PFAS Health, Toxicology Regulatory Subgroup Meeting

Virginia Department of Health Office of Drinking Water
(Discuss exposure factors)
June 9, 2021
1:30pm – 3:30pm

1. **Opening Remarks**

VDH State Toxicologist, Dwight Flammia, Ph.D. called the meeting to order 1:33 p.m. The meeting was conducted by electronic communication means (WebEx) due to the ongoing public health emergency associated with the coronavirus pandemic. The meeting was recorded. Minutes and materials provided to Subgroup members will be posted on Town Hall.

2. **Subgroup Members Present**:

Kelly Ryan (VA American Water)
Erin Reilly (James River Association)
Steve Risotto (ACC)
Benjamin Hollard (DEQ)
Paul Nyffeler (Chem Law)
William Mann (Ob/Gyn, retired)
David Jurgens (City of Chesapeake)
Dwight Flammia (VDH, State Toxicologist)

3. **Review of previous meeting**

The Subgroup did not have time to discuss May 14, 2021 meetings. Approval of these minutes will be discussed at the next meeting.

4. **Discussions**

The presentation began with a look at different lengths of animal studies and their use in developing a maximum contaminant level (MCL) which is meant to be protective over a lifetime. This was followed by a presentation of equivalent life stages of different species, NOAEL (no observed adverse effect level - the highest exposure level at which there are no biologically significant increases in the frequency or severity of adverse effect between the exposed population and its appropriate control), and a look at the Agency for Toxic Substances and Disease Registry's (ATSDR) final toxicological profile for perfluorooctane sulfonate (PFOS) and perfluorooctanoate (PFOA). Then Dwight presented all the critical PFOS and PFOA studies used by EPA to develop a reference dose (RfD), ATSDR to develop a mimimum risk level (MRL), and states with MCLs for PFOA and PFOS. Next, the group talked about the Drexel Report and Pennsylvania's use of it to develop state MCLs. There was a discussion if Drexel was correct in not using a sub-chronic to chronic uncertainty factor (UF) of 10. Instead Drexel used and UF = 1. Some of the group stated that Drexel noted that it was a chronic "effect"

study. Dwight feels that a chronic study implies that animals were dosed for the majority of their lives.

The group discussed what they would submit to the PFAS Workgroup. At a minimum, a reference dose should be presented and members think the group's job is to provide the larger group a maximum contaminant level goal (MCLG). Dwight Flammia will get more clarification on this. The thought is that the other groups will use data from the Toxicology Subgroup's work to develop an MCL. The group discussed moving forward with looking at the other four compounds toxicity listed in the bill now that they have reviewed PFOS and PFOA.

Dwight presented a condensed version of the state MCL chart prepared by ODU. The group did a side by side comparison of critical study, uncertainty factors, and the point of departure used by each state that has an MCL for PFOS and PFOA. He noticed that there were some inconsistencies in the spreadsheet and missing units. He would like the group go over the spreadsheet and make sure the data in it is correct.

David Jurgens wanted to know why the subgroup is not looking at other states that may be developing MCLs or that have advisories/notifications for PFAS in drinking water. Dwight explained that the bill asked that the workgroup to look at states with MCLs. David suggests we do look at other states because if we do not, this implies that we are not looking at the most up to date studies. Another member in the group feel the subgroup should also be looking at the European Food Administration Study. The information is newer, they did look at the science 2019 and 2020, and the UDCR final report may contain newer information.

Dwight also responded to the group that he has created a folder where ODU puts PFAS articles published in 2021. He will make sure ODU is continuing to look for newer articles to include in this folder.

5. Public Comment

No Comments

6. Closing Items

Ben Holland will work on the spreadsheet and double check inconsistencies. Paul Nyffeler will assist Ben.

Dwight will assign members one of the following to research and bring back to the group for discussion: (1) What length of study is needed to develop an MCL; (2) What are other states that do not have PFAS MCL doing to address PFAS in drinking water; and (3) How should uncertainty factors be used. Dwight will present what toxicity data states used to develop MCLs for the other four PFAS substances listed in the bill as requested by the work group.

