

***Health-based Maximum Contaminant Level
Support Document:
Perfluorooctanoic Acid (PFOA)***

**New Jersey Drinking Water Quality Institute
Health Effects Subcommittee**

September 22, 2016

Subcommittee Members:

Jessie A. Gleason, M.S.P.H., Chair

Keith R. Cooper, Ph.D.

Judith B. Klotz, M.S., Dr. P.H.

Gloria B. Post, Ph.D., DABT

George Van Orden, Ph.D.

Health Effects Subcommittee Overview

- Develops Health-based MCLs based on goals specified in 1984 A-280 Amendments to NJ Safe Drinking Water Act
 - *Carcinogens*: **One in one million risk from lifetime exposure.**
 - *Non-carcinogens*: **Not expected to result in “any adverse physiological effects from ingestion” for a lifetime.**
- Approach generally based on USEPA risk assessment guidance.
- *January 2009*: DWQI voted to pursue development of MCL recommendation for PFOA.
 - Health Effects Subcommittee extensively evaluated PFOA in 2009-10.
- *March 2014*: NJDEP Commissioner requested DWQI to recommend MCL for PFOA.
 - Health Effects Subcommittee developed current draft report in 2015-16.

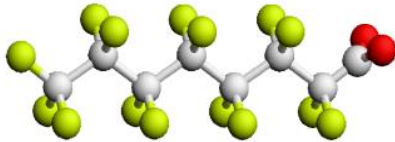
Document Development Process

- Presented in Appendix 1 of document.
- Initial literature search (April 2015) yielded more than 2000 citations.
 - Citations were screened and sorted into inclusion categories.
 - Updated with additional monthly literature searches.
- Request for additional technical information (May 2014) - Submitted information was considered
- Focus on studies of specific human and animal endpoints.
 - Key endpoints selected based on previous Subcommittee evaluations and current review.
- Developed individual study tables and/or summary tables for studies of key endpoints.

Example of Individual Study Table

Reference and Study Design	Exposure Measures	Results	Comment
<p>(Gallo, Leonardi et al. 2012)</p> <p>Study Design: Cross-sectional</p> <p>Location: United States – West Virginia and Ohio</p> <p>Population: Adults (18 years or older). Consumed water for at least 1 year from a water district with known PFOA contamination, n=47,092</p> <p>Outcome Definition: Serum biomarkers of liver function: ALT (alanine transaminase), GGT (gamma-glutamyltransferase), direct bilirubin</p>	<p>Exposure Assessment: Serum concentrations</p> <p>Population-Level Exposure: Median: 23.1 ng/mL, IQR 11.3-58.2</p>	<p>Stat Method: Linear regression of ln-transformed values, logistic regression fitted (reference levels as cut-offs for outcomes) comparing deciles of exposure, multilevel analysis comparing individual-level associations to population-level associations. Covariates and confounders considered include age, physical activity, BMI, average household income, educational level, alcohol consumption, cigarette smoking, fasting status, SES, race, and month of blood sample collection, and insulin resistance.</p> <p>Results for most adjusted models are presented.</p> <p>Outcome: ln-ALT Major Findings: $\beta = 0.022$ (95% CI 0.018, 0.025) p-value for trend < 0.001 ln-Unit OR=1.10 (95% CI 1.01, 1.13)</p> <p>Relationship consistent for both between water districts and among individuals within districts increases strength of evidence for casual association.</p> <p>Outcome: ln-GGT Major Findings: $\beta = 0.015$ (95% CI 0.010, 0.019) p-value for trend = 0.213 ln-Unit OR=1.01 (95% CI 0.99,1.04)</p> <p>Absence of trend across districts might be indicative of some confounding factor at the individual level.</p> <p>Outcome: ln-Direct bilirubin Major Findings: $\beta = 0.001$ (95% CI -0.002, 0.014) p-value for trend 0.496 ln-Unit OR=0.97 (95% CI 0.90, 1.15)</p> <p>Some evidence of geographic confounding.</p>	<p>Major Limitations: Cross sectional design precludes causal inference.</p> <p>Self-reported data of lifestyle characteristics strongly associated with exposures of interest – can hamper confounder adjustment</p> <p>Possible confounding due to unmeasured variables, and other environmental contaminants, including other PFCs.</p> <p>Funding Source: C8 Class Action Settlement Agreement between DuPont and Plaintiffs</p>

PFOA Overview

- Member of group of manmade compounds called perfluorinated chemicals (PFCs).
 - Totally fluorinated carbon chain with charged functional group (carboxylate or sulfonate).
 - Part of larger group: per- and polyfluoralkyl substances (PFAS).
- PFOA (C8) is the eight-carbon carboxylate. 
- Extremely **stable and resistant** to chemical reactions
 - Useful properties for commercial and industrial applications.
 - **Persist indefinitely** in the environment.
- **Water-soluble**
 - Unlike most other persistent, bioaccumulative, and toxic environmental contaminants.
 - Important as **drinking water contaminant**.

PFOA Occurrence in NJ Public Water Systems (PWS)

- New Jersey has more extensive PFOA occurrence data than most or all other states.
- USEPA Unregulated Contaminant Monitoring Rule 3 (UCMR3; ≥ 20 ng/L)
 - Data on **finished water** from all large and a few small PWS.
 - **Much more frequent occurrence in NJ than nationally.**
 - New Jersey PWS - 10.5%
 - United States PWS (other than NJ) - 1.9%
- NJDEP Database (NJDEP studies; other data reported to NJDEP; excludes UCMR3)
 - Data on **raw water, finished water, and individual PWS wells/intakes.**
 - **Finished water level may be lower** due to treatment and/or blending.
 - Detected above Reporting Level in **65% of NJ PWS in database.**

<i>PFOA Concentrations in NJ Public Water Systems (highest detection in any sample from the PWS)</i>		
<i>PFOA (ng/L)</i>	<i># of PWS</i>	<i>% of PWS</i>
ND	25	34.7%
RL - <10	15	20.8%
10 - <20	10	13.9%
20 - <40	10	13.9%
>40	12	16.7%

Reporting Levels (RLs) vary and range from 2.5-20 ng/L.

Human Biomonitoring and Exposure Sources

- Detected in blood serum of >99% of U.S. general population in NHANES.
 - Most recent (2011-12) data:
 - Median: 2.1 ng/ml (ppb)
 - 95th percentile: 5.7 ng/ml (ppb)
 - Levels have decreased over time since 1999-2000.
- Biomonitoring data specific to New Jersey have not been collected.
- Found in umbilical cord blood, breast milk, and seminal fluid.
- Exposure sources include diet and consumer products.
 - **Contribution from drinking water is dependent on water concentration.**

Toxicokinetics

- Well absorbed after oral exposure.
- Non-reactive, and therefore not metabolized.
- Primarily distributed to liver > blood serum > kidney.
 - **Blood serum levels reflect internal dose.**
- Slowest excretion in humans; also slowly excreted in mice and male rats, but rapidly excreted in female rats.
 - Result of differences in renal transporters that control excretion rate in kidney.
 - **Higher serum level from same dose in humans v. animals.**
 - Human-to-animal comparison in risk assessment must take internal dose differences into account.
- Excretion through urine and feces; menstruation and breastfeeding in women.
- Human half-life estimates: 2.3 - 8.9 years
 - **Accumulates in the body over time**; reaches steady state after prolonged exposure.
 - **Remains in body for many years after exposure ends.**

