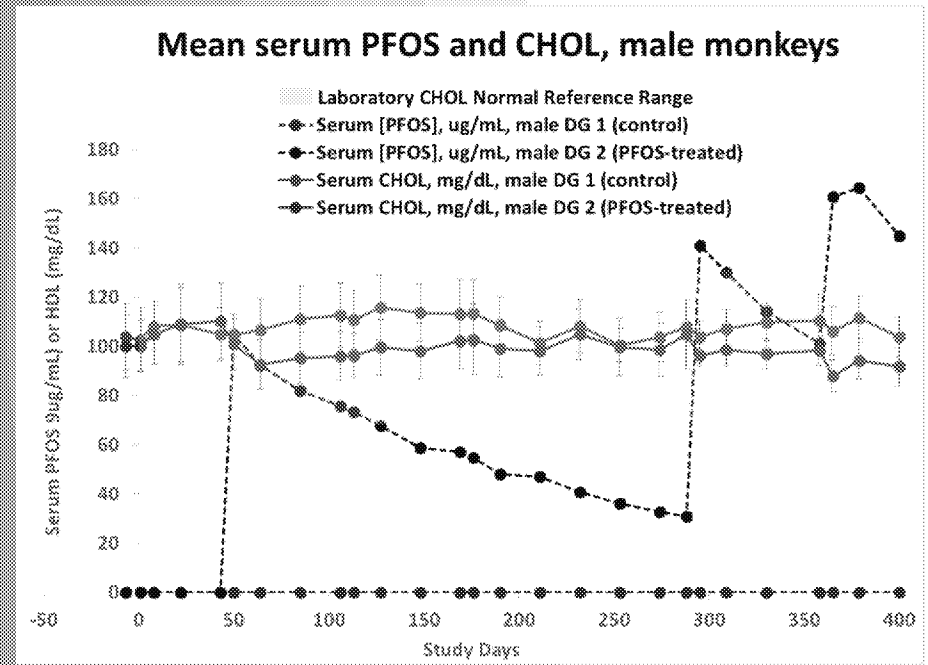
- Unreliable TSH values reported by original study laboratory
- TSH and FT4 measurements from Mayo Clinic Reference Lab did not show any compensatory changes in thyroid hormones
- No changes in thyroid histology
- Thyroid function was not comprised

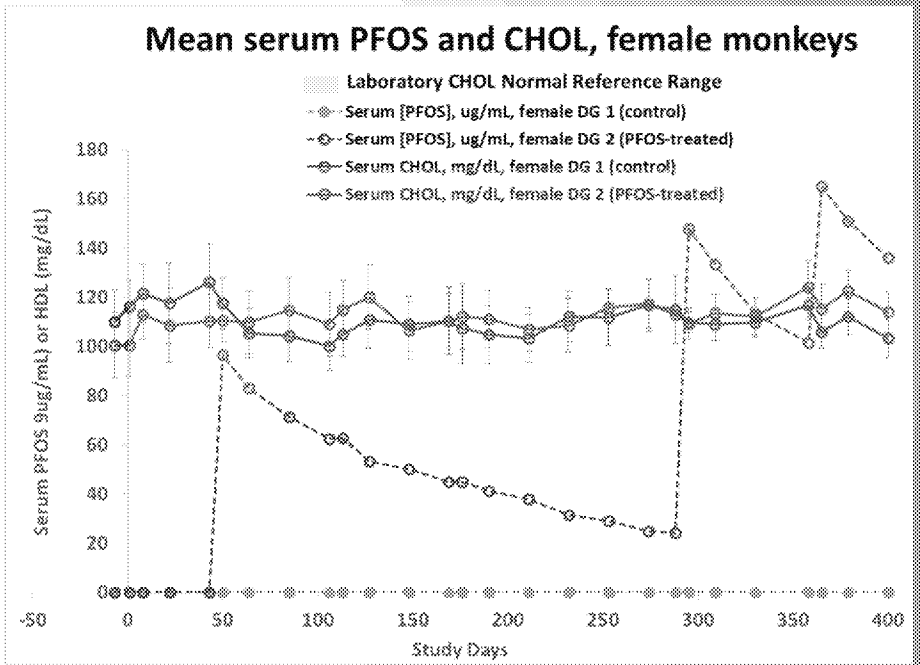
Current study

- Rigorous measurements of thyroid hormones for 27 times throughout 1+ years on the same individual animals
- Oral administration of PFOS did not have any effects (at comparable body burden to Seacat et al. study)

Conclusion → No effect on thyroid with exposure to PFOS

Current Study:
TOTAL CHOLESTEROL

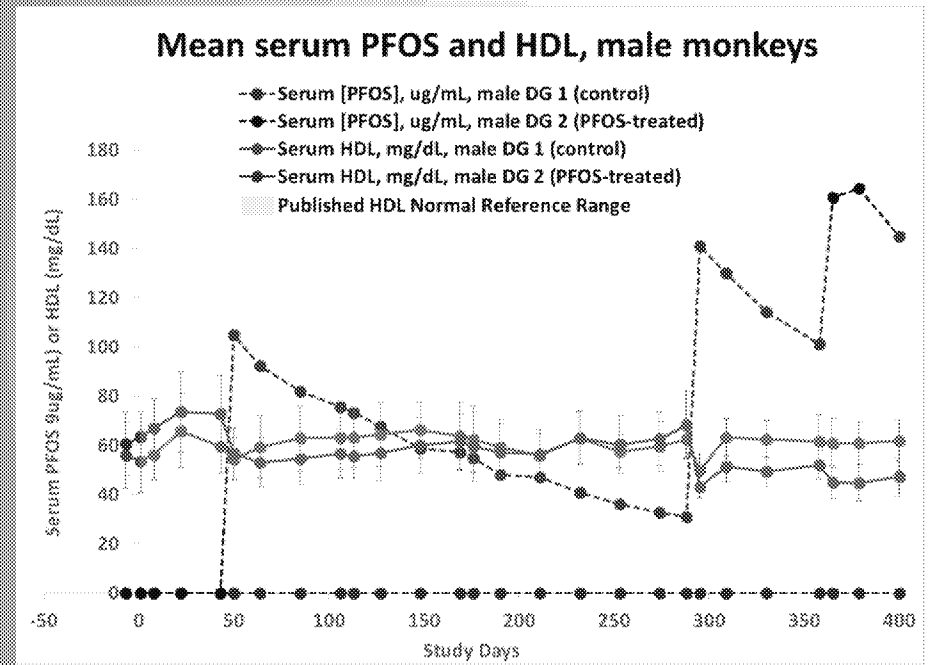


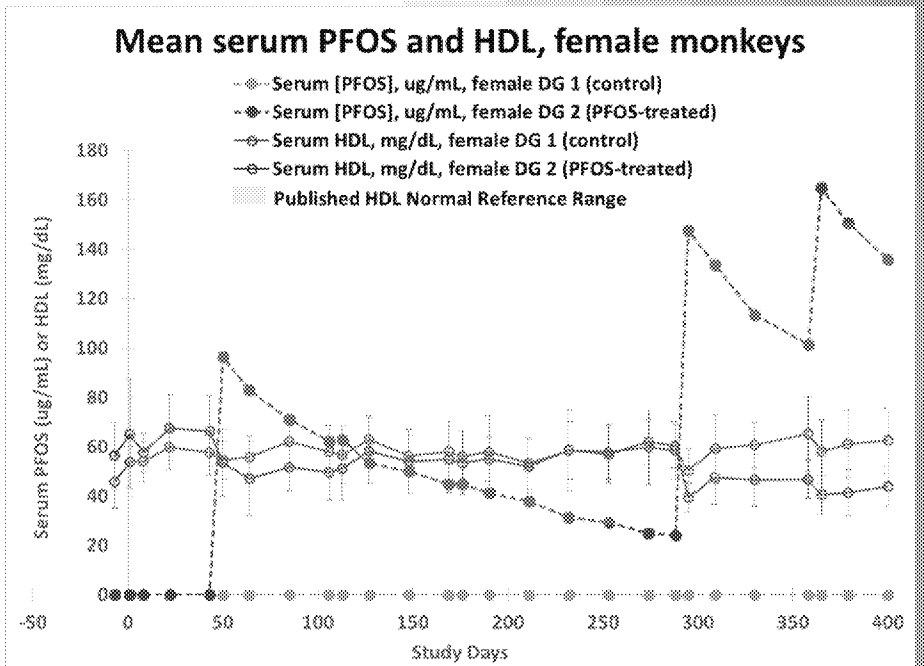


Slight reduction of total cholesterol

- Compared to time-matched control, no statistically significance
- Compared to pre-dose baseline values, statistical significance

Current Study: HDL





Slight reduction of total cholesterol

- Compared to time-matched control, no statistically significance
- Compared to pre-dose baseline values, statistical significance

Summary: PFOS and HDL

- Seacat et al. 2002 Study
  - Reduction of total cholesterol (HDL) at high dose, reversible
- Current study
  - Rigorous measurements of cholesterol and HDL for 27 times throughout 1+ years on the same individual animals
  - Oral administration of PFOS had a minor effect on total cholesterol (HDL)
- Hypolipidemia, observed in rodents and non-human primates
- Possible mode-of-action using ApoE3.Leiden.CETP mice
  - Increased lipolysis and clearance of VLDL-TG, reduced HDL synthesis (apoA1) and maturation (LCAT)

Conclusion → Subtle changes in HDL with exposure to PFOS

Current Study - Conclusions

1. No mortality
2. All monkeys appeared normal and healthy throughout the study
3. No effects on body weight and body-weight gains
4. No effects on coagulation, liver, renal, or electrolyte chemistries
5. No altered thyroid functions
6. Subtle decreases in HDL cholesterol

Path Forward

1. BMC Modeling of HDL (Bruce Allen)
   - Analyses in-progress
2. Manuscript preparation and submission
   - Target for 2016

Acknowledgements:

3M Company

Carol Ley

Geary Olsen

John Butenhoff (*ret.*)

David Ehresman (*ret.*)