PFAS Health, Toxicology Regulatory Subgroup Meeting

Virginia Department of Health Office of Drinking Water
June 9, 2021
1:30pm – 3:30pm

Opening Remarks

Member Roll Call

Review of Previous Meeting Minutes

Presentation

Discussion

Public Comment

Closing items

Establishing Regulatory Limits for PFAS in Virginia Drinking Water

PFAS Toxicology Regulatory Workgroup

Dwight Flammia, Ph.D.
State Public Health Toxicologist
Virginia Department of Health
June 9, 2021

PFAS Workgroup Meeting Overview

Meeting Overview

- Opening Remarks
- Workgroup Members Introductions
- Review of previous meeting
- Presentations
- Discussion
- Public Comment
- Next Meeting

Members

Jillian Terhune (City of Norfolk)
Kelly Ryan (VA American Water)
Mark Estes (Halifax County Service Authority)
David Jurgens (City of Chesapeake)
Erin Reilly (James River Association)
Chris Leyen (VCLV)
Steve Risotto (ACC)
Benjamin Holland (DEQ)
Dwight Flammia (VDH, State Toxicologist)
Andrea Wortzel (Mission H2O)
Steve Herzog (Hanover County)
Paul Nyffeler (Chem Law)
William Mann (Ob/Gyn, retired)

Older EPA source: Acute, sub-chronic, chronic

The 10-day HA is considered protective of these effects in a 10 kg child for each day for up to 14 days of continuous exposure and may be based on experimental studies of 30-day duration or less.

The longer-term HA, which is based on subchronic exposure studies covering 10% of an animal's lifetime, is considered protective of an exposure period in humans of up to 7 years (i.e., 10% of an individual's lifetime). The longer-term HA is developed to protect both a 10 kg child and a 70 kg adult.

The lifetime HA is considered protective of lifetime exposures and is usually based on chronic or subchronic or other more relevant experimental data. The Lifetime HA is based on the chronic oral RfD, adjusted for a 70 kg adult drinking 2 L water per day; the value is apportioned by a relative source contribution, for example, 20% of the toxicant represented by intake of water.

EPA Health Advisory Guidelines (PFOS)

Assessment endpoints for HAs can be developed for both short-term (1-day and 10-day) and lifetime exposure periods using information on the noncarcinogenic and carcinogenic toxicological endpoints of concern.

A 1-day HA is typically calculated for an infant (0 to12 months or a 10-kg child), assuming an acute exposure to the chemical; it is generally derived from a study of less than 7 days duration.

- A 10-day HA is typically calculated for an infant (0-12 months or a 10-kg child), assuming a limited period of exposure of one to two weeks; it is generally derived from a study of 7 to 30 days duration.
- A lifetime HA is derived for an adult (> 21 years old or an 80-kg adult), and assumes an exposure period over a lifetime (approximately 70 years). It is usually derived from a chronic study of 2 years duration, but subchronic studies can be used by adjusting the uncertainty factor employed in the calculation.

Approximate age at equivalent life stages in several species

In order to make comparisons among laboratory animal species and humans in terms of life stages covered, the approximate ages that correspond to specific events or life stages (e.g., birth, weaning, puberty, etc.) in different species are shown in the next slide, and these events/life stages are indicated in the figures. In a few cases, no data could be found on appropriate ages corresponding to particular life stages. In particular, the ages for mature adults and older adults often were not available, and there is some controversy about what constitutes old age.

U.S. EPA: A Review Of The Reference Dose And Reference Concentration Processes **2002**