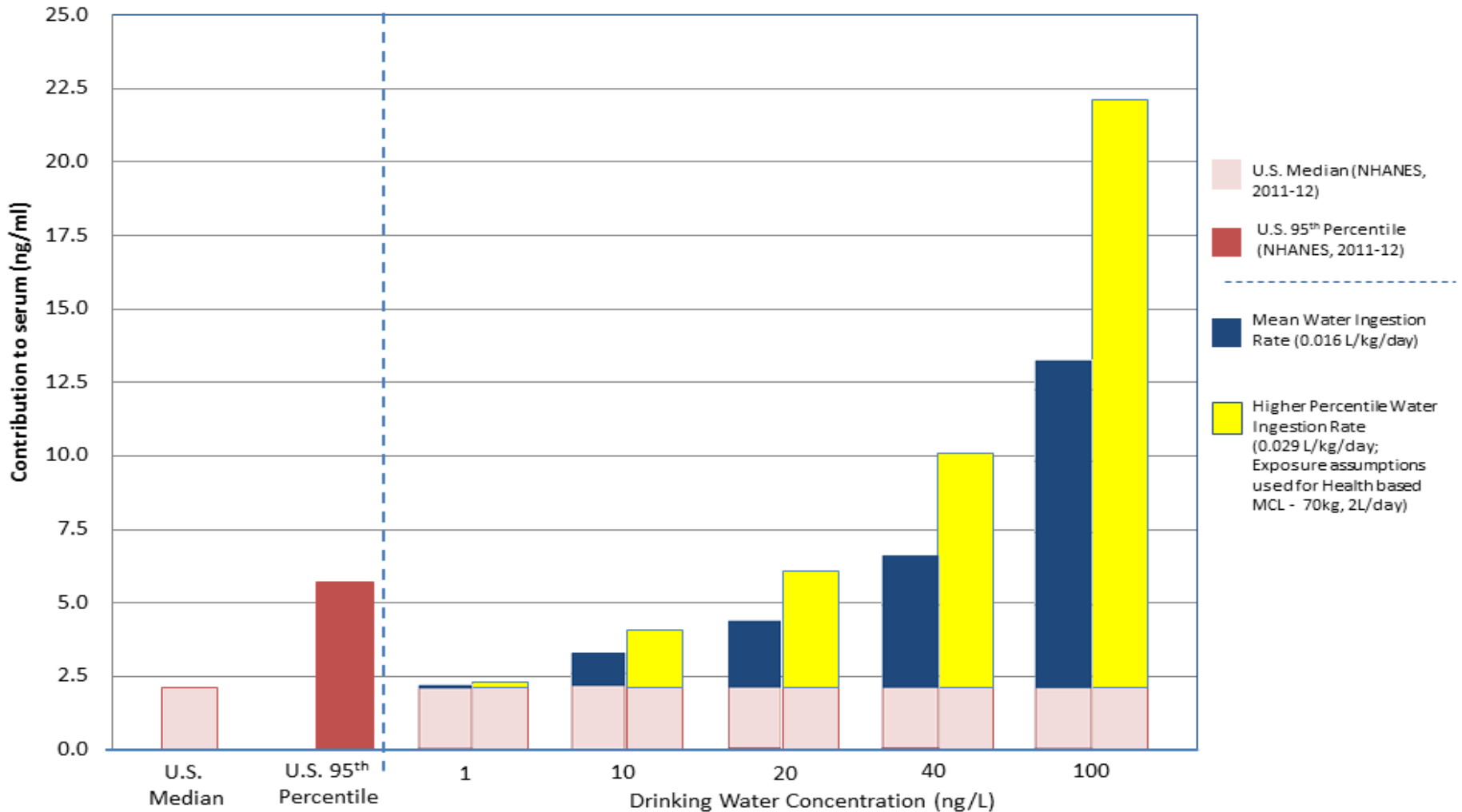
Relationship between Drinking Water Exposure and Blood Serum Levels

- **Relatively low concentrations of PFOA in drinking water substantially increases PFOA in blood serum.**
- **Ongoing exposure to PFOA in drinking water increases serum levels, on average, in a serum:drinking water ratio of at least 100:1.**
- Clearance factor developed by EPA researchers, 1.4×10^{-4} L/kg/day, relates external exposure to serum level:

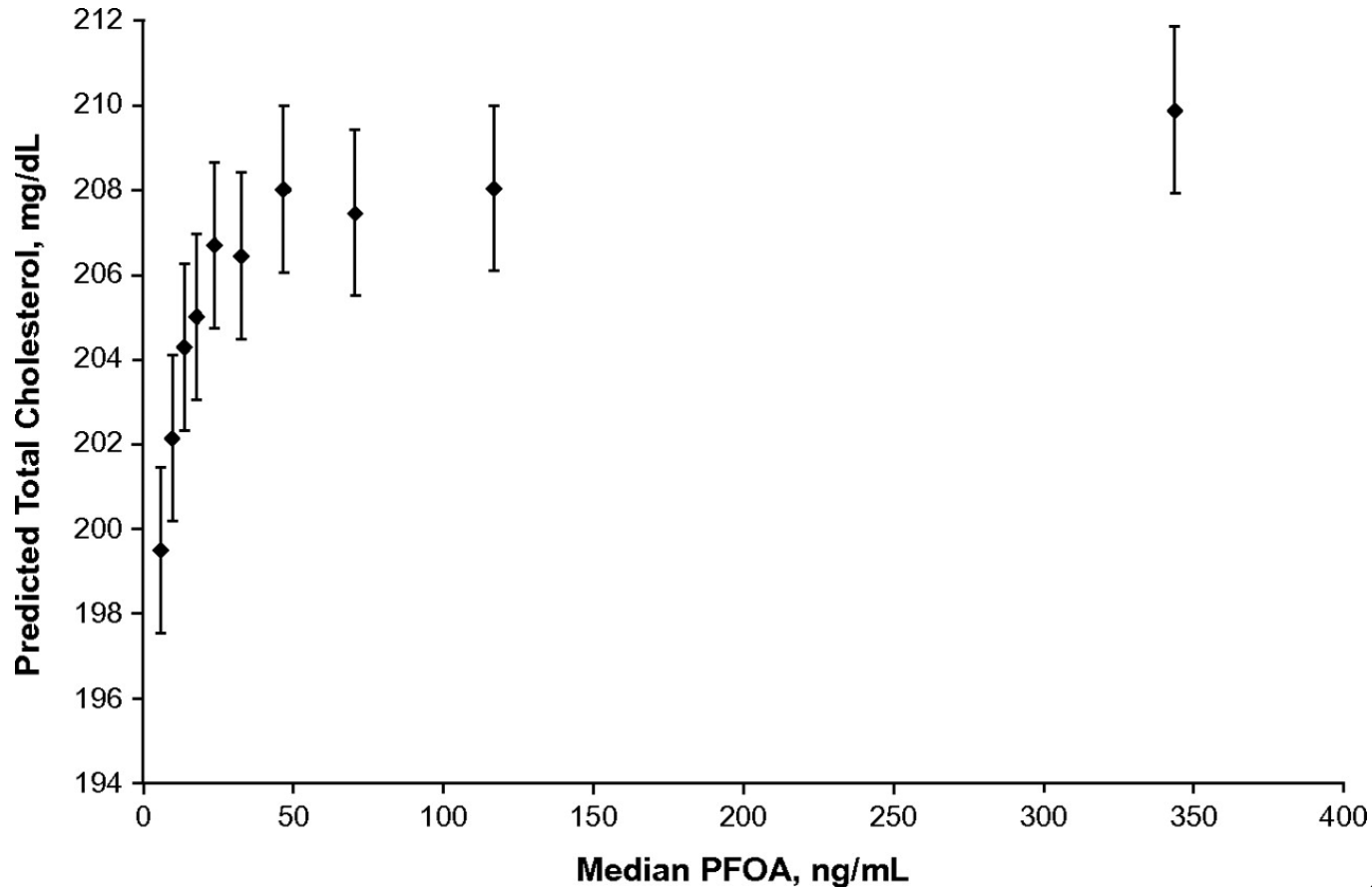
$$\text{Serum conc. } (\mu\text{g/L}) \times \text{Clearance Factor (L/kg/day)} = \text{Dose } (\mu\text{g/kg/day})$$

- Clearance factor predicts ratio of 114:1 with average water consumption and 200:1 with upper percentile consumption (2 L/day; 70 kg body wt.)
- Recent publication (Hurley et al., 2016) found higher serum levels in zip codes with UCMR3 detections.

Increases in Serum Concentrations Predicted from Ongoing Exposure to PFOA in Drinking Water



Associations of Health Effects with Low Serum PFOA Levels – Example: ↑ Cholesterol in Communities with Contaminated Drinking Water