Kara Andres

Jay Schulz

Charles River Laboratories PCS-Montreal

Ria Falvo

Anne Provencher

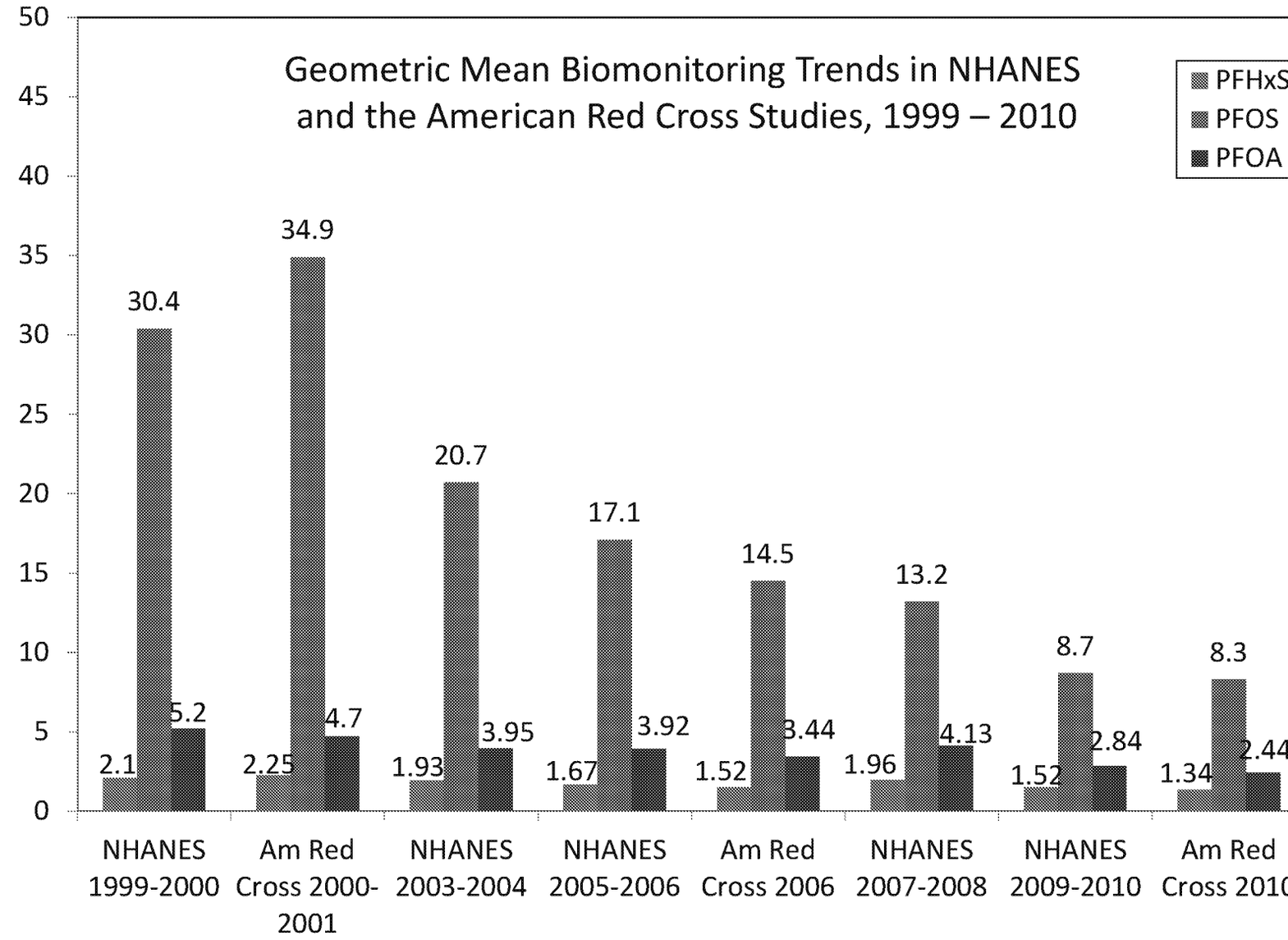
Consultant

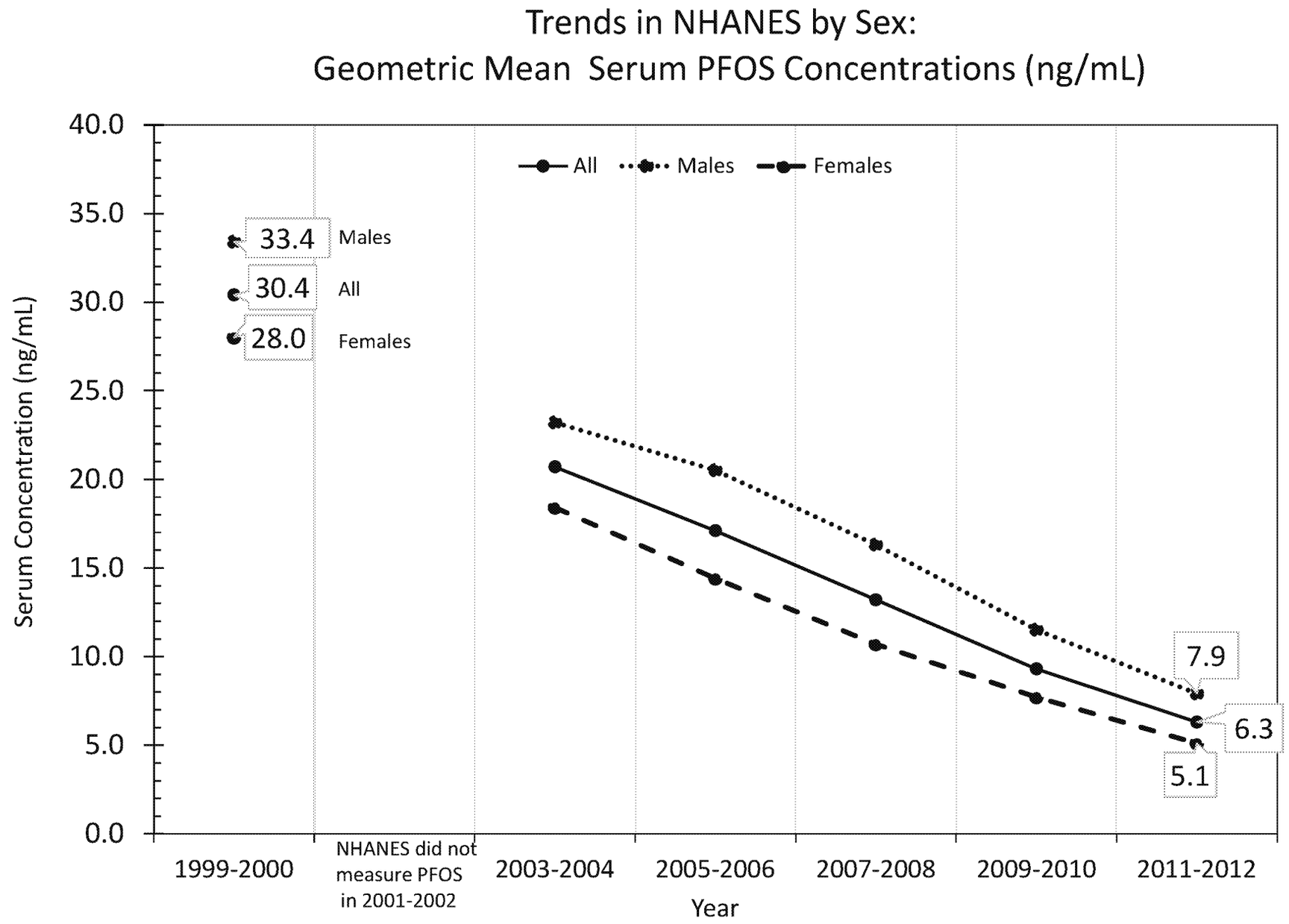
Bruce Allen

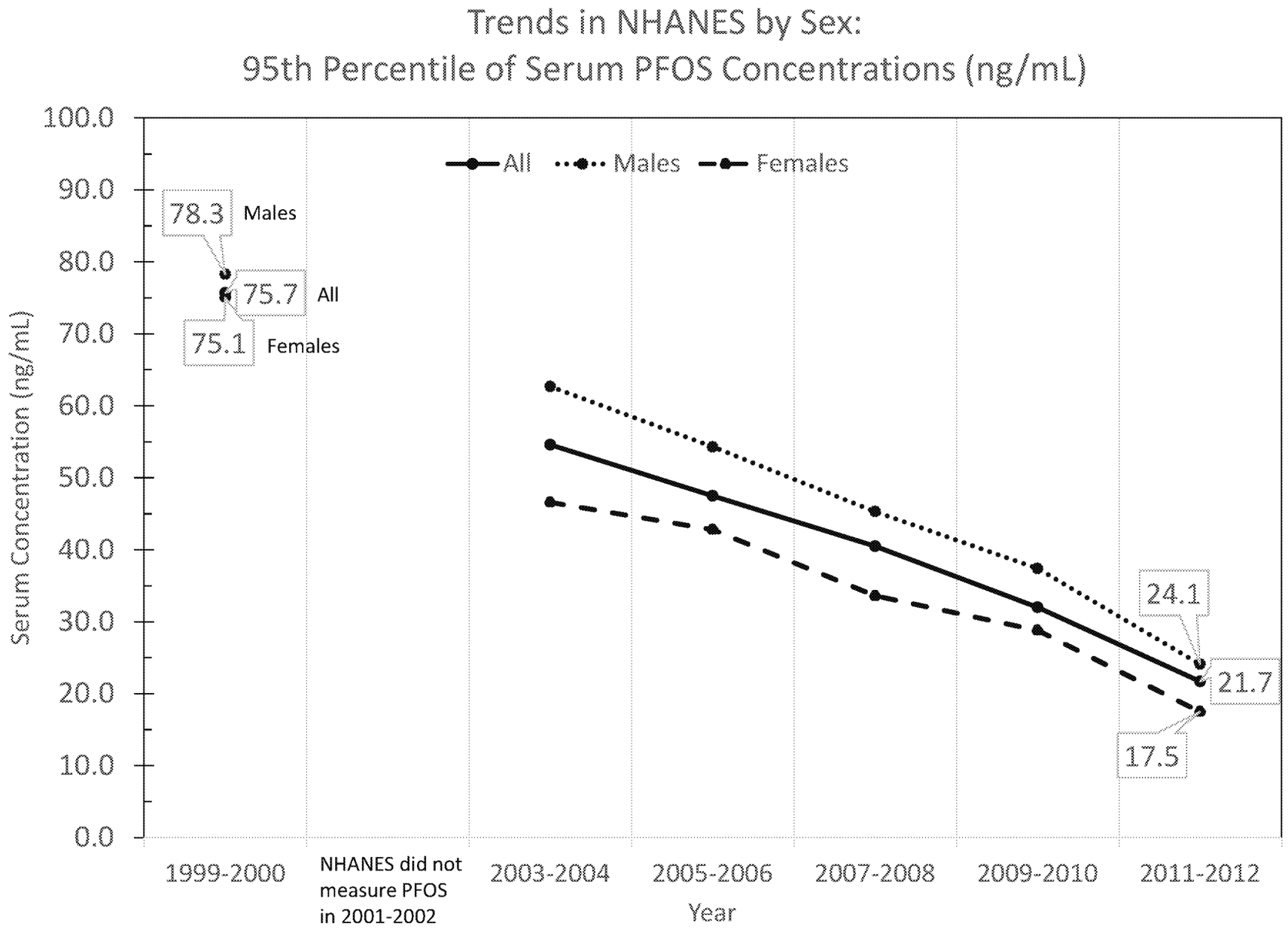
PFAS Biomonitoring and Epidemiology Research Update

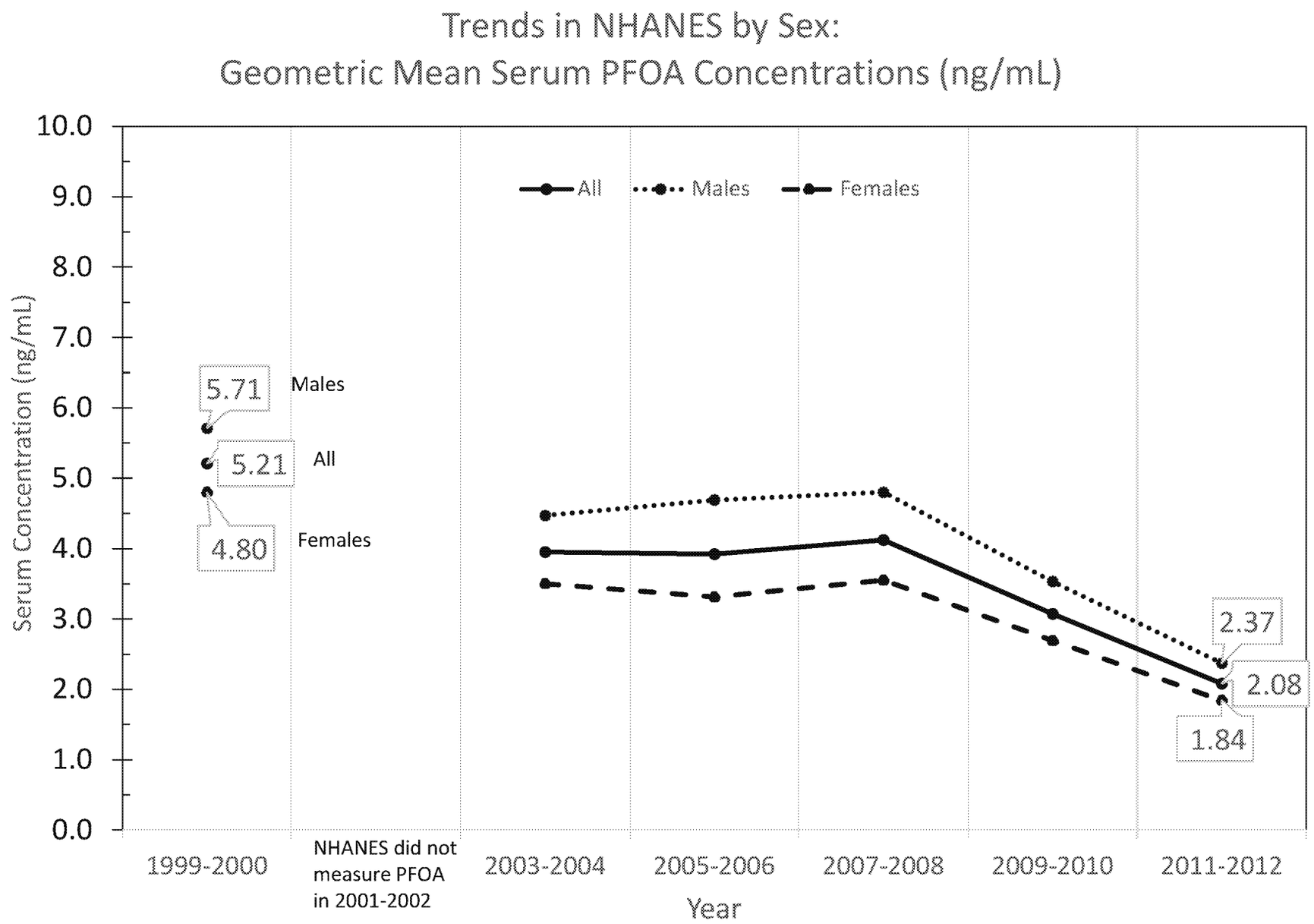
Geary Olsen DVM, PhD
Medical Dept.
3M Company