Rat		Mouse		Rabbit		Beagle dog		Human	
Life stage	**Age**	**Life stage**	**Age**	**Life stage**	**Age**	**Life stage**	**Age**	**Life stage**	**Age**
Embryonic	GD 0–16	Embryonic	GD 0–15	Embryonic	GD 0–19	Embryonic	GD 0–30?	Embryonic	GD 0–58
Fetal[a]	GD 16–22 (22–23 days)	Fetal	GD 15–20 (18–22 days)	Fetal	GD 19–32 (30–32 days)	Fetal	GD 30–63 (53–71 days)	Fetal	GD 58–267
Neonate[b]	PND 0–14	Neonate	PND 0–14	Neonate	PND 0–21?	Neonate	PND 0–21	Neonate	PND 0–30
Weaning[c]	PND 21	Weaning	PND 21 (19–28)	Weaning	PND 42 (42–56)	Weaning	PND 42	Infancy	PND 30–1 yr
								Toddler	2–3 yrs
Young	PND 22–35	Young	PND 21–35	Young	PND 42–?	Young	1.5–5 mos	Preschool	3–6 yrs
								Elementary school age	6–12 yrs
Puberty	PND 35–60	Puberty	PND 35–?	Puberty	3–8 mos	Puberty	5–7 mos	Adolescence	12–21 yrs
Sexual maturity	2.5–3 mos	Breeding age	1.5–2 mos	Breeding age	6–9 mos	Breeding age	12 mos	Young adult	21–40 yrs
Mature adult	5–18 mos	Mature adult		Mature adult		Mature adult		Mature adult	40–65 yrs?
Old adult	18 mos–2 yrs+	Old adult		Old adult		Old adult	~15 yrs	Old adult	>65 yrs?

[a] Range of gestation length in parentheses.
[b] Some neonatal events in rodents occur in utero in humans.
[c] Range of weaning ages in parentheses.

GD = gestation day
PND = postnatal day

3-3

Reference Dose

The RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. It can be derived from a NOAEL, LOAEL, or benchmark dose, with uncertainty factors generally applied to reflect limitations of the data used. The RfD is derived after a thorough review of the health effects data base for an individual chemical, and identification of the most sensitive and relevant endpoint (the "critical effect") and the principal study(ies) demonstrating that endpoint.

NOAEL

In an experiment with several NOAELs, the regulatory focus is normally on the highest one, leading to the common usage of the term NOAEL as the highest experimentally determined dose without a statistically or biologically significant adverse effect.

ATSDR Minimal Risk Level

An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified route and duration of exposure.

MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (≥365 days) durations and for the oral and inhalation routes of exposure.

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that are not expected to cause adverse health effects.

PFOS – steady state

Animal Data. Adequate studies were available for short-term, sub-chronic, chronic, developmental, and reproductive parameters in rats, mice, and primates. Sub-chronic, chronic, and reproductive toxicity animal studies, all with exposure duration greater than 60 days, have been summarized in Table 4-1. Shorter duration studies that focused on immunotoxicity endpoints and developmental toxicity studies are summarized in Table 4-2. Although the exposure durations are shorter in developmental studies, they are important in quantification of dose-response because the exposures occur during critical windows of development and are often symptomatic of effects that can occur later in life. It is noted, however, that in some of these studies, steady states of PFOS might not have been achieved due to the long half-life of PFOS in animal models (see discussion of steady state in section 4.1.1.1)

PFOS

Species	Study Duration	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Critical Effect(s)	Reference
Monkey	90 days	ND	0.5	diarrhea, anorexia	Goldenthal et al. 1979
Monkey	182 days (6 months)	0.15	0.75	↓ survival, body wt gain ↑ liver wt; hepatocyte hypertrophy, ↓T3 and ↑TSH	Seacat et al. 2002
Rat	90 days	ND	2.0	↑ liver wt hepatocyte hypertrophy	Goldenthal et al. 1978b
Rat	98 days (14 weeks)	0.40 (F) 0.34 (M)	1.56 (F) 1.33 (M)	↑ liver wt ↓ cholesterol (M) ↑ ALT (M), ↑BUN (M/F) ↑ liver hypertrophy hepatic centrilobular vacuolization	Seacat et al. 2003
Rat	2 generation (84 days; 12 weeks)	0.1	0.4	↓ adult body wt gain ↓ pup body wt	Luebker et al. 2005b
Rat	1 generation (females only) (63 days)	0.4	0.8	↓ maternal wt gain ↓ gestation length ↓ pup survival	Luebker et al. 2005a
Rat	1 generation (females only) (63 days)	ND	0.4	↓ pup body weight	Luebker et al. 2005a
Rat	728 days (104 weeks; 2 yrs)	0.120 (F) 0.024 (M)	0.299 (F) 0.098 (M)	Cystic degeneration, centrilobular vacuolation (M) and centrilobular eosinophilic granules (F); ↑hepatic necrosis centrilobular vacuolation at higher doses	Thomford 2002/Butenhoff et al. 2012
Mouse	60 days	0.008	0.083	↑ liver wt ↑ splenic NK cell activity; ↓ SRBC response	Dong et al. 2009
Mouse	90 days	0.43	2.15	Impaired spatial learning and memory	Long et al. 2013