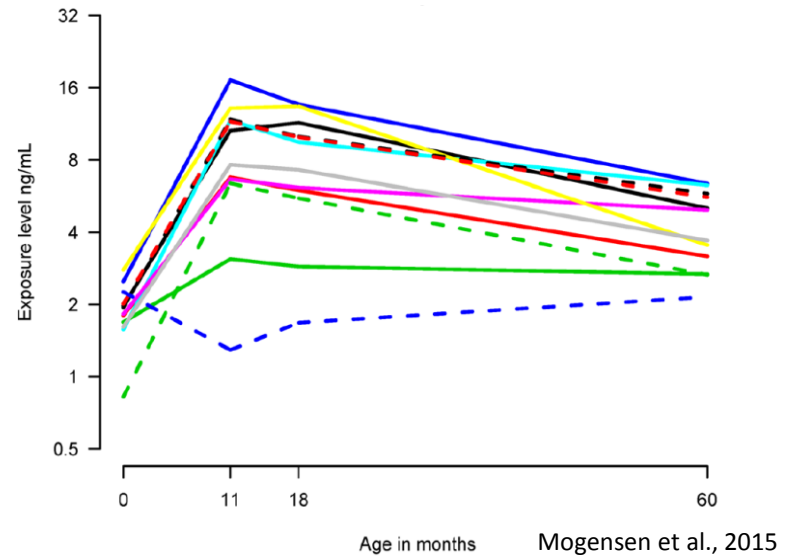
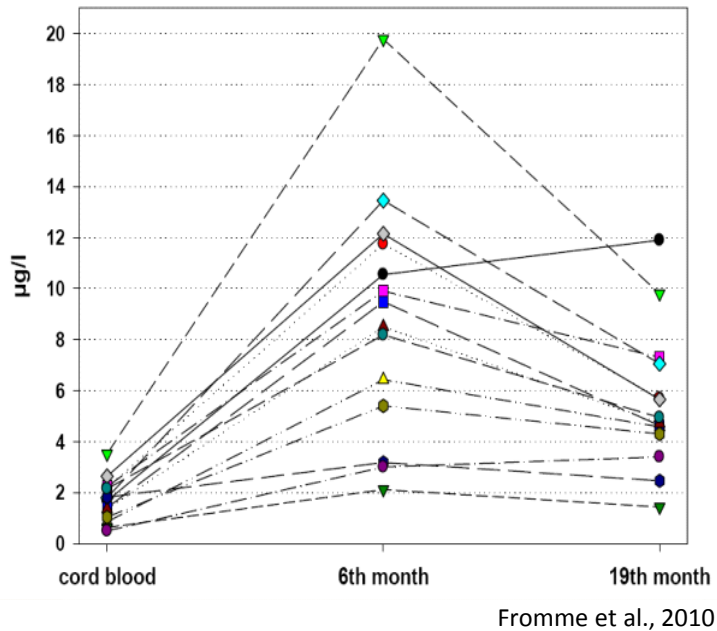
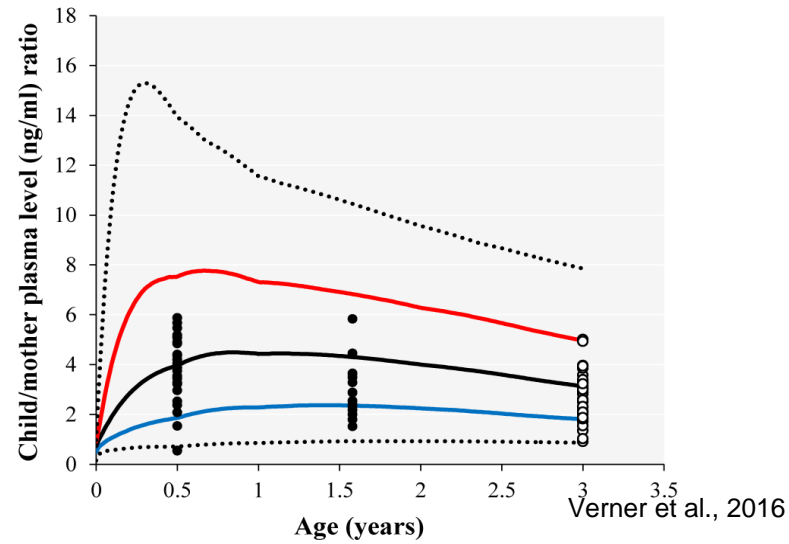
Steenland et al., 2009

Other associations at low serum levels include ↑ cholesterol, ↑ liver enzymes, ↓ vaccine response, and ↓ birth weight in general population.

Developmental Exposures (Prenatal & Early Life)

- Of concern because **early life effects are sensitive endpoints** for PFOA toxicity.
- Found in human amniotic fluid, umbilical cord blood, and breast milk.
- Serum levels in infants
 - At birth, similar to maternal serum levels.
 - **Increase several fold during first few months of life.**
- **Exposures in infants are much higher than in older individuals.**
 - From breast milk or formula prepared with contaminated water.
 - Breast milk concentrations similar or higher than in maternal drinking water.
 - Consume more fluid per body weight.

Increases in Infant PFOA Serum Levels after Birth



Human Studies

- 54 human epidemiology studies reviewed in detail. Endpoints selected for in depth review include:
 - Serum cholesterol/lipids
 - Liver enzymes/bilirubin and liver disease
 - Uric acid
 - Thyroid function and thyroid disease
 - Antibody concentrations following vaccination
- Reviews of other endpoints by authoritative groups were also evaluated:
 - Fetal growth (e.g. birth weight)
 - Cancer
- Many studies have been published on numerous other endpoints that were not evaluated by Health Effects Subcommittee.

Designs and Populations in Studies Reviewed in Detail

- Study Populations
 - *General population* (29 studies) - lowest exposures.
 - *Communities with contaminated drinking water* (15 studies) - higher exposures.
 - Most (14) from C8 Health Study population in Ohio and WV.
 - *Occupationally exposed workers* (14 studies) – highest exposures.
 - From U.S., Canada, Europe, and Asia.
 - Differ as to age group, pregnancy status, basis for enrollment, and PFOA exposure range.
- Study designs
 - *Cross-sectional* (42 studies)
 - Exposure and outcome evaluated at same point in time, limiting interpretation of temporality.
 - *Case-control* (2 studies)
 - *Cohort/longitudinal* (7 studies)
 - *Prospective (birth) cohort* (8 studies)

Associations for Endpoints Reviewed in Detail

- *Strongest evidence*
 - ↑ serum cholesterol
 - ↑ ALT (liver enzyme)
 - ↑ uric acid
- *Limited/Minimal evidence*
 - ↓ antibody response following vaccination.
 - Association consistently observed.
 - However, specificity difficult to evaluate because each vaccine type assessed in only one or a few studies.
 - LDL
 - GGT & AST (liver enzymes), bilirubin, liver disease
 - Thyroid disease
- *No evidence*
 - HDL
 - TSH and thyroid hormones
 - ALP (liver enzyme)

Endpoints Evaluated by Other Authoritative Groups

Birth Weight

- Systematic review using Navigation Guide methodology.
- Most studies are from general population (low exposure).
- **“Sufficient” human evidence for reduced fetal growth from prenatal exposure.**

Cancer

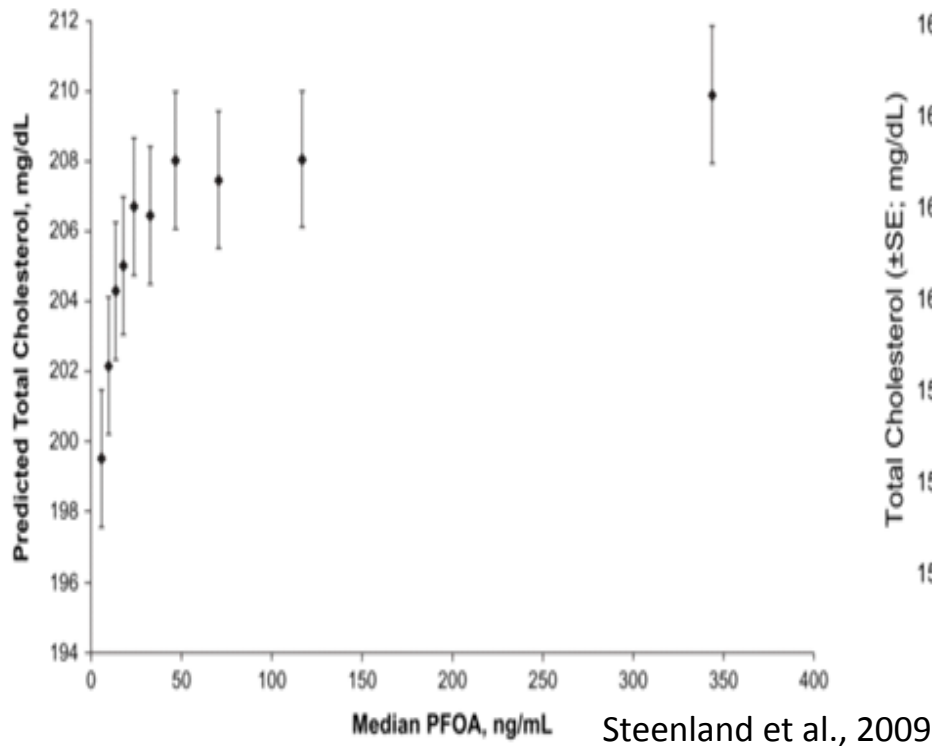
- USEPA SAB (2006) - **“likely carcinogen”**.
- IARC (2015) - **“possibly carcinogenic”**.
- USEPA Office of Water (2016) - **“suggestive carcinogen”**.
- Associations with **kidney and testicular cancer** in communities with drinking water exposure are noted.