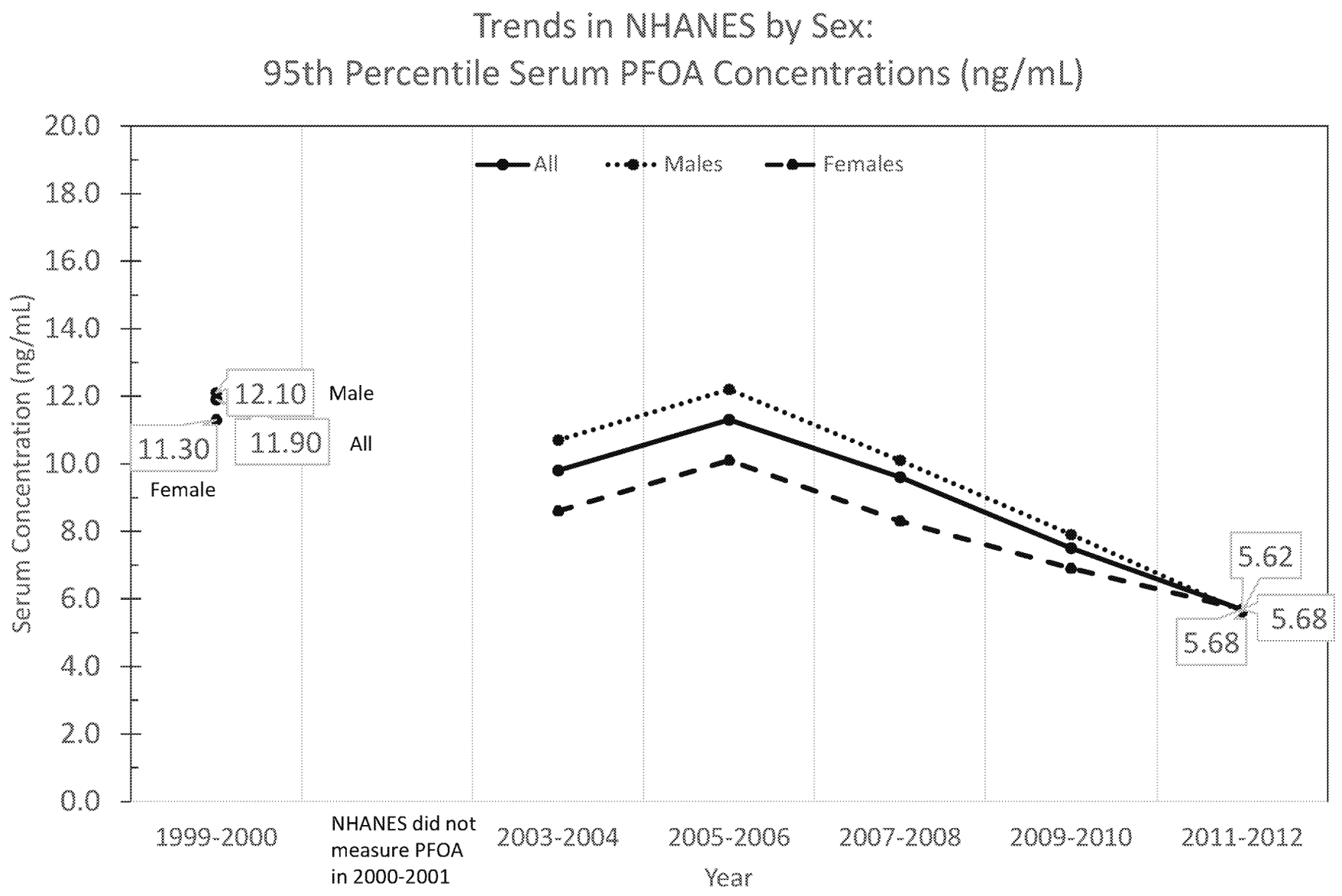
October 28, 2015


Geometric Mean Biomonitoring Trends in NHANES and the American Red Cross Studies, 1999 – 2010
PFHxS
PFOS
PFOA
50
45
40
35
30
25
20
15
10
5
0
2.1
30.4
5.2
2.25
34.9
4.7
1.93
20.7
3.95
1.67
17.1
3.92
1.52
14.5
3.44
1.96
13.2
4.13
1.52
8.7
2.84
1.34
8.3
2.44
NHANES 1999-2000
Am Red Cross 2000-2001
NHANES 2003-2004
NHANES 2005-2006
Am Red Cross 2006
NHANES 2007-2008
NHANES 2009-2010
Am Red Cross 2010


Trends in NHANES by Sex:
Geometric Mean Serum PFOS Concentrations (ng/mL)
Serum Concentration (ng/mL)
40.0
35.0
30.0
25.0
20.0
15.0
10.0
5.0
0.0
All
Males
Females
33.4
Males
30.4
All
28.0
Females
7.9
6.3
5.1
1999-2000
NHANES did not measure PFOS in 2001-2002
2003-2004
2005-2006
2007-2008
2009-2010
2011-2012
Year


Trends in NHANES by Sex:
95th Percentile of Serum PFOS Concentrations (ng/mL)
All
Males
Females
78.3
Males
75.7
All
75.1
Females
24.1
21.7
17.5
Serum Concentration (ng/mL)
100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0.0
1999-2000
NHANES did not measure PFOS in 2001-2002
2003-2004
2005-2006
2007-2008
2009-2010
2011-2012
Year


Trends in NHANES by Sex:
Geometric Mean Serum PFOA Concentrations (ng/mL)
Serum Concentration (ng/mL)
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
All
Males
Females
5.71
Males
5.21
All
4.80
Females
2.37
2.08
1.84
1999-2000
NHANES did not measure PFOA in 2001-2002
2003-2004
2005-2006
2007-2008
2009-2010
2011-2012
Year

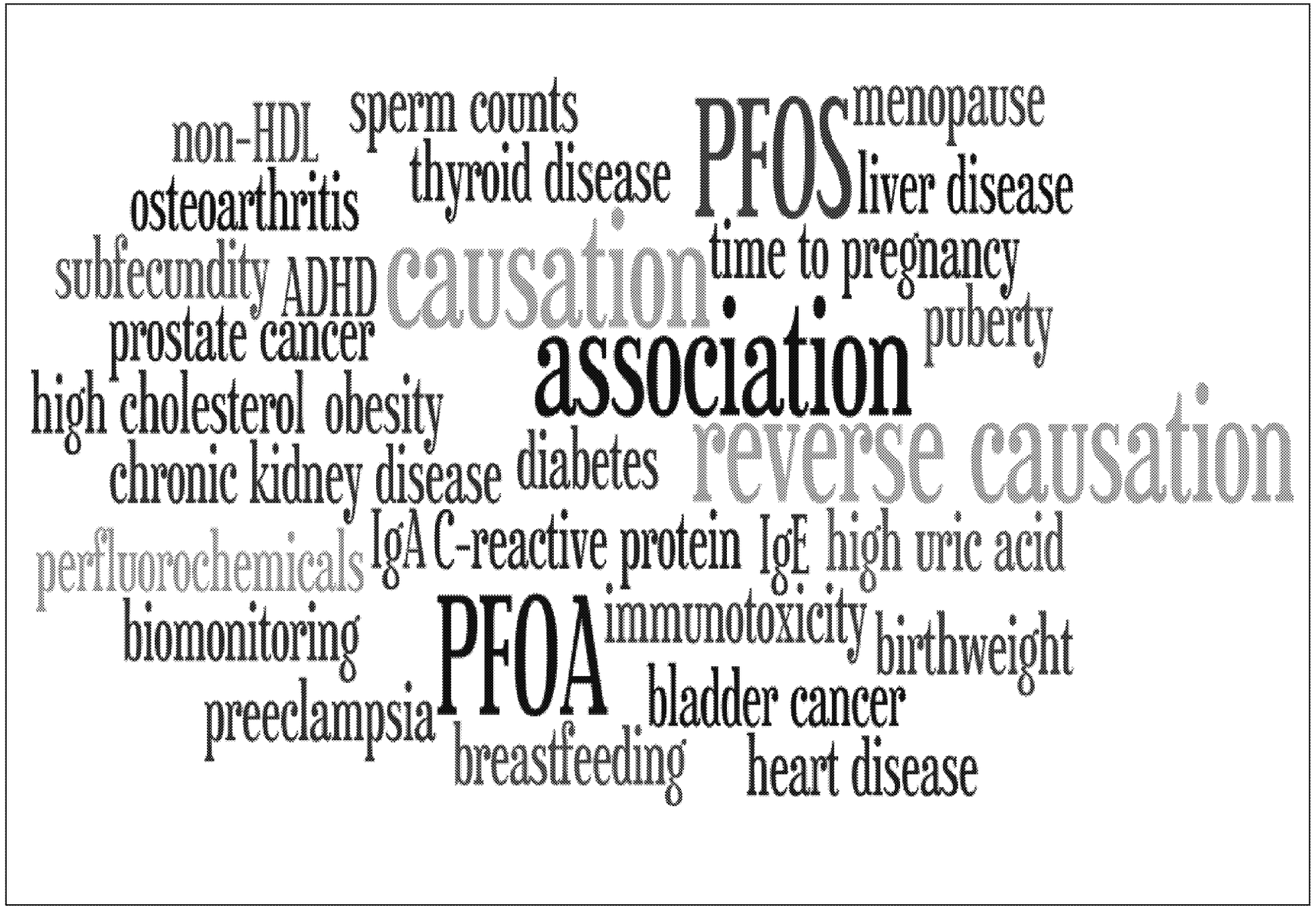

Trends in NHANES by Sex:
95th Percentile Serum PFOA Concentrations (ng/mL)
Serum Concentration (ng/mL)
20.0
18.0
16.0
14.0
12.0
10.0
8.0
6.0
4.0
2.0
0.0
All
Males
Females
12.10
Male
11.30
11.90
All
Female
5.62
5.68
5.68
1999-2000
NHANES did not measure PFOA in 2000-2001
2003-2004
2005-2006
2007-2008
2009-2010
2011-2012
Year

Is Clearance a Common Explanation Across the Epidemiological Associations Reported at "Low" PFOA and PFOS Concentrations?