Notes: ND = not determined
BUN = blood urea nitrogen

Table 4-2. NOAEL/LOAEL Data for Short-Term Oral Studies of PFOS

Species	Study Duration	NOAEL (mg/kg/day)	LOAEL (mg/kg/day)	Critical Effect(s)	Reference
Rat	28 days	ND (F) 0.14 (M)	0.15 (F) 1.33 (M)	↑ relative liver wt (M/F), ↓T4 (M/F)	Curran et al. 2008
Rat	GDs 1–21	0.1	2.0	↓ pup survival histopathological changes to lungs (pups)	Chen et al. 2012
Rat	GD 0 to PND 20	-	0.5	↓ body weight impaired glucose tolerance	Lv et al. 2013
Rat	GDs 11–19	-	5	↓body weight, ↓ fetal Leydig cells, and ↓testosterone	Zhao et al. 2014
Rat	GDs 2–20	1.0	2.0	↓ dam and pup body weight ↓ pup survival	Thibodeaux et al. 2003; Lau et al. 2003
Rat	GD 0–PND 20	0.3	1.0	↑ motor activity and decreased habituation in male pups	Butenhoff et al. 2009
Rat	GDs 0–20	0.8	2.5	↑water maze escape distance and escapre latency	Y. Wang et al. 2015
Rat	GD 0–LD 21	0.8	2.5	↑water maze escape distance and escapre latency	Y. Wang et al. 2015
Mouse	GDs 1–17	1.0	5.0	↑ liver wt, dams and pups; delayed eye opening	Thibodeaux et al. 2003; Lau et al. 2003
Mouse	GD 3–PND 21 (dams) (offspring evaluated on PND 63)	0.3	3.0	↑ liver weight, increased insulin resistance	Wan et al. 2014a
Mouse	21 days	1	5	↑liver weight hepatic steatosis	Wan et al. 2012
Mouse	28 days	0.00017 (M) 0.0033 (F)	0.0017 (M) 0.017 (F)	↓ SRBC plaque-forming cell response	Peden-Adams et al. 2008
Mouse	GDs 1–17	(M) 1 (F)	1 (M) 5 (F)	↓ NK cell activity at postnatal week 8	Keil et al. 2008

Note: M = male: F = female

ATSDR 2021 Final PFOS

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name:	Perfluorooctane sulfonic acid (PFOS)
CAS Numbers:	1763-23-1
Date:	March 2020
Profile Status:	Final
Route:	Oral
Duration:	Intermediate
MRL:	$2x10^{-6}$ mg/kg/day
Critical Effect:	Delayed eye opening and decreased pup body weight
Reference:	Luebker et al. 2005a
Point of Departure:	0.000515 mg/kg/day
Uncertainty Factor:	30
Modifying Factor:	10
LSE Graph Key:	35
Species:	Rat

MRL Summary: An intermediate-duration oral MRL of $2x10^{-6}$ mg/kg/day was derived for PFOS based on delayed eye opening and transient decrease in F2 body weight during lactation in the offspring of rats administered PFOS via gavage in a 2-generation study (Luebker et al. 2005a). The MRL is based on a HED NOAEL of 0.000515 mg/kg/day and a total uncertainty factor of 30 (3 for extrapolation from animals to humans with dosimetric adjustments and 10 for human variability) and a modifying factor of 10 for concern that immunotoxicity may be a more sensitive endpoint than developmental toxicity.