Immunotoxicity

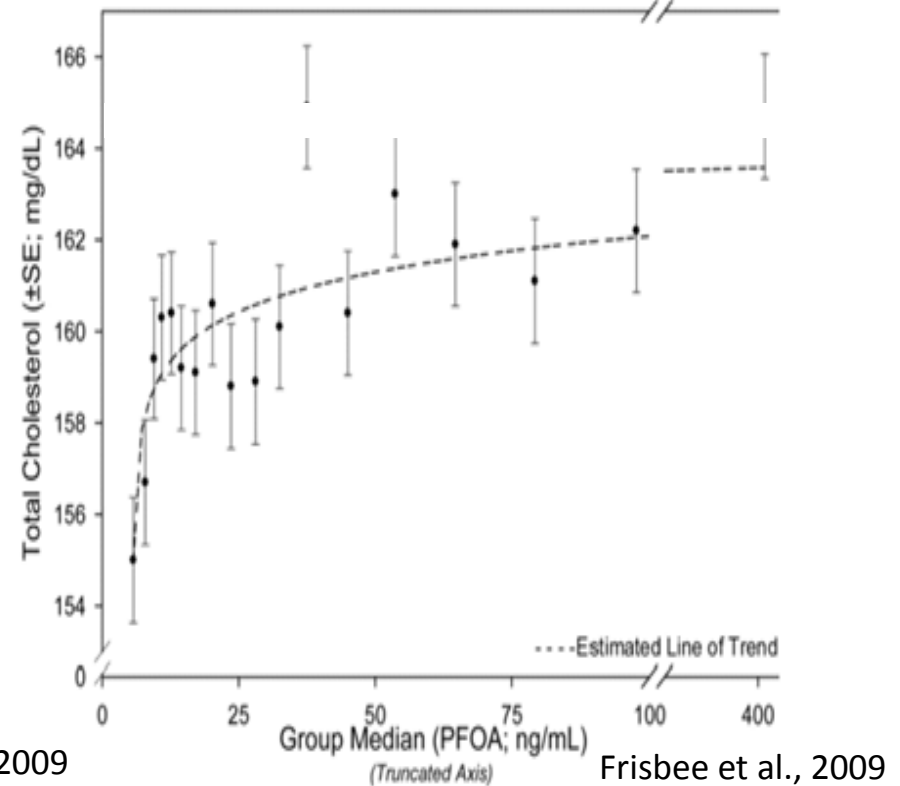
- Systematic review by National Toxicology Program.
- Most studies are from general population (low exposure).
- “Moderate” level of human evidence and “high” level of animal evidence for suppression of antibody response.
- **Overall conclusion: “presumed immune hazard to humans”**.

Steep Dose-Response for Some Health Effects at Low PFOA Serum Levels - Example: ↑ Cholesterol in Communities with Contaminated Drinking Water

Adults



Adolescents



Other associations at low serum levels include ↑ cholesterol, ↑ liver enzymes, ↓ vaccine response, and ↓ birth weight in general population.

Conclusions: Human Epidemiology Data

- PFOA is **associated with carcinogenic and non-carcinogenic effects** in humans.
 - Much more data than for most other contaminants evaluated by DWQI.
- Notable features of human data:
 - **Consistency** of results in different populations.
 - **Concordance** with effects in animal toxicology studies.
 - Use of serum concentrations as measure of **internal exposure**.
 - Associations within **exposure range of the general population**.
- Although magnitude of change is small for some endpoints:
 - Can have a meaningful impact on population health.
 - May be an indicator of other effects that were not evaluated.
- Although limitations preclude use of human data as quantitative basis for Health-based MCL...
 - **Human data provide strong support for public health protective approach based on animal toxicology data.**
 - **Justify concern about substantial increase in blood levels from drinking water.**

Toxicological Studies

- Key endpoints selected for detailed review:
 - Hepatic (liver) toxicity
 - Developmental effects
 - Immune system toxicity
 - Carcinogenicity
- Criteria for choice of endpoints for detailed review:
 - Well established
 - Sensitive
 - Provide data needed for quantitative risk assessment
- Other toxicological effects that are also reviewed include:
 - Persistent neurobehavioral effects from developmental exposure
 - Male reproductive toxicity
- Non-human primate (i.e. monkey) studies also reviewed in detail.

Hepatic Toxicity

- Toxicological findings and mode of action reviewed in detail.
- ***Increased liver weight:***
 - **Sensitive endpoint** – occurs at same or lower doses as immune effects and most developmental effects.
 - Observed in many studies of non-human primates and rodents.
 - **Can co-occur with or progress to more severe hepatic effects.**
- ***Histopathological damage and increased serum liver enzymes:***
 - Not evaluated in many of the studies that evaluated liver weight.
 - **Occur at doses similar to those that increase liver weight.**
 - Developmental exposure to low doses in mice caused adverse cellular changes that persisted until adulthood.
 - Much lower doses than those that caused increased liver weight in other studies.

Reproductive and Developmental Toxicity

- Not studied in non-human primates.
- In rodents, **mouse is more appropriate model** because of very rapid excretion in female rat.
- Effects occur from **prenatal or neonatal (breast milk) exposure**.
- Effects in rodents (mice and/or rats):
 - Full litter resorption.
 - ↓ postnatal survival and growth.
 - Delayed development.
 - Accelerated sexual maturation (males).
 - Limb, tail, and heart defects.
 - Male reproductive toxicity.
 - ↑ liver weight.
 - **Persistent liver toxicity***
 - **Delayed mammary gland development***

**Occurs at lower doses than increased liver weight.*

Delayed Mammary Gland Development

- Occurs at **much lower doses** than most other developmental effects.
 - Most sensitive endpoint with data for dose-response modeling.
- Conclusions of detailed evaluation: **adverse** and **relevant to humans**.
- Reported in **nine separate studies** from perinatal (fetal or neonatal) exposure to mice.
 - Reported in dams and female offspring, in two strains of mice, and from gestational and/or lactational exposure.
 - Not found in one study with problematic issues.
 - **Structural changes that persist until adulthood.**
- Effects differ with lifestage (perinatal v. peripubertal exposure).
- Insufficient toxicology data to make conclusions about effects on lactational function.
 - Possibly relevant – several humans studies associated PFOA with decreased duration of breastfeeding.

Immune System Suppression

- *Rhesus monkeys*
 - ↓ bone marrow cellularity
 - Lymphoid atrophy
- *Mice*
 - ↓ spleen and thymus weight
 - ↓ thymocyte and splenocyte count
 - ↓ immunoglobulin response
 - Changes in total numbers and/or specific populations of lymphocytes.
- *Rats*
 - No immune effects at doses causing effects in mice.
- Immune effects not used as basis for quantitative risk assessment because:
 - Increased liver weight occurs at same or lower doses than immune system effects.

Conclusions: Non-Carcinogenic Toxicological Effects

- PFOA causes **multiple toxicological effects** in non-human primates and rodents.
- Toxicological endpoints are **generally consistent with human data**.
- *Increased liver weight and delayed mammary gland development* selected for Reference Dose development:
 - Well-established.
 - Considered adverse and relevant to humans.
 - Most sensitive endpoints with data needed for dose-response modeling.

Carcinogenicity in Toxicological Studies

- *Rats* – Chronic carcinogenicity studies:
 - *Males* - Hepatic, pancreatic, and/or testicular tumors.
 - *Females* - Tumor incidence not increased.
- *Mice* – No chronic carcinogenicity studies:
 - Preferable species for evaluation of females due to rapid excretion in female rats.
 - Preliminary evidence suggests liver tumors from developmental exposures; no firm conclusions to date.