Geary Olsen*, Sue Chang, John Butenhoff,
Carol Ley, Larry Zobel

April 4, 2012

*Presenter

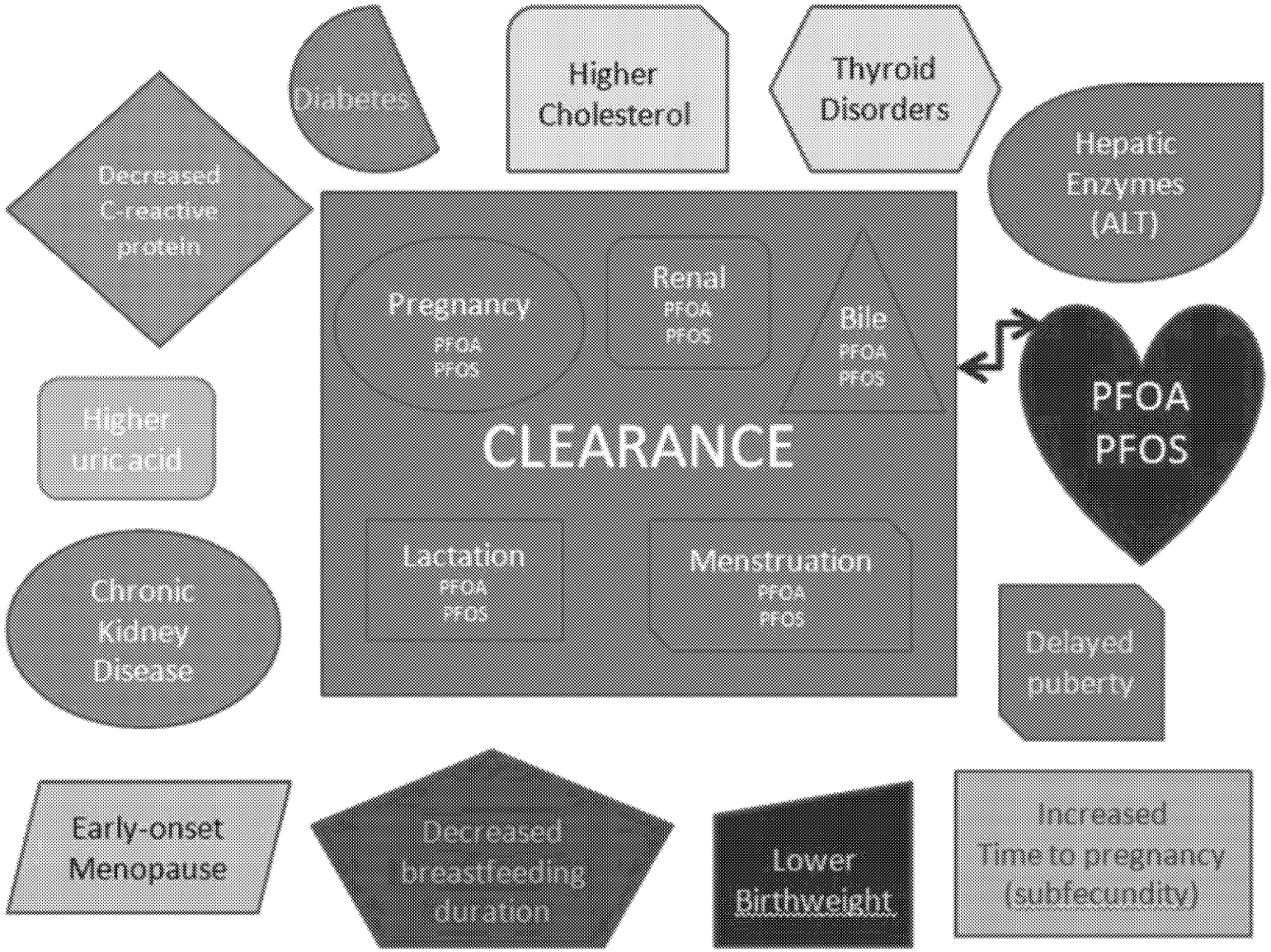

non-HDL
sperm counts
PFOS
menopause
thyroid disease
liver disease
osteoarthritis
subfecundity
ADHD
causation
time to pregnancy
prostate cancer
association
puberty
high cholesterol
obesity
reverse causation
chronic kidney disease
diabetes
perfluorochemicals
IgA
C-reactive protein
IgE
high uric acid
biomonitoring
PFOA
immunotoxicity
birthweight
preeclampsia
bladder cancer
breastfeeding
heart disease

Pharmacokinetic Variability and the Miracle of Modern Analytical Chemistry

Matthew Longnecker (NIEHS) Epidemiology 2006;17:350-351

"The impressive capabilities of modern analytical chemistry are being applied with increasing frequency in epidemiologic studies. With [illegible] exposures being evaluated, and [illegible] concentrations being measured, it seems opportune to bear in mind that a great proportion of variation in measured levels among subjects may be accounted for by differences in metabolism and excretion. The measurements we obtain may afford only a glimpse of a byproduct of the underlying pharmacokinetics, systems, biology, and pathogenesis. While these are not entirely new concepts, their importance may be clearer today than ever before."

Is Clearance a Common Explanation Across Many of these Epidemiological Associations?



All EHP content is accessible to individuals with disabilities. A fully accessible (Section 508–compliant) HTML version of this article is available at http://dx.doi.org/10.1289/ehp.1307175.

Commentary

The Navigation Guide Systematic Review Methodology: A Rigorous and Transparent Method for Translating Environmental Health Science into Better Health Outcomes

Tracey J. Woodruff and Patrice Sutton

Program on Reproductive Health and the Environment, University of California, San Francisco, Oakland, California, USA

Background: Synthesizing what is known about the environmental drivers of health is instrumental to taking prevention-oriented action. Methods of research synthesis commonly used in environmental health lag behind systematic review methods developed in the clinical sciences over the past 20 years.

Objectives: We sought to develop a proof of concept of the "Navigation Guide," a systematic and transparent method of research synthesis in environmental health.

Discussion: The Navigation Guide methodology builds on best practices in research synthesis in evidence-based medicine and environmental health. Key points of departure from current methods of expert-based narrative review prevalent in environmental health include a prespecified protocol, standardized and transparent documentation including expert judgment, a comprehensive search strategy, assessment of "risk of bias," and separation of the science from values and preferences. Key points of departure from evidence-based medicine include assigning a "moderate" quality rating to human observational studies and combining diverse evidence streams.

Conclusions: The Navigation Guide methodology is a systematic and rigorous approach to research synthesis that has been developed to reduce bias and maximize transparency in the evaluation of environmental health information. Although novel aspects of the method will require further development and validation, our findings demonstrated that improved methods of research synthesis under development at the National Toxicology Program and under consideration by the U.S. Environmental Protection Agency are fully achievable. The institutionalization of robust methods of systematic and transparent review would provide a concrete mechanism for linking science to timely action to prevent harm.

Citation: Woodruff TJ, Sutton P. 2014. The Navigation Guide systematic review methodology: a rigorous and transparent method for translating environmental health science into better health outcomes. Environ Health Perspect 122:1007–1014; http://dx.doi.org/10.1289/ehp.1307175

about how environmental health science is translated into strength of evidence conclusions have been lacking (Bero et al. 2005; Gee 2008; National Research Council (NRC) 2009, 2011).

Today, methods of research synthesis prevalent in environmental health mirror that of clinical medicine > 40 years ago when the clinical sciences largely relied on a system of expert-based narrative reviews on which to recommend treatment decisions (Rennie and Chalmers 2005). In a landmark paper published in 1992 in the *Journal of the American Medical Association*, Antman et al. (1992) showed the superiority of systematic review methods by comparing

Address correspondence to T.J. Woodruff, UCSF Program on Reproductive Health and the Environment, 1388 Sutter St., Suite 1135, Oakland, CA 94613 USA. Telephone: (510) 385-1241. E-mail: woodruff@ucsf.edu

We are indebted to D. Axelrad, D. Bero, P. Johnson, E. Koustas, and J. Lam for providing invaluable comments and suggestions on this commentary. D. Axelrad also provided research assistance.

All EHP content is accessible to individuals with disabilities. A fully accessible (Section 508–compliant) HTML version of this article is available at http://dx.doi.org/10.1289/ehp.1307177.

Review

The Navigation Guide—Evidence-Based Medicine Meets Environmental Health: Systematic Review of Nonhuman Evidence for PFOA Effects on Fetal Growth

Erica Koustas,[1] Juleen Lam,[1] Patrice Sutton,[2] Paula I. Johnson,[3] Dylan S. Atchley,[3] Saunak Sen,[3] Karen A. Robinson,[4,5,6] Daniel A. Axelrad,[7] and Tracey J. Woodruff[2]

[1]Oak Ridge Institute for Science and Education (ORISE) Postdoctoral Fellow, National Center for Environmental Economics, Office of Policy, U.S. Environmental Protection Agency, Washington, DC, USA; [2]Program on Reproductive Health and the Environment, University of California, San Francisco, Oakland, California, USA; [3]Department of Epidemiology and Biostatistics, University of California, San Francisco, San Francisco, California, USA; [4]Department of Medicine, [5]Department of Epidemiology, and [6]Health Policy & Management, Johns Hopkins School of Medicine, Baltimore, Maryland, USA; [7]National Center for Environmental Economics, Office of Policy, U.S. Environmental Protection Agency, Washington, DC, USA

Background: In contrast to current methods of expert-based narrative review, the Navigation Guide is a systematic and transparent method for synthesizing environmental health research from multiple evidence streams. The Navigation Guide was developed to effectively and efficiently translate the available scientific evidence into timely prevention-oriented action.

Objectives: We applied the Navigation Guide systematic review method to answer the question "Does fetal developmental exposure to perfluorooctanoic acid (PFOA) or its salts affect fetal growth in animals?" and to rate the strength of the experimental animal evidence.

Methods: We conducted a comprehensive search of the literature, applied prespecified criteria to the search results to identify relevant studies, extracted data from studies, obtained additional information from study authors, conducted meta-analyses, and rated the overall quality and strength of the evidence.

Results: Twenty-one studies met the inclusion criteria. From the meta-analysis of eight mouse gavage data sets, we estimated that exposure of pregnant mice to increasing concentrations of PFOA was associated with a change in mean pup birth weight of −0.923 g (95% CI: −1.029, −0.816) per 1-unit increase in dose (milligrams per kilogram body weight per day). The evidence, consisting of 15 monotonic and 6 nonmonotonic studies, was rated as "moderate" and "low" quality, respectively.

Conclusions: Based on this first application of the Navigation Guide methodology, we found sufficient evidence that fetal developmental exposure to PFOA reduces fetal growth in animals.

Citation: Koustas E, Lam J, Sutton P, Johnson PI, Atchley DS, Sen S, Robinson KA, Axelrad DA, Woodruff TJ. 2014. The Navigation Guide—evidence-based medicine meets environmental health: systematic review of nonhuman evidence for PFOA effects on fetal growth. Environ Health Perspect 122:1015–1027; http://dx.doi.org/10.1289/ehp.1307177

are, for primarily ethical reasons, unavailable in environmental health. The Navigation Guide was developed to bridge this gap between clinical and environmental health sciences. The methodology provides the capacity to systematically and transparently evaluate the quality and strength of evidence from both human and nonhuman streams of evidence about the relationship between the environment and reproductive and developmental health (Woodruff and Sutton 2014; Woodruff et al. 2011a).

To test and refine the Navigation Guide systematic review methodology, we applied it to the evaluation of experimental animal evidence for the effects of exposure to the environmental contaminant perfluorooctanoic acid (PFOA) on fetal growth. The results of applying the method to the human evidence and integrating the animal and human data into an overarching strength of evidence rating are presented elsewhere (Johnson et al. 2014; Lam et al. 2014).

Rationale for selecting PFOA

All EHP content is accessible to individuals with disabilities. A fully accessible (Section 508–compliant) HTML version of this article is available at http://dx.doi.org/10.1289/ehp.1307893.

Review

The Navigation Guide—Evidence-Based Medicine Meets Environmental Health: Systematic Review of Human Evidence for PFOA Effects on Fetal Growth

Paula I. Johnson,[1] Patrice Sutton,[1] Dylan S. Atchley,[1] Erica Koustas,[2] Juleen Lam,[2] Saunak Sen,[3] Karen A. Robinson,[4,5,6] Daniel A. Axelrad,[7] and Tracey J. Woodruff[1]

[1]Program on Reproductive Health and the Environment, University of California, San Francisco, Oakland, California, USA; [2]Oak Ridge Institute for Science and Education (ORISE) Postdoctoral Fellowship, National Center for Environmental Economics, Office of Policy, U.S. Environmental Protection Agency, Washington, DC, USA; [3]Department of Epidemiology and Biostatistics, University of California, San Francisco, San Francisco, California, USA; [4]Department of Medicine, [5]Department of Epidemiology, and [6]Department of Health Policy & Management, Johns Hopkins University, Baltimore, Maryland, USA; [7]National Center for Environmental Economics, Office of Policy, U.S. Environmental Protection Agency, Washington, DC, USA

Background: The Navigation Guide methodology was developed to meet the need for a robust method of systematic and transparent research synthesis in environmental health science. We conducted a case study systematic review to support proof of concept of the method.

Objective: We applied the Navigation Guide systematic review methodology to determine whether developmental exposure to perfluorooctanoic acid (PFOA) affects fetal growth in humans.

Methods: We applied the first 3 steps of the Navigation Guide methodology to human epidemiological data: 1) specify the study question, 2) select the evidence, and 3) rate the quality and strength of the evidence. We developed a protocol, conducted a comprehensive search of the literature, and identified relevant studies using prespecified criteria. We evaluated each study for risk of bias and conducted meta-analyses on a subset of studies. We rated quality and strength of the entire body of human evidence.