PFOS Intermediate oral

Species and exposure duration	NOAEL (mg/kg/day)	LOAEL[a] (mg/kg/day)	Effect	Reference
Hepatic				
Monkey 26 weeks	0.15	0.75	Increased liver weight, decreased serum cholesterol, hepatocellular hypertrophy, lipid vacuolation	Seacat et al. 2002
Neurological				
Mouse 3 months	0.43	2.15	Impaired spatial learning and memory	Long et al. 2013
Immunological				
Mouse 28 days	0.00016	0.00166	Suppressed response to sRBC	Peden-Adams et al. 2008
Mouse 21 days	0.005	0.025	Decreased resistance to influenza virus	Guruge et al. 2009
Mouse 60 days	0.0083	0.083	Impaired response to sRBC	Dong et al. 2009
Mouse 60 days	0.0167	0.083	Impaired response to sRBC	Dong et al. 2011
Developmental				
Mouse GDs 1–21		0.3	Decreased locomotion, muscle strength, motor coordination in adult offspring	Onishchenko et al. 2011
Rat 84 days	0.1	0.4	Delayed eye opening	Luebker et al. 2005a
Rat 67 days		0.4	Decreased pup weight	Luebker et al. 2005b

Luebker 2005 PFOS Two generation study

Male and female rats were dosed via oral gavage at dose levels of 0, 0.1, 0.4, 1.6, and 3.2 mg/(kg day) for 6 weeks prior to mating, during mating, and, for females, through gestation and lactation, across two generations.

continuation into the second generation was limited to *F*1 pups from the 0, 0.1, and 0.4 mg/(kg day)

Statistically significant reductions in body-weight gain and feed consumption were observed in *F*0 generation males and females at dose levels of 0.4 mg/(kg day) and higher, but not in *F*1 adults.

NOAELs for a number of reproductive functions ≥ 0.4 mg/kg-day

Mean maternal serum PFOS at LD 21: 18.9 µg/mL at 0.4 mg/(kg day),

Mean serum PFOS values for *F*0 males after 42–56 days of dosing 45.4 µg/mL at 0.4 mg/(kg day)

Dong 2009 PFOS chronic immunotoxicity study

In this study, **adult male** C57BL/6 mice were exposed to PFOS **daily via gavage** for **60 days** [0, 0.5, 5, 25, 50, or 125 mg/kg total administered dose (TAD)].

The results showed that liver mass was significantly increased at ≥ 5 mg PFOS/kg TAD and in a dose-dependent manner

Plaque forming cell (PFC) response was suppressed beginning at 5 mg/kg TAD.

the NOAEL and LOAEL for male mice exposed PFOS for 60 days was 0.5 and 5 mg/kg TAD, respectively

serum concentrations at these dose levels were

0.674 and 7.132 mg/l, respectively

Dong 2011 PFOS sub-chronic study immunotoxicity study

Adult male C57BL/6 mice were exposed to PFOS daily via gavage for **60 days** [0, 0.5, 1, 5, 25, or 50 mg/kg total administered dose (TAD)].

The results showed that IL-4 secretion was increased at exposure C5 mg PFOS/kg TAD in a dose-dependent manner...Serum levels of sheep red blood cells (SRBC)-specific IgM synthesis decreased significantly with PFOS exposure in a dose-related manner

after a long-term exposure to PFOS, a host's immune state is likely to be characterized by a shift toward a more TH2-like state that, in turn, may lead to enhancement of their humoral response and suppression of their cellular response at levels of upper range for occupationally exposed workers or approximately 150-fold for general human population.

Using our LOAEL of 5 mg PFOS/kg TAD for suppressed IL-4 cytokine production and the associated serum PFOS concentration of 10.75 mg/L

Researcher's discussion: Serum levels of PFOS in the general human population have been reported to be 75 lg/L (Lau et al. 2007) and approximately 2.44 mg/L (range: 0.25–12.83 mg/L) after occupational exposures

EPA 2016 PFOS LTHA

The RfD of 0.00002 mg/kg/day calculated from HED average serum values from Luebker et al. (2005b) was selected. This RfD is derived from reduced pup body weight in the two-generation study in rats. The POD for the derivation of the RfD for PFOS is the HED of 0.00051 mg/kg/day that corresponds to a NOAEL that represents approximately 30% of steady-state concentration. A UF of 30 (10 UFH and 3 UFA) was applied to the HED NOAEL to derive an RfD of 0.00002 mg/kg/day.