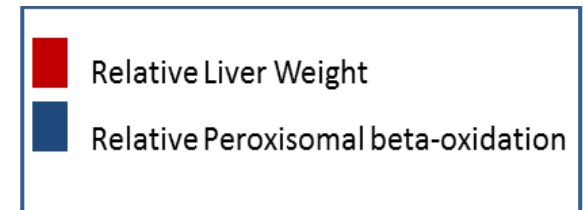
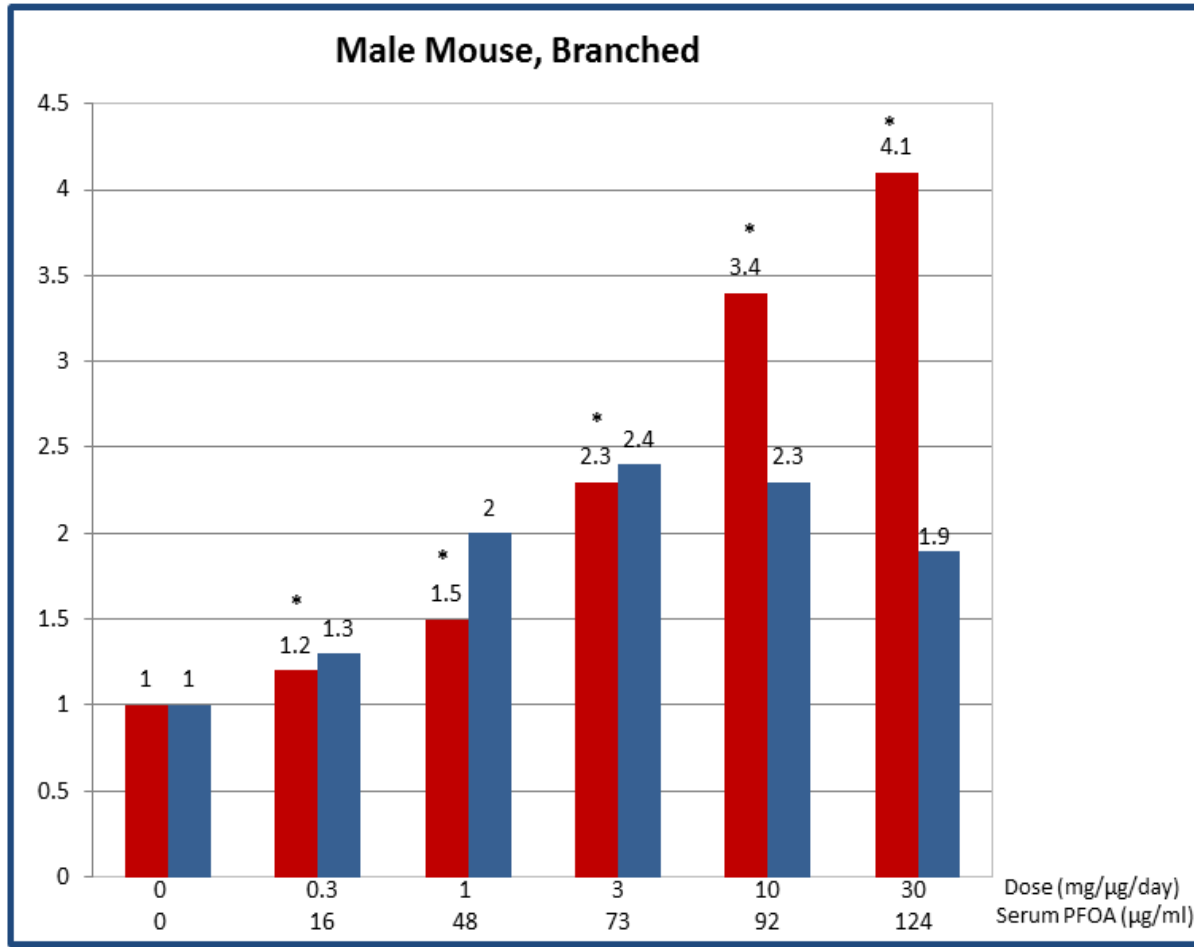
Modes of Action (MOA)

- Health Effects Subcommittee conducted a **thorough and original evaluation of MOA data.**
- PFOA interacts with multiple receptors that regulate expression of genes which control many biological pathways.
- Major focus on peroxisome proliferator activated receptor-alpha (PPAR-alpha) in the PFOA toxicology and risk assessment literature.
 - Role of PPAR-alpha in PFOA toxicity.
 - Human relevance of effects of PFOA mediated by PPAR-alpha.
- Several other potential modes of action.
- Not genotoxic.
- Modes of action are not fully characterized.

Mode of Action: Non-carcinogenic Effects

- Evaluated hepatic toxicity, developmental toxicity (including delayed mammary gland development), and immunotoxicity.
- Extensive review of data from:
 - Non-human primates (monkeys),
 - Standard strains of rodents.
 - PPAR-alpha null (“knockout”) mice.
 - Mice with humanized PPAR-alpha.
 - Human tissues.
 - *In vitro* studies.
- Overall conclusion: **These toxicological effects of PFOA are relevant to humans for the purposes of risk assessment.**

Example of Approach Used in MOA Evaluation of Hepatic Effects



Mode of Action: Carcinogenic Effects

Hepatic tumors

- When rodent liver tumors are mediated by PPAR-alpha, human relevance is uncertain due to lower levels and/or activity in humans.
- ***USEPA Science Advisory Board (2006): Liver tumors from PFOA in rats are potentially relevant to humans.***
 - Similar hepatic effects in non-human primates and rodents.
 - Limited data showing hepatic effects in PPAR-alpha null mice.
- ***More recent data support SAB (2006) conclusion:***
 - Additional data showing hepatic effects in PPAR-alpha null mice.
 - PFOA promotion of liver tumors in rainbow trout.
 - Lack PPAR-alpha; model species for human liver cancer.

Testicular and pancreatic tumors:

- Mode of action has not been established
- ***USEPA risk assessment guidance: Tumors are considered relevant to humans when mode of action is not known.***

Development of Health-Based MCL

- Non-carcinogenic and carcinogenic effects were evaluated.
- Considered higher internal dose in humans compared to animals from same dose, due to longer human half-life.
 - *Non-cancer effects*: Dose-response modeling based on serum PFOA data from end of dosing period.
 - *Cancer effects*: Serum PFOA data not available, so animal-to-human internal dose comparison is based on half-life differences.

Reference Dose for Delayed Mammary Gland Development

- Most sensitive effect with data needed for dose-response modeling.
- Based on effects of gestational exposure in female mouse offspring (Macon et al., 2011).
 - Effects at age 3 weeks, based on serum PFOA levels at age 1 day (end of dosing period).
- Benchmark Dose (BMD) modeling for 10% change (Post et al., 2012).
 - ↓ mammary gland developmental score - 24.9 ng/ml.
 - ↓ number of terminal end buds - 22.9 ng/ml.
- Uncertainty Factor (UF) = 30
 - 10 - Intra-human variability.
 - 3 - Animal-to-human toxicodynamic differences.
- **Target Human Serum Level = 0.8 ng/ml.**
 - Equivalent to Reference Dose, on a serum level basis.
 - **Below median serum level in general population (2.1 ng/ml).**

Reference Dose for Delayed Mammary Gland Development (cont.)

- Clearance factor (relates serum level to external dose) applied to Target Human Serum Level:

$$800 \text{ ng/L} \times 1.4 \times 10^{-4} \text{ L/kg/day} = 0.11 \text{ ng/kg/day}$$

Where: 800 ng/L = Target Human Serum Level

1.4 x 10⁻⁴ L/kg/day = Clearance

0.11 ng/kg/day = Reference Dose (RfD)

- **Health-based MCL based on this RfD is not recommended:**
 - Health Effects Subcommittee concluded that this effect is **well-established, adverse, and relevant to humans**.
 - Health-based MCL supported by RfD of 0.11 ng/kg/day is **0.77 ng/L** (using default exposure assumptions).
 - However, **no precedent** for use of this effect as primary basis for risk assessment.
 - Concluded that **uncertainty factor to protect for this and other more sensitive effects** should be included in RfD based on ↑ liver weight.

Reference Dose for Increased Relative Liver Weight

- Male mice exposed to branched/linear PFOA for 14 days (Loveless et al., 2006)
 - Data appropriate for Benchmark Dose modeling.
 - Study is of sufficient duration - Liver weight does not continue to ↑ with longer exposure, but can progress to more severe liver toxicity over time.
- BMD modeling of serum PFOA data.
 - BMDL for 10% ↑ in relative liver weight - 4350 ng/mL.
- **Uncertainty Factor (UF) = 300.**
 - 10 - intra-human variability.
 - 3 - animal-to-human toxicodynamic differences.
 - 10 - more sensitive effects.
 - No UF for less-than-chronic duration because effect does not increase with longer exposure.
- **Target Human Serum Level = 14.5 ng/ml**

RfD for Increased Relative Liver Weight (cont.)