Results: We identified 18 human studies that met our inclusion criteria, and 9 of these were combined through meta-analysis. Through meta-analysis, we estimated that a 1-ng/mL increase in serum or plasma PFOA was associated with a −18.9 g (95% CI: −29.8, −7.9) difference in birth weight. We concluded that the risk of bias across studies was low, and we assigned a "moderate" quality rating to the overall body of human evidence.

Conclusions: On the basis of this first application of the Navigation Guide systematic review methodology, we concluded that there is "sufficient" human evidence that developmental exposure to PFOA reduces fetal growth.

Citation: Johnson PI, Sutton P, Atchley DS, Koustas E, Lam J, Sen S, Robinson KA, Axelrad DA, Woodruff TJ. 2014. The Navigation Guide—evidence-based medicine meets environmental health: systematic review of human evidence for PFOA effects on fetal growth. Environ Health Perspect 122:1028–1039; http://dx.doi.org/10.1289/ehp.1307893

clinical research are primarily applied to randomized controlled clinical trials, the evidence streams for environmental health science are different. The Navigation Guide systematic review methodology was developed to apply best practices in research synthesis in clinical medicine and environmental health to the evidence streams common in environmental health science (i.e., experimental toxicological studies and observational human studies) in order to reach an overall conclusion about the strength of evidence (Woodruff et al. 2011a). Additional background on the Navigation Guide is given in a companion commentary (Woodruff and Sutton 2014).

We undertook a case study to apply the Navigation Guide methodology. For this first case study, we evaluated the evidence for the effects of exposure to perfluorooctanoic acid (PFOA) on fetal growth. PFOA has been used for > 50 years in the manufacture of fluoropolymers used in industrial applications and consumer products to impart certain characteristics, such as fire and stain resistance

All EHP content is accessible to individuals with disabilities. A fully accessible (Section 508–compliant) HTML version of this article is available at http://dx.doi.org/10.1289/ehp.1307913.

Review

The Navigation Guide—Evidence-Based Medicine Meets Environmental Health: Integration of Animal and Human Evidence for PFOA Effects on Fetal Growth

Juleen Lam,[1] Erica Koustas,[1] Patrice Sutton,[2] Paula I. Johnson,[3] Dylan S. Atchley,[3] Saunak Sen,[3] Karen A. Robinson,[4,5,6] Daniel A. Axelrad,[7] and Tracey J. Woodruff[2]

[1]Oak Ridge Institute for Science and Education (ORISE) Postdoctoral Fellow, National Center for Environmental Economics, Office of Policy, U.S. Environmental Protection Agency, Washington, DC, USA; [2]Program on Reproductive Health and the Environment, University of California, San Francisco, Oakland, California, USA; [3]Department of Epidemiology and Biostatistics, University of California, San Francisco, San Francisco, California, USA; [4]Department of Health Policy & Management, [5]Department of Medicine, and [6]Department of Epidemiology, Johns Hopkins University, Baltimore, Maryland, USA; [7]National Center for Environmental Economics, Office of Policy, U.S. Environmental Protection Agency, Washington, DC, USA

Background: The Navigation Guide is a novel systematic review method to synthesize scientific evidence and reach strength of evidence conclusions for environmental health decision making.

Objective: Our aim was to integrate scientific findings from human and nonhuman studies to determine the overall strength of evidence for the question "Does developmental exposure to perfluorooctanoic acid (PFOA) affect fetal growth in humans?"

Methods: We developed and applied prespecified criteria to systematically and transparently 1) rate the quality of the scientific evidence as "high," "moderate," or "low"; 2) rate the strength of the human and nonhuman evidence separately as "sufficient," "limited," "moderate," or "evidence of lack of toxicity"; and 3) integrate the strength of the human and nonhuman evidence ratings into a strength of the evidence conclusion.

Results: We identified 18 epidemiology studies and 21 animal toxicology studies relevant to our study question. We rated both the human and nonhuman mammalian evidence as "moderate" quality and "sufficient" strength. Integration of these evidence ratings produced a final strength of evidence rating in which review authors concluded that PFOA is "known to be toxic" to human reproduction and development based on sufficient evidence of decreased fetal growth in both human and nonhuman mammalian species.

Conclusions: We concluded that developmental exposure to PFOA adversely affects human health based on sufficient evidence of decreased fetal growth in both human and nonhuman mammalian species. The results of this case study demonstrate the application of a systematic and transparent methodology, via the Navigation Guide, for reaching strength of evidence conclusions in environmental health.

Citation: Lam J, Koustas E, Sutton P, Johnson PI, Atchley DS, Sen S, Robinson KA, Axelrad DA, Woodruff TJ. 2014. The Navigation Guide—evidence-based medicine meets environmental health: integration of animal and human evidence for PFOA effects on fetal growth. Environ Health Perspect 122:1040–1051; http://dx.doi.org/10.1289/ehp.1307923

have been identified, indicating, in particular, that a robust, systematic, and transparent methodology is needed (NRC 2011). To the extent that science informs decision making, limitations in the methods for evaluating the strength of evidence in environmental health impedes our capability to act on the science in a timely way to improve health outcomes (Woodruff and Sutton 2014).

In the clinical sciences, methods of research synthesis—which integrate transparent and systematic approaches to evidence collection and evaluation—have been developed and refined over the past three decades and have played a transformative role in evidence-based decision making for medical interventions (GRADE Working Group 2013; Higgins and Green 2011). For example, a systematic review and cumulative meta-analysis (continually updating the meta-analysis with results from more recent clinical trials) in cardiovascular medicine found discrepancies between recommendations by clinical experts and meta-analytic evidence. Experts often did not recommend treatments that pooled evidence demonstrated as effec-

Navigation Guide Methodology

Step 1. Specify the study question

Step 2. Select the evidence

Step 3. Rate the quality and strength of the evidence

Step 4. Grade the strength of the recommendation

Koustas et al. 2014

Background: In contrast to current methods of expert-based narrative review, the Navigation Guide is a systematic and transparent method for synthesizing environmental health research from multiple evidence streams. The Navigation Guide was developed to effectively and efficiently translate the available scientific evidence into timely prevention-oriented action.

Objectives: We applied the Navigation Guide systematic review method to answer the question "Does fetal developmental exposure to perfluorooctanoic acid (PFOA) or its salts affect fetal growth in animals ?" and to rate the strength of the experimental animal evidence.

Methods: We conducted a comprehensive search of the literature, applied prespecified criteria to the search results to identify relevant studies, extracted data from studies, obtained additional information from study authors, conducted meta-analyses, and rated the overall quality and strength of the evidence.

Results: Twenty-one studies met the inclusion criteria. From the meta-analysis of eight mouse gavage data sets, we estimated that exposure of pregnant mice to increasing concentrations of PFOA was associated with a change in mean pup birth weight of −0.023 g (95% CI: −0.029, −0.016) per 1-unit increase in dose (milligrams per kilogram body weight per day). The evidence, consisting of 15 mammalian and 6 nonmammalian studies, was rated as "moderate" and "low" quality, respectively.

Conclusion: Based on this first application of the Navigation Guide methodology, we found sufficient evidence that fetal developmental exposure to PFOA reduces fetal growth in animals.

Johnson et al. 2014

Background: The Navigation Guide methodology was developed to meet the need for a robust method of systematic and transparent research synthesis in environmental health science. We conducted a case study systematic review to support proof of concept of the method.

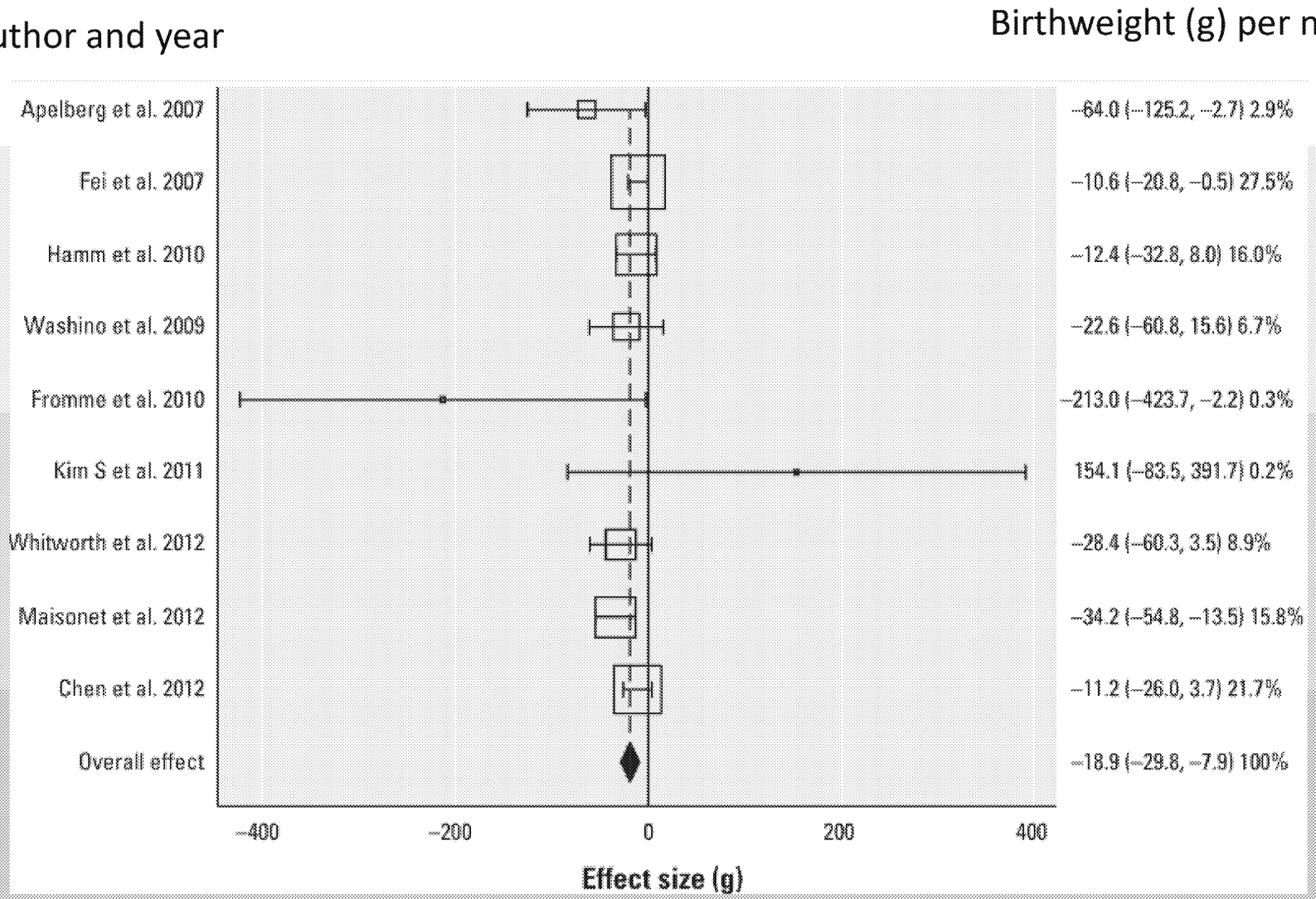
Objective: We applied the Navigation Guide systematic review methodology to determine whether developmental exposure to perfluorooctanoic acid (PFOA) affects fetal growth in humans.

Methods: We applied the first 3 steps of the Navigation Guide methodology to human epidemiological data: *1*) specify the study question, *2*) select the evidence, and *3*) rate the quality and strength of the evidence. We developed a protocol, conducted a comprehensive search of the literature, and identified relevant studies using prespecified criteria. We evaluated each study for risk of bias and conducted meta-analyses on a subset of studies. We rated quality and strength of the entire body of human evidence.

Results: We identified 18 human studies that met our inclusion criteria, and 9 of these were combined through meta-analysis. Through meta-analysis, we estimated that a 1-ng/mL increase in serum or plasma PFOA was associated with a −18.9 g (95% CI: −29.8, −7.9) difference in birth weight. We concluded that the risk of bias across studies was low, and we assigned a "moderate" quality rating to the overall body of human evidence.

Conclusion: On the basis of this first application of the Navigation Guide systematic review methodology, we concluded that there is "sufficient" human evidence that developmental exposure to PFOA reduces fetal growth.

Johnson et al. 2014



Lam et al. 2014

Background: The Navigation Guide is a novel systematic review method to synthesize scientific evidence and reach strength of evidence conclusions for environmental health decision making.

Objective: Our aim was to integrate scientific findings from human and nonhuman studies to determine the overall strength of evidence for the question "Does developmental exposure to perfluorooctanoic acid (PFOA) affect fetal growth in humans?"