ATSDR 2021 Final PFOA

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:**	Perfluorooctanoic acid (PFOA)
CAS Numbers:	335-67-1
Date:	March 2020
Profile Status:	Final
Route:	Oral
Duration:	Intermediate
***MRL*:**	$3x10^{-6}$ mg/kg/day
Critical Effect:	Skeletal alterations in adult offspring
Reference:	Koskela et al. 2016
Point of Departure:	0.000821 mg/kg/day
Uncertainty Factor:	300
LSE Graph Key:	63
Species:	Mouse

MRL Summary: An intermediate-duration oral MRL of $3x10^{-6}$ mg/kg/day was derived for PFOA based on skeletal alterations at 13 and 17 months of age in the offspring of mice fed a diet containing PFOA on GD 1 through GD 21 (Koskela et al. 2016). The MRL is based on a HED LOAEL of 0.000821 mg/kg/day and a total uncertainty factor of 300 (10 for use of a LOAEL, 3 for extrapolation from animals to humans with dosimetric adjustments, and 10 for human variability).

ATSDR PFOA Intermediate Studies

Table A-6. Summary of the Adverse Effects Observed in Laboratory Animals Following Intermediate-Duration Oral Exposure

Species and exposure duration	NOAEL (mg/kg/day)	LOAEL[a] (mg/kg/day)	Effect	Reference
Immunological				
Mouse 15 days	0.94	1.88	Reduced antibody response	DeWitt et al. 2016
Mouse 15 days	1.88	3.75	Reduced sRBC response	DeWitt et al. 2008
Reproductive				
Mouse GDs 1–17		0.0024	Delayed mammary gland development in dams (3-generation study)	White et al. 2011
Mouse GDs 1–17		1	Delayed mammary gland development in dams (single-generation study)	White et al. 2011
Developmental				
Mouse GD 7–PND 22		0.0024	Impaired development of mammary glands	White et al. 2011
Mouse GDs 10–17		0.01	Impaired development of mammary glands	Macon et al. 2011
Mouse GDs 1–17		0.01	Impaired development of mammary glands	Tucker et al. 2015
Mouse GD 7–PND 21		0.1	Neurodevelopmental	Sobolewski et al. 2014
Mouse GDs 1–21		0.3	Altered exploratory behavior in adult offspring; increased global activity in males	Onishchenko et al. 2011
Mouse GDs 1–21		0.3	Skeletal alterations in mature offspring	Koskela et al. 2016
Mouse GDs 1–17		0.3	Impaired development of mammary glands	Macon et al. 2011

Loveless 2006 PFOA linear/branched toxicity study

Rats and mice were given doses by oral gavage ranging from 0.3 to 30 mg/kg of either the linear/branched, linear, or branched ammonium perfluorooctanoate for 14 days.

In rats, serum PFOA levels were 20–51 ppm at Lowest Observed Effect Levels (LOEL) of 0.3–1 mg/kg, based primarily upon lipid parameters.

In mice, serum PFOA levels were 10–14 ppm at the LOEL of 0.3 mg/kg, based primarily upon relative liver weight.

Koskela 2016 PFOA effect on bone

In this study, pregnant C57BL/6 mice were exposed orally to 0.3 mg PFOA/kg/day throughout pregnancy, and female offspring were studied at the age of 13 or 17 months.

Pregnant dams received PFOA (n = 6) (purity 96%, Sigma-Aldrich) mixed with food at the dose of 0.3 mg/kg/day throughout the pregnancy starting from GD 1 (total dose 0.3 × 21 = 6.3 mg/kg).

Maternal exposure to PFOA during pregnancy resulted in accumulation of the compound in bones of the offspring so that elevated concentrations were detectable even at the age of 17 months, which is practically the whole lifetime of a mouse.