- Clearance factor (relates serum level to external dose) applied to Target Human Serum Level:

$$**14,500 ng/L x 1.4 x 10^{-4} L/kg/day = 2 ng/kg/day**$$

Where:

14,500 ng/L = Target Human Serum Level

1.4 x 10⁻⁴ L/kg/day = Clearance Factor

2 ng/kg/day = Reference Dose

Health-based MCL - Increased Relative Liver Weight

- Default adult drinking water exposure assumptions:
 - 2 L/day water consumption, 70 kg body weight.
- Default Relative Source Contribution factor - 20%:
 - Accounts for non-drinking water exposures.
 - Also implicitly accounts for **much greater exposures in infants** than older individuals at same drinking water concentration.
 - Must be considered because the most sensitive effects are from early life exposures and/or occur in short timeframe relevant to developmental exposures.

$$\frac{2 \text{ ng/kg/day} \times 70 \text{ kg} \times 0.2}{2 \text{ L/day}} = 14 \text{ ng/L (0.014 } \mu\text{g/L)}$$

Where:

2 ng/kg/day = Reference Dose

70 kg = assumed adult body weight

0.2 = Relative Source Contribution from drinking water

2 L/day = assumed adult daily drinking water intake

Health-based MCL = 14 ng/L (0.014 μ g/L)

Health-based MCL - Carcinogenic Effects

- Testicular tumor data from chronic dietary rat study (Butenhoff et al., 2012).
 - Only tumor type with data needed for dose-response modeling.
- **BMDL** for 5% tumor incidence: 2.36 mg/kg/day .
- Corresponding **cancer slope factor** in rats: $0.021 (\text{mg/kg/day})^{-1}$.
- **Dose in rats for one-in-one million (1×10^{-6}) risk:** $4.8 \times 10^{-5} \text{ mg/kg/day}$.
- Ratio of human-to-rat half-lives (used to convert rat administered dose to human administered dose resulting in same internal dose):
 $840 \text{ days}/7 \text{ days} = 120$
- **Human dose at 1×10^{-6} lifetime cancer risk:**
 $(4.8 \times 10^{-5} \text{ mg/kg/day})/120 = 4 \times 10^{-7} \text{ mg/kg/day}$ (0.4 ng/kg/day)
- **Health-based MCL** at 1×10^{-6} lifetime cancer risk, using default drinking water assumptions (2 L/day water consumption; 70 kg body weight):

$$\frac{0.4 \text{ ng/kg/day} \times 70 \text{ kg}}{2 \text{ L}} = \mathbf{14 \text{ ng/L}}$$
 ($0.014 \mu\text{g/L}$)

Summary - Recommended Health-based MCL

- A Health-based MCL based on the RfD for delayed mammary gland development is not recommended.
- The Health-based MCL based on increased relative liver weight is 14 ng/L.
- The Health-based MCL based on a lifetime cancer risk of 1×10^{-6} is also 14 ng/L.
- **Therefore, the recommended Health-based MCL is 14 ng/L (0.014 µg/L).**

Uncertainties

- **Human and animal data suggest that continued exposure to even relatively low concentrations of PFOA in drinking water results in elevated body burdens that increase the risk of health effects. These data indicate a need for caution about exposures from drinking water.**
 - Health effects are associated with general population-level exposures to PFOA, even without additional exposure from drinking water.
 - Continued exposure to 14 ng/L in drinking water is predicted to increase serum levels to approximately twice the general population median of 2.1 ng/L.
- **Serum level increases from PFOA in drinking water are predicted to be greater in infants, a sensitive subpopulation for PFOA's effects.**
 - Subtle effects later in life may result from very low exposures during the developmental period. Further research on this issue is needed.

Uncertainties (cont.)

- Uncertainty about human relevance of effects observed in animals is inherent to all risk assessments based on animal data. Available information indicates that toxicological effects of PFOA are relevant to humans for the purposes of risk assessment.
- The toxicological endpoints that were identified as most sensitive are not used as primary basis for the Health-based MCL.
- Chronic toxicity and carcinogenicity have been studied only in rats. This species is not an ideal model for females due to very rapid excretion in female rats.
- **Potential additive toxicity of PFOA and other PFCs was not considered.**

NJDEP (2007) Health-based Guidance for PFOA in Drinking Water

- Health-based lifetime drinking water guidance of 40 ng/L developed by NJDEP in 2007
- Compared humans to animals based on serum PFOA levels (internal dose).
- Used 100:1 serum:drinking water ratio to develop health-based drinking water concentrations.
- Based on key toxicological studies identified in USEPA (2005) draft PFOA risk assessment
- **Large body of important recent information was not considered, including:**
 - **Mouse developmental effects**
 - **Human epidemiology studies**

USEPA Drinking Water Health Advisory for PFOA - Overview

- At request of NJDEP, Health Effects Subcommittee reviewed USEPA PFOA Health Advisory.
 - Presented in Appendix 2 of Health Effects Subcommittee document.
- Issued May 2016: **70 ng/L for PFOA, or total of PFOA + PFOS.**
- USEPA Office of Water Health Advisories are **technical guidance, not regulation.** States may develop more stringent guidance or standards than USEPA.
- Intended to protect for **lifetime exposure.**
- PFOA advisory based on **developmental endpoints** from animal studies
- Sensitive subpopulations – pregnant and lactating women; breastfed and bottle-fed infants.
 - Assume **90th percentile drinking water consumption for lactating woman** (higher rate than in other adults)
- “Alternative” Health Advisories for other adults – 100 ng/L
 - Based on standard adult drinking water exposure assumptions

Comparison of USEPA and DWQI - General Statements

- **USEPA:** *“Protects the most sensitive populations, with a margin of protection from lifetime exposure” at Health Advisory of 70 ng/L.*
- **Health Effects Subcommittee:** *“Used a risk assessment approach intended to be protective for chronic (lifetime) exposure” to develop a Health-based MCL of 14 ng/L.*

Comment: Substantial evidence indicates that PFOA may cause human health effects in the general population even without additional exposure from drinking water.

PFOA also causes developmental effects in animal studies at serum levels relevant to human exposures.

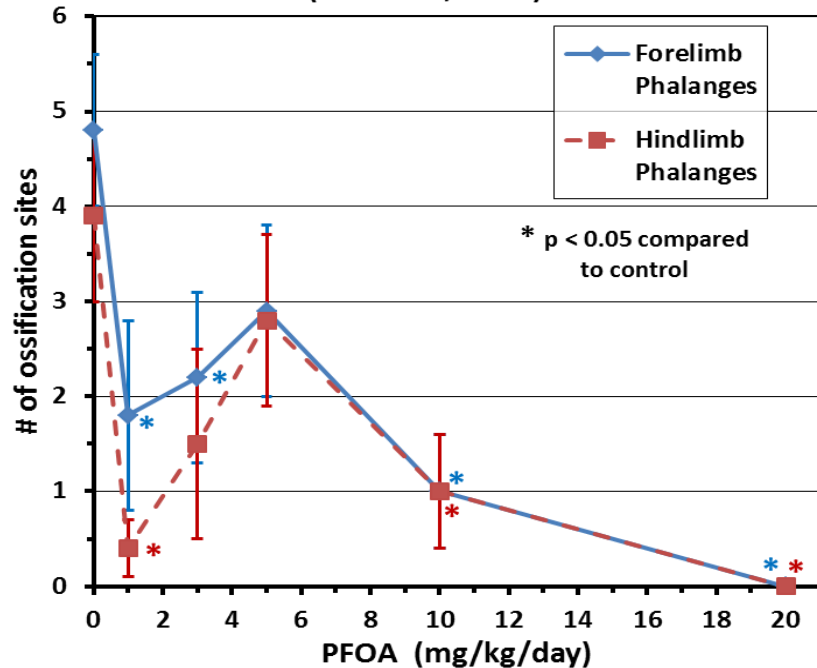
Therefore, it cannot be concluded that exposure to these drinking water concentrations is protective of the most sensitive populations with a margin of exposure.

Comparison of USEPA and DWQI Reference Doses

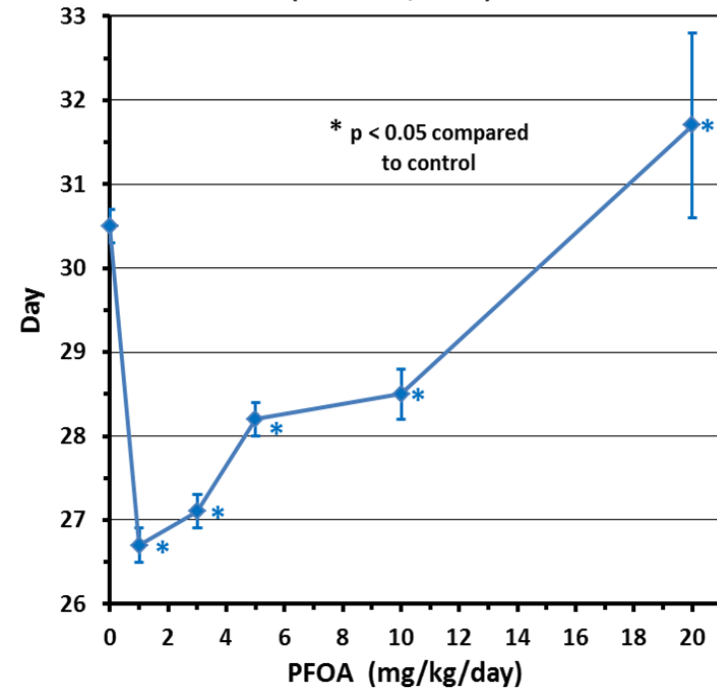
- ***USEPA RfD*** – Based on **delayed ossification** and **accelerated puberty** in males in mouse developmental study (Lau et al., 2006).
 - **Data do not follow typical dose-response curve** (see next slide). This issue is not discussed in the USEPA document.
 - LOAEL-to-NOAEL UF of 10 with such dose-response curves appears to be without precedent and may be subject to debate.
 - **Did not consider more sensitive toxicological effects at doses ~100-fold lower than endpoints used.**
 - Delayed mammary gland development
 - Persistent liver toxicity from developmental exposures
- ***Health Effects Subcommittee RfD*** – Primary basis is **increased liver weight** in male mice.
 - **Typical dose-response curve.** RfD based on Benchmark Dose modeling.
 - **Includes uncertainty factor of 10 for more sensitive developmental endpoints** (delayed mammary gland development, persistent liver toxicity, and others).