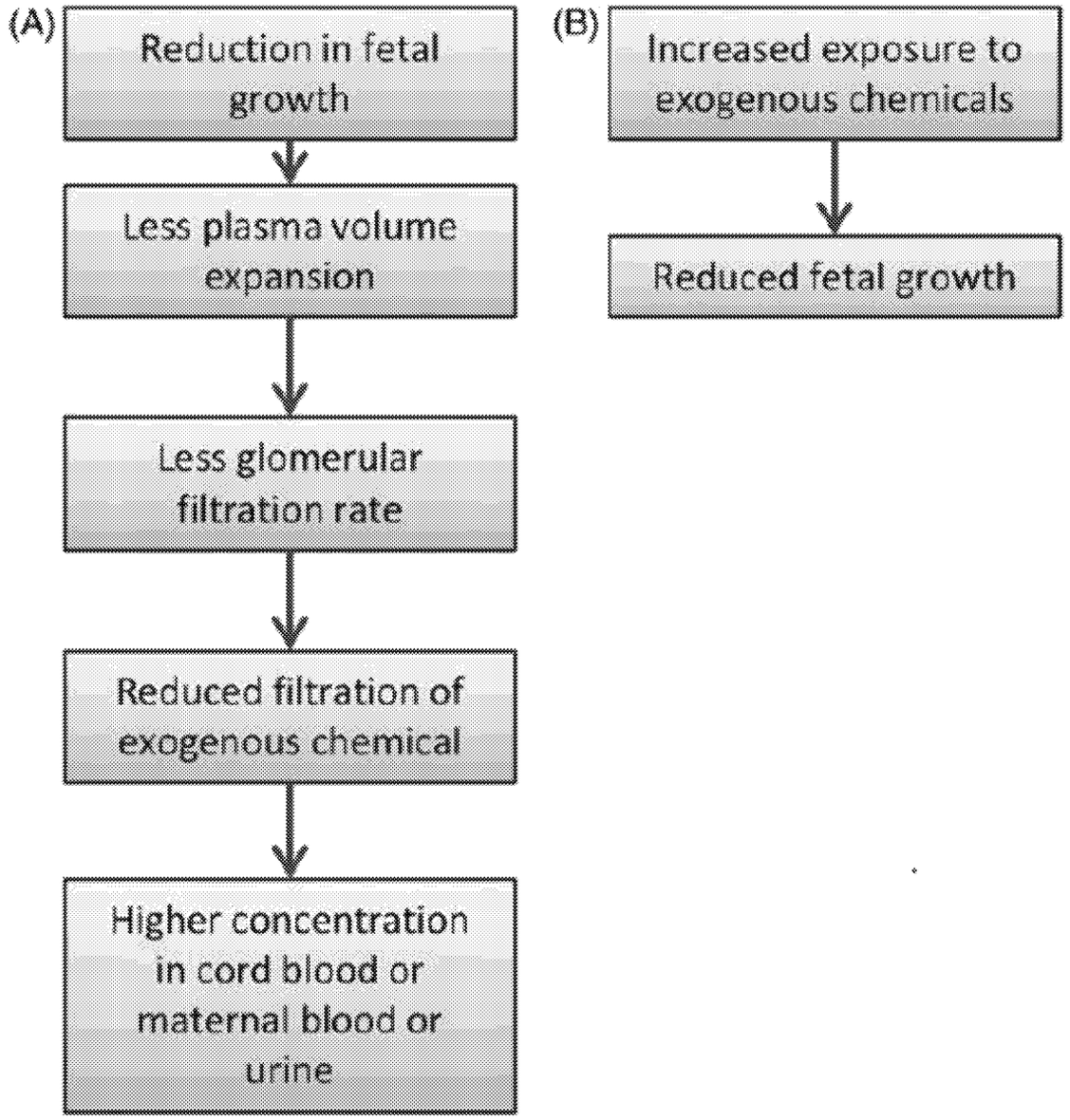
Methods: We developed and applied prespecified criteria to systematically and transparently *a*) rate the quality of the scientific evidence as "high," "moderate," or "low"; *b*) rate the strength of the human and nonhuman evidence separately as "sufficient," "limited," "moderate," or "evidence of lack of toxicity"; and *c*) integrate the strength of the human and nonhuman evidence ratings into a strength of the evidence conclusion.

Results: We identified 18 epidemiology studies and 21 animal toxicology studies relevant to our study question. We rated both the human and nonhuman mammalian evidence as "moderate" quality and "sufficient" strength. Integration of these evidence ratings produced a final strength of evidence rating in which review authors concluded that PFOA is "known to be toxic" to human reproduction and development based on sufficient evidence of decreased fetal growth in both human and nonhuman mammalian species.

Conclusion: We concluded that developmental exposure to PFOA adversely affects human health based on sufficient evidence of decreased fetal growth in both human and nonhuman mammalian species. The results of this case study demonstrate the application of a systematic and transparent methodology, via the Navigation Guide, for reaching strength of evidence conclusions in environmental health.

Lam et al. 2014

In recent years, several scientists have hypothesized that maternal and fetal physiology may influence measured blood levels indicating an exposure; in particular for PFOA and reduced birth weight, these associations may be due to reverse causality whereby women who have smaller babies have higher measures of PFOA as a result of a lower glomerular filtration rate caused by lower plasma volume expansion (Loccisano et al. 2013; Savitz 2007; Whitworth et al. 2012). If this reverse causality hypothesis were true, it would explain some or all of the relationship observed in human cross-sectional studies documenting an inverse association between fetal growth and prenatal exposure to exogenous chemicals with renal clearance, such as PFOA.


(A)
Reduction in fetal growth
Less plasma volume expansion
Less glomerular filtration rate
Reduced filtration of exogenous chemical
Higher concentration in cord blood or maternal blood or urine
(B)
Increased exposure to exogenous chemicals
Reduced fetal growth

THE JOURNAL OF MATERNAL-FETAL & NEONATAL MEDICINE

http://informahealthcare.com/jmf
ISSN: 1476-7058 (print), 1476-4954 (electronic)

J Matern Fetal Neonatal Med, 2015; 28(18): 2176–2181
© 2014 Informa UK Ltd.
DOI: 10.3109/14767058.2014.980809

informa healthcare

ORIGINAL ARTICLE

Fetal growth and maternal glomerular filtration rate: a systematic review

Hanna M. Vesterinen[1], Paula I. Johnson[1,2], Dylan S. Atchley[1], Patrice Sutton[1], Juleen Lam[3], Marya G. Zlatnik[4], Saunak Sen[5], and Tracey J. Woodruff[1]

[1]*Department of Obstetrics, Gynecology, and Reproductive Sciences, UCSF Program on Reproductive Health and the Environment, University of California, San Francisco, CA, USA,* [2]*California Department of Public Health, Occupational Health Branch, Richmond, CA, USA,* [3]*Department of Health, Policy and Management, John Hopkins University, Baltimore, MD, USA,* [4]*Department of Obstetrics, Gynecology, and Reproductive Sciences, Division of Maternal Fetal Medicine, UCSF, San Francisco, CA, USA, and* [5]*Department of Epidemiology and Biostatistics, UCSF, San Francisco, CA, USA*

Abstract

Objective: Glomerular filtration rate (GFR) may influence concentrations of biomarkers of exposure and their etiologic significance in observational studies of associations between environmental contaminants and fetal growth. It is unknown whether the size of a developing fetus affects maternal GFR such that a small fetus leads to reduced plasma volume expansion (PVE), reduced GFR and subsequent higher concentrations of biomarkers in maternal serum. Our objective was to answer the question: "Is there an association between fetal growth and maternal GFR in humans?"

Methods: We adapted and applied the Navigation Guide systematic review methodology to assess the evidence of an association between fetal growth and GFR, either directly or indirectly via reduction in PVE.

Results: We identified 35 relevant studies. We rated 31 human and two non-human observational studies as "low" quality and two experimental non-human studies as "very low" quality. We rated all three evidence streams as "inadequate". The association between fetal growth and GFR was "not classifiable" according to pre-specified definitions.

Conclusions: There is currently insufficient evidence to support the plausibility of a reverse causality hypothesis for associations between exposure to environmental chemicals during pregnancy and fetal growth. Further research would be needed to confirm or disprove this hypothesis.

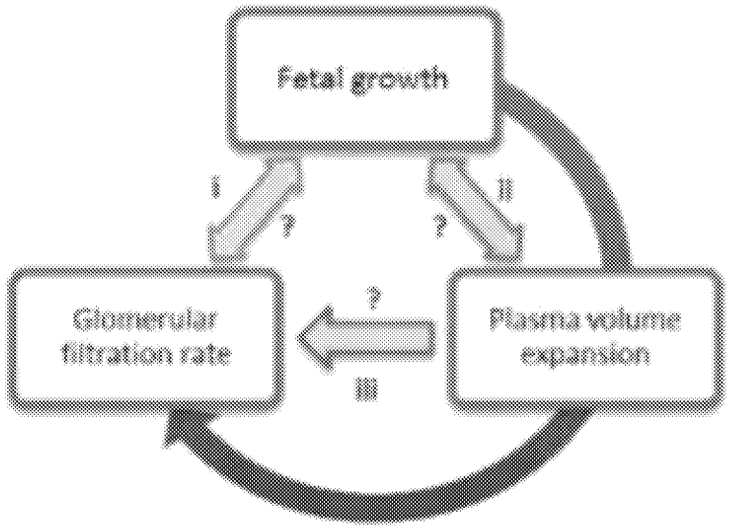
Keywords

Fetal growth, glomerular filtration rate, perfluorooctanoic acid, plasma volume expansion, reproductive environmental health, reverse causality, the navigation guide

History

Received 15 July 2014
Revised 18 October 2014
Accepted 22 October 2014
Published online 3 December 2014

A.


Fetal growth
I
?
II
?
Glomerular filtration rate
?
III
Plasma volume expansion

Vesterinen et al. 2015

- Our rationale for ''inadequate'' human studies was based on the ''low'' quality of evidence, the indeterminate direction of effect and a lack of confidence in the effect between fetal growth and GFR, either directly or via change in PVE. Although we were confident in the effect between fetal growth and PVE, based on data from the two largest studies [13,14], we had low confidence in the evidence on the association between fetal growth and GFR, or PVE and GFR. Thus, a new, well-designed and adequately powered study would be likely to change our certainty in the strength of the effect between fetal growth and GFR, or between PVE and GFR.

Maternal Glomerular Filtration Rate in Pregnancy and Fetal Size

Nils-Halvdan Morken[1,2,3]*, Gregory S. Travlos[4], Ralph E. Wilson[4], Merete Eggesbø[5], Matthew P. Longnecker[6]

1 Department of Global Public Health and Primary Care, University of Bergen, Bergen, Norway, 2 Department of Clinical Sciences, University of Bergen, Bergen, Norway, 3 Department of Obstetrics and Gynecology, Haukeland University Hospital, Bergen, Norway, 4 Cellular and Molecular Pathology Branch, National Institute of Environmental Health Sciences, National Institutes of Health, Department of Health and Human Services, Research Triangle Park, North Carolina, United States of America, 5 Division of Epidemiology, Norwegian Institute of Public Health, Oslo, Norway, 6 Epidemiology Branch, National Institute of Environmental Health Sciences, National Institutes of Health, Department of Health and Human Services, Research Triangle Park, North Carolina, United States of America

Abstract

Background: The relationship of maternal glomerular filtration rate (GFR) in pregnancy to fetal size needs to be better characterized as it impacts an ongoing debate about confounding effect of maternal GFR in investigations of important environmental contaminants. We aimed to characterize the size of the association between maternal GFR and infant birth weight.

Materials and Methods: A sub-cohort of 953 selected women (470 women with and 483 women without preeclampsia) in the Norwegian Mother and Child Cohort (MoBa), recruited during 2003–2007 were analyzed. GFR in the second trimester was estimated based on plasma creatinine. Birth weight was ascertained from the Medical Birth Registry of Norway. Multivariate linear regression was used to evaluate the association between maternal GFR in second trimester (estimated by the Cockroft-Gault [GFR-CG] and the modification of diet in renal disease [GFR-MDRD] formulas) and infant birth weight. Partial correlation coefficients were also calculated.