Question: appears that animals were dosed for 21 days – does that constitute a chronic study.

Lau 2006 PFOA effect during pregnancy

Timed pregnant CD-1 mice were given 1, 3, 5, 10, 20, or 40 mg/kg PFOA by oral gavage daily from gestational day (GD) 1 to 17; controls received an equivalent volume (10 ml/kg) of water.

Dose-dependent growth deficits were detected in all PFOA treated litters except the 1-mg/kg group.

Benchmark Dose approach used to calculate BMD_5

Onishchenko 2010 PFOA motor function

In the present study we have found that dietary exposure of mice to 0.3 mg/kg of PFOS or PFOA throughout pregnancy results in different distribution pattern in the offspring brain and liver.

0.3 mg/kg of PFOS or PFOA throughout gestation results in altered locomotor activity level and circadian distribution, muscle strength and motor coordination in the exposed offspring.

Moreover, the outcome of prenatal exposure appears to be sex-related and differs between PFOS and PFOA

male mice exposed prenatally to PFOS showed significantly less locomotor activity than controls

Macon 2011 PFOA developmental effects study

The overarching goal of these two studies was to establish a LOAEL and a NOAEL for mammary gland effects following prenatal exposure to PFOA

Timed-pregnant CD-1 mice were gavage dosed with PFOA for all or half of gestation.

In the full-gestation study, mice were administered 0, 0.3, 1.0, and 3.0 mg PFOA/kg body weight (BW)/day from gestation days (GD) 1–17.

In the late-gestation study, mice were administered 0, 0.01, 0.1, and 1.0 mg PFOA/kg BW/day from GD 10–17.

In both studies, the offspring of all PFOA-treated dams exhibited significantly stunted mammary epithelial growth as assessed by developmental scoring.

Due to the low-dose sensitivity of mammary glands to PFOA in CD-1 mice, a NOAEL for mammary developmental delays was not identified in these studies.

Researchers not: It is also critical to establish a mode of action (MOA) for the

developmental mammary gland growth effects following PFOA exposure to determine whether this MOA is biologically relevant to humans.

EPA 2016 PFOA LTHA

The RfD of 0.00002 mg/kg/day calculated from HED average serum values from Lau et al. (2006) was selected. This RfD is derived from reduced ossification of the proximal phalanges (forelimb and hindlimb) and accelerated puberty in male pups (4 days earlier than controls) as the critical effects. The POD for the derivation of the RfD for PFOA is the HED of 0.0053 mg/kg/day that corresponds to a LOAEL that represents approximately 60% of steady-state concentration. An UF of 300 (10 UFH, 3 UFA, and 10 UFL) was applied to the HED LOAEL to derive an RfD of 0.00002 mg/kg/day.

Drexel – Penn - PFOA

PFOA	
Dose Response Modeling Method	**LOAEL**
POD	The average serum concentration was estimated in the mice (8.29 mg/L) using a three-compartment pharmacokinetic model (Wambaugh 2013) using animal species, strain, sex-specific parameters. (ATSDR 2018)
HED = POD x DAF (mg/kg/d)	DAF = Ke x Vd Ke = 0.000825175 (8.2×10^{-4}) based on a human serum half-life of 840 days (Bartell 2010) Vd = 0.17 L/kg (Thompson 2010) $HED_{LOAEL} = POD_{LOAEL} \times DAF$ $HED_{LOAEL} = POD_{LOAEL} \times Ke \times Vd$ $HED_{LOAEL} = 8.29$ mg/L x 0.0000825175 x 0.17 L/kg $HED_{LOAEL} = 0.001163$ mg/kg/d or 1.163×10^{-3} mg/kg/d
Uncertainty Extrapolation	
Human Variability (UFH)	10 (standard)
Animal to Human (UFA)	3 (DAF applied)
Subchronic to Chronic (UFS)	1 (Chronic effect studied)
LOAEL to NOAEL (UFL)	10 (standard)
Database (UFD)	1
Total Composite (UFT)	300

Notes

Public Comments

Next Meeting – Wednesday July 14, 2021