Dose-Response for Developmental Endpoints Used as Basis for USEPA PFOA Health Advisory

Ossification of Phalanges in Offspring
(Lau et al., 2006)

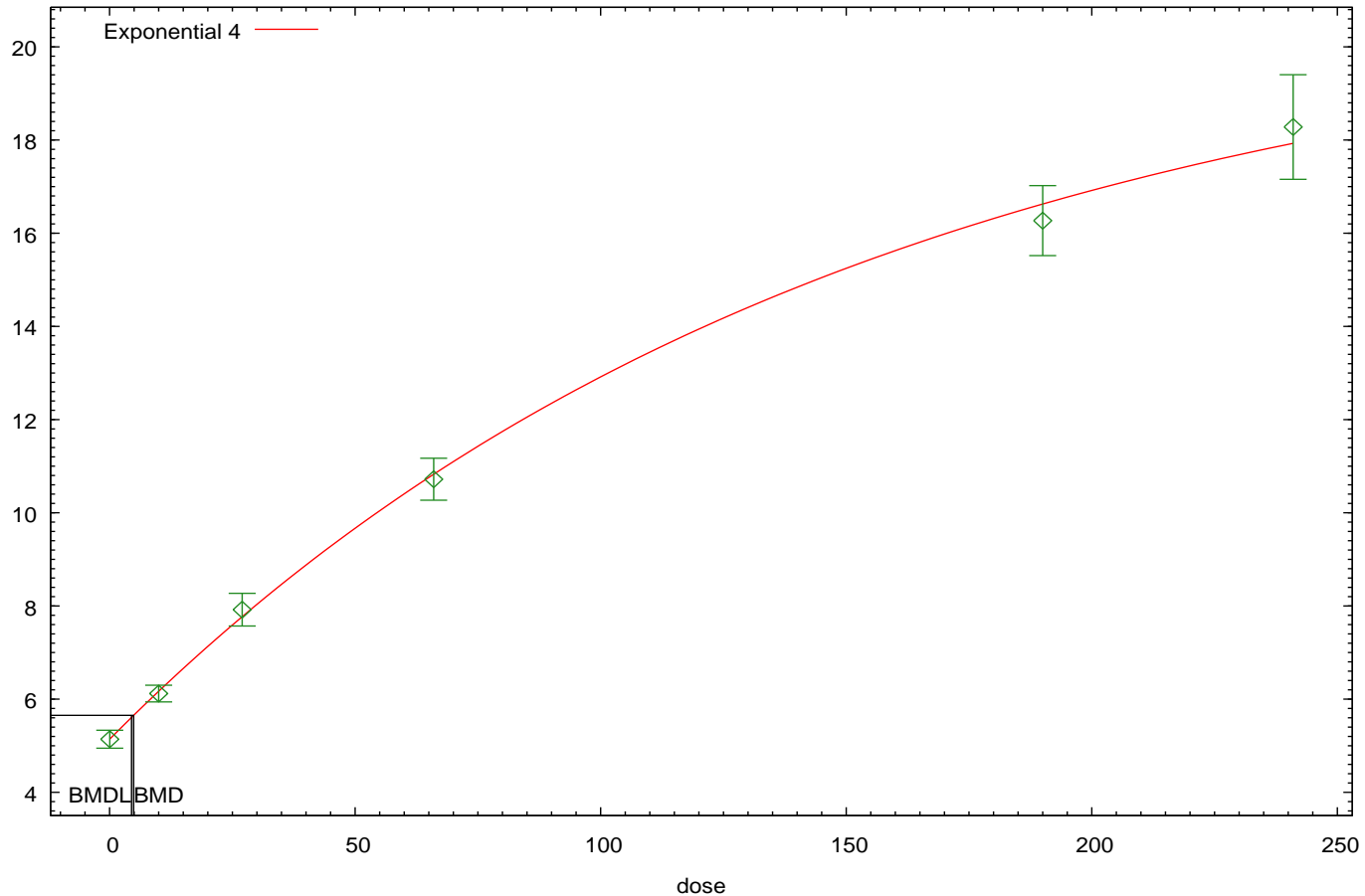


Day of Puberty in Male Offspring
(Lau et al., 2006)



Dose-Response for Increased Relative Liver Weight Used as Basis for Health Effects Subcommittee RfD

Exponential 4 Model, with BMR of 0.1 Rel. Dev. for the BMD and 0.95 Lower Confidence Limit for the BMDL



Comparison of USEPA and DWQI - Reference Dose (cont.)

- **USEPA and DWQI Reference Doses are identical numerically with the exception of additional DWQI uncertainty factor for more sensitive developmental effects.**
- USEPA's reasons for **dismissing mammary gland effects** at low doses of PFOA appear to lack scientific validity and/or apply equally or more so to endpoints used by USEPA. Detailed explanation is provided in Appendix 2.
 - Mode of action not known.
 - Functional significance unclear.
 - Differences in sensitivity in different strains of mice.
- USEPA **did not consider persistent liver toxicity** from developmental exposure to low doses of PFOA.

Comparison of USEPA and DWQI - Cancer Risk Assessment

- **USEPA and Health Effects Subcommittee cancer potency factors from testicular tumor data in chronic rat study are essentially identical.**
- However, USEPA **did not consider longer half-life in humans versus rats** in cancer risk assessment, although it was considered in non-cancer assessment.
 - USEPA states that drinking water concentration at one in one million (10^{-6}) risk level is **500 ng/L**.
- If longer half-life in humans versus rats is considered:
 - Drinking water concentration at one in one million (10^{-6}) risk level is **14 ng/L**.

Comment: It is generally accepted that PFOA risk assessment must consider interspecies half-life differences. Health Effects Subcommittee concludes that USEPA approach for cancer evaluation does not appear to be logical or consistent with its non-cancer evaluation.

Consideration of Human Data by USEPA

- USEPA acknowledges associations of PFOA with health effects in general population and in communities exposed through drinking water, with some effects consistently found in multiple studies.
- **However, USEPA does not consider the serum PFOA levels or drinking water concentrations associated with these health effects.** USEPA states that they are unknown or uncertain.
- Reasons provided by USEPA why serum PFOA levels are not considered:
 - May have decreased prior to blood sampling
 - May result from metabolism of precursors to PFOA.
 - Uncertainty due to co-exposure to other PFCs, even when accounted for in the epidemiology analysis.