Results: Maternal GFR-CG (β: 0.73 g/ml/min, $p = 0.04$) and GFR-MDRD (β: 0.83 g/ml/min, $p = 0.04$) were associated with infant birth weight in models adjusted for maternal weight in kilograms, preeclampsia, and gestational age at delivery (days). Partial correlation coefficients for the association between infant birth weight and GFR were 0.07 for both formulas. Although the birth weight-GFR association was stronger among the women with preeclampsia, the difference from women without preeclampsia was not statistically significant.

Conclusion: These data support an association between GFR during pregnancy and infant birth weight, and indicate that GFR may confound selected epidemiologic associations.

Citation: Morken N-H, Travlos GS, Wilson RE, Eggesbø M, Longnecker MP (2014) Maternal Glomerular Filtration Rate in Pregnancy and Fetal Size. PLoS ONE 9(7): e101897. doi:10.1371/journal.pone.0101897

Editor: Olivier Baud, Hôpital Robert Debré, France

Received March 3, 2014; **Accepted** June 12, 2014; **Published** July 8, 2014

This is an open-access article, free of all copyright, and may be freely reproduced, distributed, transmitted, modified, built upon, or otherwise used by anyone for any lawful purpose. The work is made available under the Creative Commons CC0 public domain dedication.

Funding: Nils-Halvdan Morken was supported with funding from the University of Bergen and the Unger-Vetlesen Medical Fund. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: The authors have declared that no competing interests exist.

* Email: nils-halvdan.morken@klu.uib.no

Adjusted coefficients with standard errors (SE) from multiple linear regression analysis of the association between infant birth weight and maternal glomerular filtration rate (GFR) in second-trimester estimated by Cockroft-Gault (CG), modification of diet in renal disease (MDRD) and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formulas, based on data from 470 women with preeclampsia, 483 women without preeclampsia and the total cohort of 953 pregnant women from the Norwegian Mother and Child Cohort, Norway 2003–2007.

	Women with preeclampsia	Women without preeclampsia	The total cohort
	Adjusted β[a]	Adjusted β[a]	Adjusted β[b]
	(SE)	(SE)	(SE)
GFR by CG formula	1.1* (0.49)	0.24 (0.52)	0.73* (0.36)
GFR by MDRD formula	1.3* (0.58)	0.23 (0.58)	0.83* (0.41)
GFR by CKD-EPI formula	3.0* (1.3)	1.3 (1.1)	0.04 (0.82)

*significance at the 0.05 level.

[a]adjusted for maternal weight (kg) and gestational age in days. The unit for β with SE in gram.

[b]adjusted for maternal weight (kg), preeclampsia and gestational age in days. The unit for β with SE in gram.

ehp ENVIRONMENTAL HEALTH PERSPECTIVES
http://www.ehponline.org

Associations of Perfluoroalkyl Substances (PFASs) with Lower Birth Weight: An Evaluation of Potential Confounding by Glomerular Filtration Rate Using a Physiologically Based Pharmacokinetic Model (PBPK)

Marc-André Verner, Anne E. Loccisano, Nils-Halvdan Morken, Miyoung Yoon, Huali Wu, Robin McDougall, Mildred Maisonet, Michele Marcus, Reiko Kishi, Chihiro Miyashita, Mei-Huei Chen, Wu-Shiun Hsieh, Melvin E. Andersen, Harvey J. Clewell III, and Matthew P. Longnecker

http://dx.doi.org/10.1289/ehp.1408837

Received: 16 June 2014
Accepted: 19 May 2015
Advance Publication: 22 May 2015

Abstract

Background: Prenatal exposure to perfluoroalkyl substances (PFAS) has been associated with lower birth weight in epidemiologic studies. This association could be attributable to glomerular filtration rate (GFR) which is related to PFAS concentration and birth weight.

Objectives: To use a physiologically based pharmacokinetic (PBPK) model of pregnancy to assess how much of the PFAS-birth weight association observed in epidemiologic studies might be attributable to GFR.

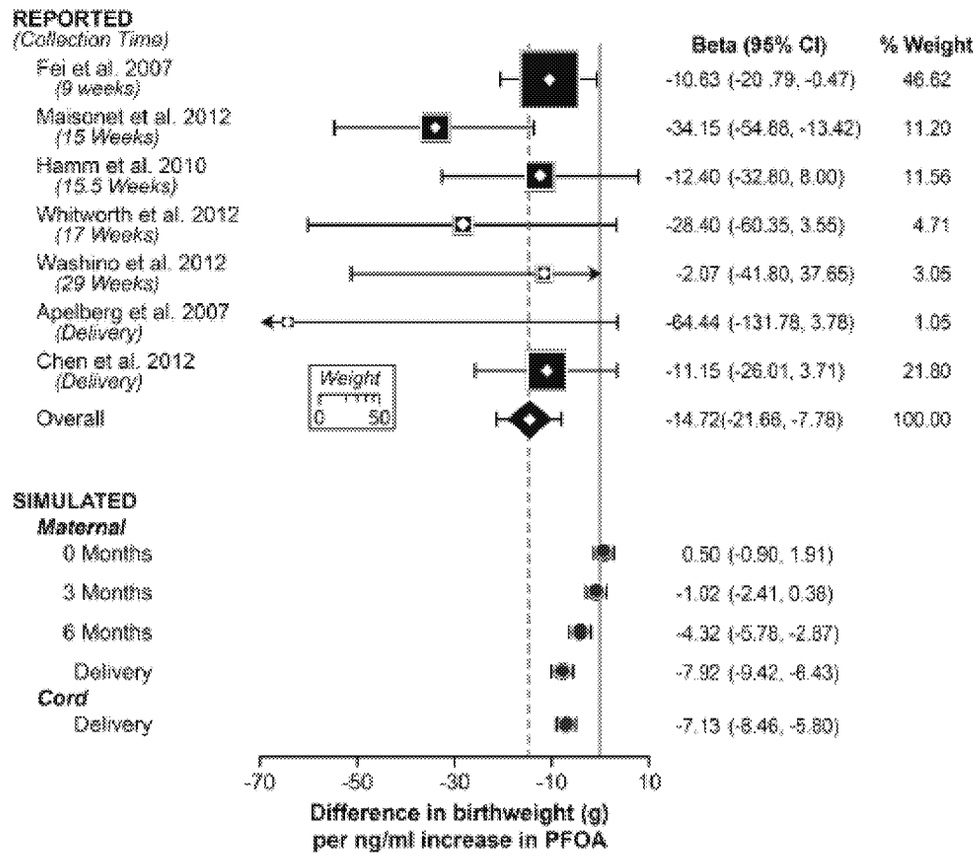
Methods: We modified a PBPK model to reflect the association of GFR with birth weight (estimated from three studies of GFR and birth weight) and used it to simulate PFAS concentrations in maternal and cord plasma. The model was run 250,000 times, with variation in parameters, to simulate a population. Simulated data were analyzed to evaluate the association between PFAS levels and birth weight due to GFR. We compared simulated estimates to those from a meta-analysis of epidemiologic data.

Results: The reduction in birth weight for each 1 ng/ml increase in simulated cord plasma for perfluorooctane sulfonate (PFOS) was 2.72 g (95% CI: -3.40, -2.04), and for perfluorooctanoic acid (PFOA) was 7.13 g (95% CI: -8.46, -5.80); results based on maternal plasma at term were similar. Results were sensitive to variations in PFAS level distributions and the strength of the GFR-birth weight association. In comparison, our meta-analysis of epidemiologic studies suggested that each 1 ng/ml increase in prenatal PFOS and PFOA levels was associated with 5.00 g (95% CI: -21.66, -7.78) and 14.72 g (95% CI: -8.92, -1.09) reductions in birth weight.

Conclusion: Results of our simulations suggest that a substantial proportion of the association between prenatal PFAS and birth weight may be attributable to confounding by GFR and that confounding by GFR may be more important in studies with sample collection later in pregnancy.

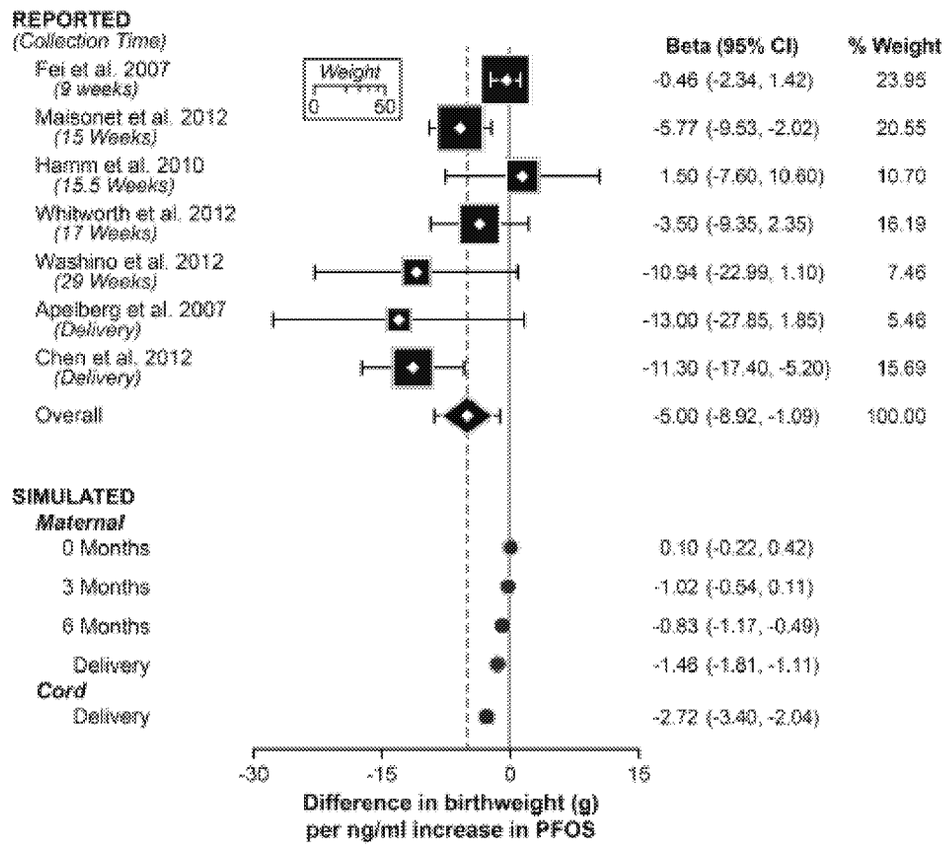
Environ Health Perspect DOI: 10.1289/ehp.1408837
Advance Publication: Not Copyedited

Figure 3A.