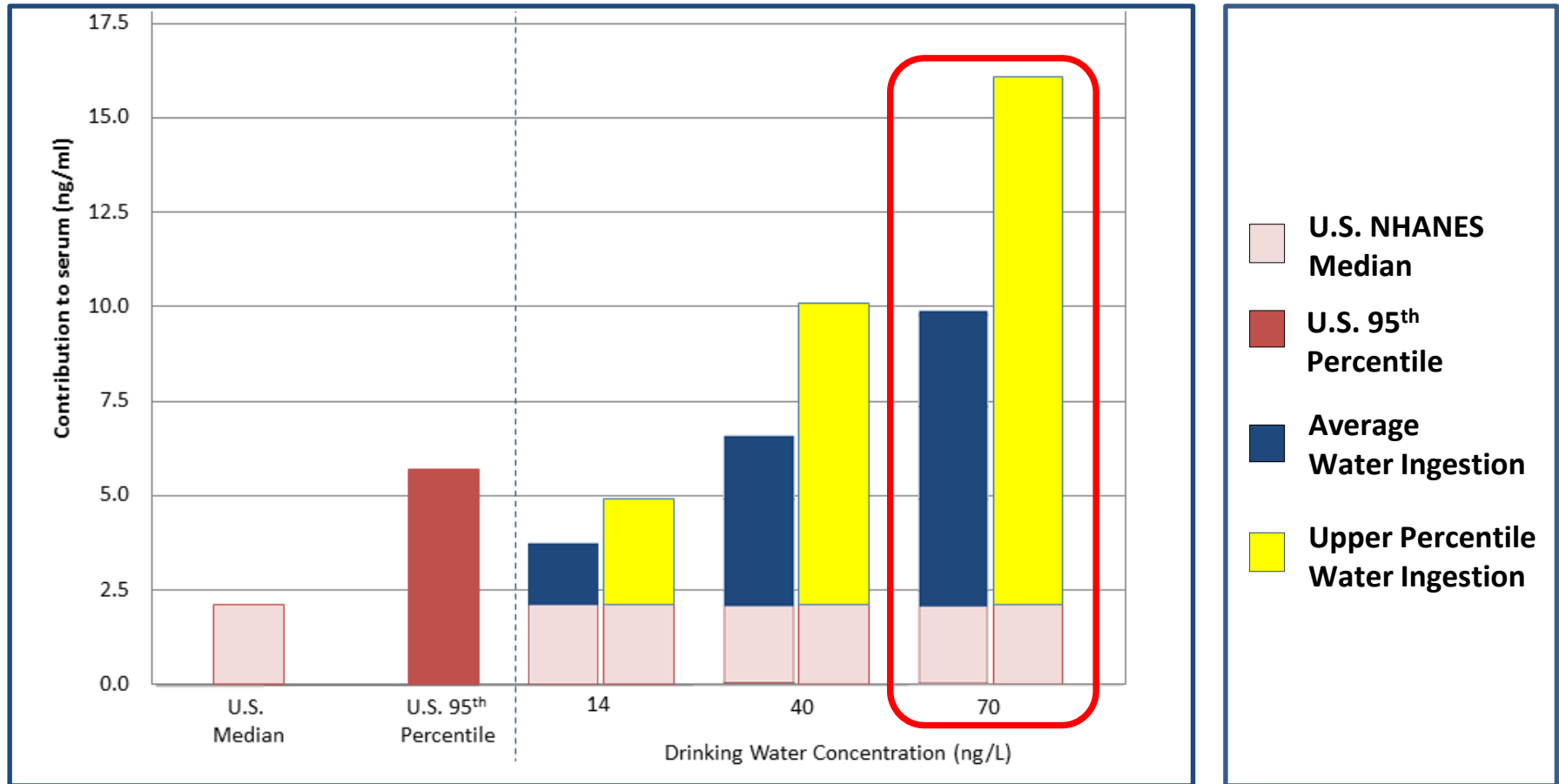
Comment: Health Effects Subcommittee disagrees that these are valid reasons to dismiss consideration of serum PFOA levels from epidemiology studies. Detailed explanation is provided in Appendix 2.

Consideration of Increase in Human Serum PFOA Levels from USEPA Health Advisory (70 ng/L)

- **USEPA does not acknowledge that the increase in serum PFOA levels from ongoing exposure to 70 ng/L can be easily predicted.**
- PFOA clearance factor published by USEPA scientists (Lorber and Egeghy, 2011) relates low-level human exposures to serum levels.
 - Factor is used in USEPA assessment to convert animal serum PFOA levels to human doses.
 - However, USEPA says that it is not possible to easily predict human serum PFOA levels from drinking water exposures.

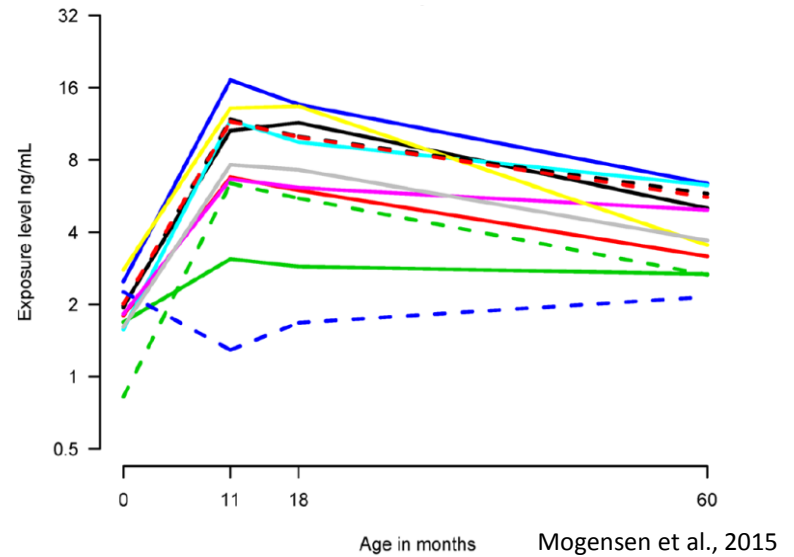
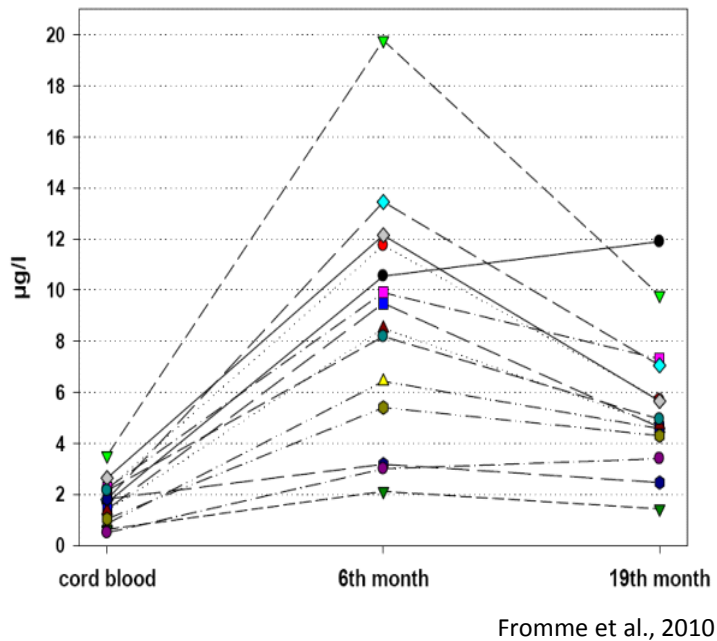
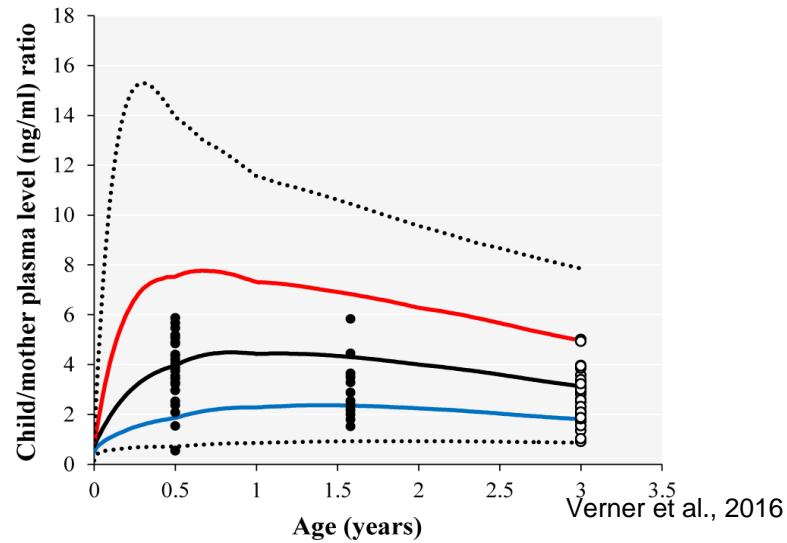
Comment: **Health Effects Subcommittee concludes that use of clearance factor to predict increased human serum PFOA levels from drinking water exposures is technically sound and is not subject to debate.**

Increase in Serum PFOA Predicted from USEPA Health Advisory (70 ng/L)



- Predicted increases of ~5-fold with average ingestion and ~8-fold with upper percentile (2 L/day). Greater increases in infants (next slide).
- Several health effects are associated with serum levels below these.
- **Health Effects Subcommittee concludes that these increases are not desirable and may not be protective of public health.**

Increases in Serum PFOA are Greater in Infants



USEPA Health Advisory - Sensitive Subpopulations

- USEPA states that sensitive subpopulations for developmental effects are pregnant and lactating women, and bottle-fed infants.
- USEPA does not include women who plan to become pregnant in sensitive subpopulations.
- USEPA stated that states or local authorities may choose to expand definition of sensitive subgroups to women of child-bearing age.

Comment: **Health Effects Subcommittee concludes that exclusion of women who plan to become pregnant does not appear to be scientifically supportable.** The body burden of PFOA remains elevated for many years after exposure ends, and developmental effects are sensitive endpoints for PFOA.

Conclusions

- USEPA Health Advisory may not be sufficiently protective of public health because:
 - Sensitive toxicological endpoints that are well established and considered relevant to humans were not considered.
 - Increases in human serum PFOA levels expected from exposure to 70 ng/L, as compared to serum PFOA levels associated with human health effects, were not considered.
- Sensitive subpopulations should include women who plan to become pregnant (or similar language).