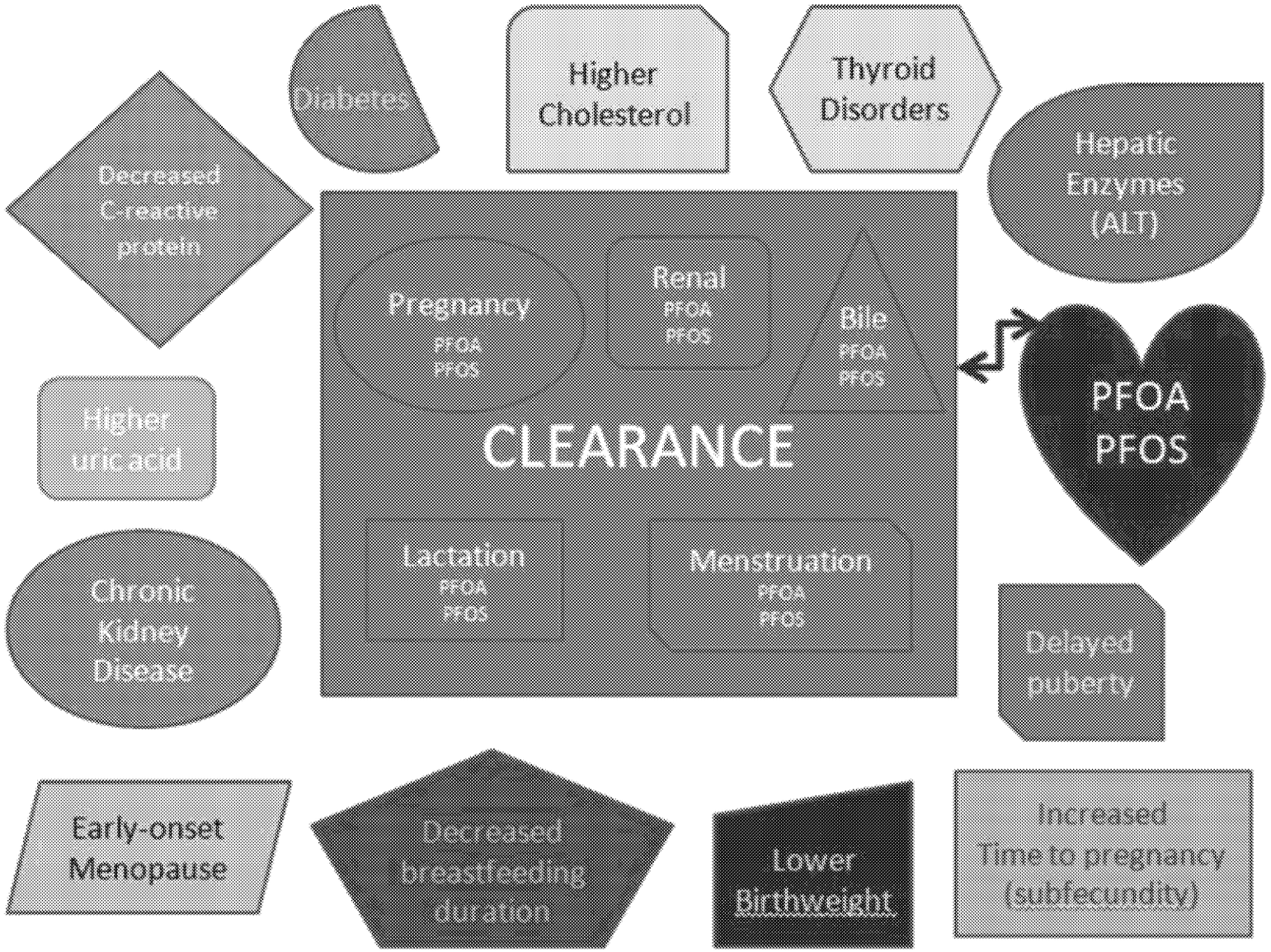


Environ Health Perspect DOI: 10.1289/ehp.1408837
Advance Publication: Not Copyedited

Figure 3B.



Is Clearance a Common Explanation Across Many of these Epidemiological Associations?



Exposure to Perfluoroalkyl Acids and Markers of Kidney Function among Children and Adolescents Living near a Chemical Plant

Deborah J. Watkins,[1] Jyoti Josson,[2] Beth Elston,[1] Scott M. Bartell,[3] Hyeong-Moo Shin,[4] Veronica M. Vieira,[5] David A. Savitz,[1] Tony Fletcher,[2] and Gregory A. Wellenius[1]

[1]Department of Epidemiology, Brown University, Providence, Rhode Island, USA; [2]Social and Environmental Health Research, London School of Hygiene and Tropical Medicine, London, UK; [3]Program in Public Health, and [4]School of Social Ecology, University of California, Irvine, Irvine, California, USA; [5]Department of Environmental Health, Boston University School of Public Health, Boston, Massachusetts, USA

BACKGROUND: Serum levels of perfluorooctanoic acid (PFOA) have been associated with decreased renal function in cross-sectional analyses, but the direction of the association is unclear.

OBJECTIVES: We examined the association of measured and model-predicted serum PFOA concentrations with estimated glomerular filtration rate (eGFR), a marker of kidney function, in a highly exposed population (median serum PFOA, 28.3 ng/mL).

METHODS: We measured serum creatinine, PFOA, perfluorooctane sulfonate (PFOS), perfluorononanoic acid (PFNA), and perfluorohexane sulfonate (PFHxS) and calculated eGFR in 9,660 children 1 to < 18 years of age at study enrollment. We predicted concurrent and historical serum PFOA concentrations using a validated environmental, exposure, and pharmacokinetic model based on individual residential histories, and used linear regression to estimate the association between eGFR and measured and predicted serum PFOA concentrations. We hypothesized that predicted serum PFOA levels would be less susceptible to reverse causation than measured levels.

RESULTS: An interquartile range increase in measured serum PFOA concentrations [IQR ln(PFOA) = 1.63] was associated with a decrease in eGFR of 0.75 mL/min/1.73 m^2 (95% CI: −1.41, −0.10; $p = 0.02$). Measured serum levels of PFOS, PFNA, and PFHxS were also cross-sectionally associated with decreased eGFR. In contrast, predicted serum PFOA concentrations at the time of enrollment were not associated with eGFR (−0.10; 95% CI: −0.80, 0.60; $p = 0.78$). Additionally, predicted serum PFOA levels at birth and during the first ten years of life were not related to eGFR.

CONCLUSIONS: Our findings suggest that the cross-sectional association between eGFR and serum PFOA observed in this and prior studies may be a consequence of, rather than a cause of, decreased kidney function.

KEY WORDS: adolescent, children, eGFR, kidney function, perfluoroalkyl acids, perfluorooctane sulfonate, perfluorooctanoic acid, reverse causation. *Environ Health Perspect* 121:625–630 (2013). http://dx.doi.org/10.1289/ehp.1205838 [Online 11 March 2013]

creatinine (Costa et al. 2009; Emmett et al. 2006), a recent analysis of NHANES data found that serum concentrations of PFOA and PFOS were associated with decreased estimated glomerular filtration rate (eGFR) and increased odds of having an eGFR < 60 mL/min/1.73 m^2, a clinically relevant cut point indicative of chronic kidney disease in adults (Shankar et al. 2011b).

Because NHANES is a cross-sectional survey, Shankar et al. (2011b) were unable to determine whether high levels of PFOA and PFOS in serum preceded reduced kidney function and chronic kidney disease, or vice versa. In addition, serum concentrations of PFOA and PFOS are moderately or strongly correlated in the general population (Calafat et al. 2007), making it difficult to distinguish the association with one from the other. Finally, the association between PFAA exposure and kidney function among children or adolescents has never been examined. Because chronic kidney disease in children may eventually require dialysis or kidney transplantation, and early diagnosis is a key component of successful treatment, understanding

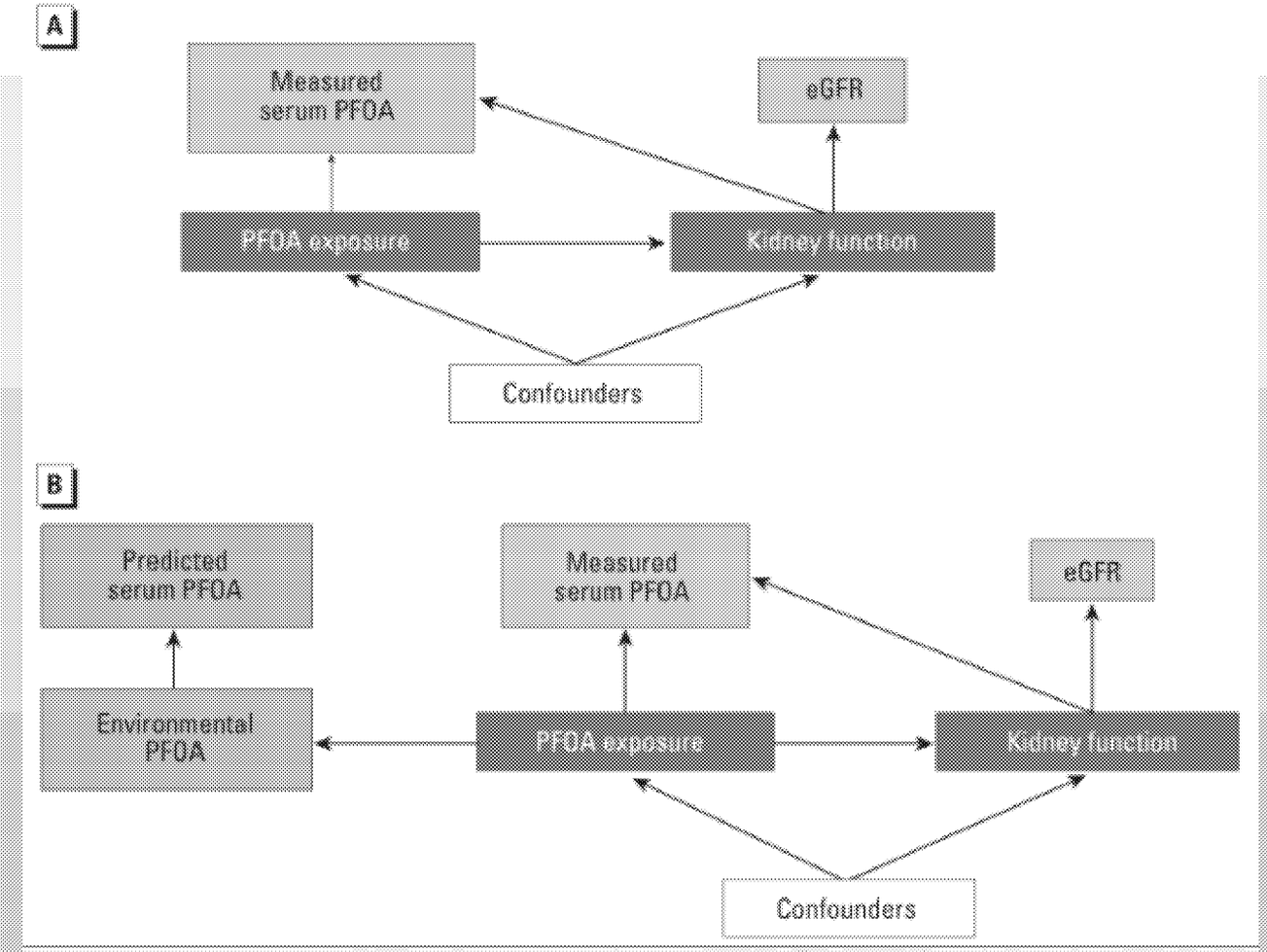

A
Measured serum PFOA
eGFR
PFOA exposure
Kidney function
Confounders
B
Predicted serum PFOA
Measured serum PFOA
eGFR
Environmental PFOA
PFOA exposure
Kidney function
Confounders

Table 2. Associations between serum perfluoroalkyl acid (PFAA) concentrations and estimated glomerular filtration rate (eGFR).[a]

PFAA	*n*	IQR	Model 1[b]		Model 2[c]	
			Change in eGFR (95% CI)[f]	*p*-Value	Change in eGFR (95% CI)[f]	*p*-Value
Measured						
PFOA	9,660	1.63	–0.75 (–1.41, –0.10)	0.02	–0.73 (–1.38, –0.08)	0.03
PFOS	9,660	0.64	–1.10 (–1.66, –0.53)	0.0001	–1.34 (–1.91, –0.77)	< 0.0001
PFNA	9,660	0.51	–0.83 (–1.35, –0.30)	0.002	–0.88 (–1.41, –0.36)	0.001
PFHxS	9,660	1.27	–0.95 (–1.57, –0.32)	0.003	–1.02 (–1.64, –0.40)	0.001
Estimated PFOA						
Early[d]	4,787	2.10	–0.03 (–0.99, 0.93)	0.95	–0.09 (–1.04, 0.87)	0.86
Recent[e]	6,060	1.88	–0.04 (–0.76, 0.68)	0.91	–0.06 (–0.77, 0.65)	0.87
Enrollment[f]	6,060	1.84	–0.10 (–0.80, 0.60)	0.78	–0.12 (–0.81, 0.58)	0.75

[a]Expressed as the mean change in eGFR per interquartile range (IQR) increase in each natural log-transformed PFAA.
[b]Model 1: adjusted for age, sex, race, smoking, and household income. [c]Model 2: adjusted for model 1 covariates plus regular exercise and BMI *z*-score. [d]First 10 years of life, or current age if < 10 years of age. [e]During 3 years before enrollment. [f]At time of enrollment (2005–2006).

Pharmacodynamic Modeling of PFOA Exposure Based on Data from a Phase I Clinical Trial

Timothy R. Church[1], Matteo Convertino[1], Geary W. Olsen[2]

[1]Division of Environmental Health Sciences, University of Minnesota School of Public Health, Minneapolis, MN; [2]Medical Department, 3M Company, St. Paul, MN

Poster presented at FLUOROS 2015

July 2015

DEVELOPMENT OF HISTORIC PFOS-RELATED TEAM-BASED SIMILAR EXPOSURE GROUPS (SEGs) AT THE 3M DECATUR PLANT

T-412

Covington, D.G.[1,2], Morey, S.L.[1,2], Logan, P.W.[1], Batista, S.M.[1], Andres, K.L.[1], and Olsen, G.W.[1]

[1]3M Company, St. Paul, MN; [2]Consultants

Poster presented at FLUOROS 2015

July 2015