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May 10, 2021

Tyler Saechao
Office of Environmental Health Hazard Assessment
1001 I Street
P.O. Box 4010, MS-12B
Sacramento, California 95812-4010

Submitted electronically via https://oehha.ca.gov/comments

Re: Response to Request for Relevant Information on the Reproductive Toxicity Hazard of Perfluorohexanesulfonic Acid and Its Salts (PFHxS)

Dear Mr. Saechao:

The 3M Company ("3M") appreciates the opportunity to respond to the California Environmental Protection Agency's Office of Environmental Health Hazard Assessment's ("OEHHA") March 26, 2021 information request, "Chemical Selected for Consideration for Listing by the Developmental and Reproductive Toxicant Identification Committee and Request for Relevant Information on the Reproductive Toxicity Hazard of: . . . Perfluorohexanesulfonic Acid and its Salts [collectively, "PFHxS"], . . ." (the "Information Request").

In response, 3M first reiterates and highlights the scientific data cited and discussed in its November 16, 2020 submission to the Developmental and Reproductive Toxicant Identification Committee ("DARTIC") for its December 10, 2020 Prioritization Meeting. Though that meeting related to various chemicals, 3M submitted comments related only to PFHxS. 3M specifically incorporates by reference the data and discussion at pages 5-13 of its November 16, 2020 submission, attached hereto as Exhibit A.

Through this response, 3M also highlights the recent 2021 Andersen et al. review article titled "Using Quantitative Modeling Tools to Assess Pharmacokinetic Bias in Epidemiological Studies Showing Associations Between Biomarkers and Health Outcomes at Low Exposures."[1] In doing so, 3M emphasizes as it did in its November 16, 2020 comments that it is conceivable that some of the epidemiologic associations that have been identified as statistically significant findings in the OEHHA epidemiologic screen process may be confounded by the underlying pharmacokinetics of PFHxS as related to the pathophysiology of these outcomes.

It is imperative that OEHHA recognize that pharmacokinetic bias is indeed a viable explanation for some of the 24 epidemiologic studies related to PFHxS given the low exposures measured for PFHxS. It behooves epidemiologists to examine for such potential pharmacokinetic bias when reporting associations of health outcomes and biomarkers when measured at low

[1] Melvin Andersen et al., 197 *Env't Rsch.* 111183 (2021), https://pubmed.ncbi.nlm.nih.gov/33887277/. The full article is publicly available at https://www.sciencedirect.com/science/article/pii/S0013935121004771?via%3Dihub (last visited May 10, 2021).

exposures as was done for *all* 24 studies shown in Table 3 of 3M's November 16, 2020 submission. Such associations have been reported for the longer chain perfluoroalkyls, perfluorooctanoic acid (PFOA) or perfluorooctane sulfonate (PFOS) but were likely a result of confounding or toxicokinetic bias (i.e., reverse causation) when related to time to pregnancy (subfecundity) (Bach et al. 2018;[2] Bach et al. 2015;[3] Fei et al. 2009;[4] Fei et al. 2012;[5] Olsen et al. 2009;[6] Velez et al. 2015;[7] Whitworth et al. 2012[8]), birth weight (Dzierlenga et al. 2020;[9] Steenland et al. 2018;[10] Verner et al. 2015;[11] Vesterinen et al. 2015[12]), delayed menarche (Lopez-Espinosa et al. 2011;[13] Wu et al. 2015[14]), and early onset menopause (Knox et al. 2011;[15] Ruark et al. 2017;[16] Taylor et al. 2014[17]).

3M looks forward to this information and analysis being fully considered and given the proper weight in evaluating whether to list PFHxS as a reproductive toxicant under Proposition 65. If fully considered and given the proper weight, the only scientifically supported conclusion is that PFHxS should not be so listed. Thank you for providing 3M with this opportunity to respond to the Information Request.

Regards,

Oyebode A. Taiwo, MD, MPH

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[2] C. Bach et al., *Conditioning on Parity in Studies of Perfluoroalkyl Acids and Time to Pregnancy: An Example from the Danish National Birth Cohort*, 126 *Env't Health Perspectives* 117003 (2018).
[3] C. Bach et al., *Perfluoroalkyl and Polyfluoroalkyl Substances and Human Fetal Growth: A Systematic Review*, 45 *Critical Rev. of Toxicology* 53 (2015).
[4] C Fei et al., *Maternal Levels of Perfluorinated Chemicals and Subfecundity*, 24 *Human Reproduction* 1200 (2009).
[5] C. Fei et al.. *Commentary: Perfluorinated Chemicals and Time to Pregnancy: A Link Based on Reverse Causation?*23 *Epidemiology* 264 (2012).
[6] G.W. Olsen, *Perfluoroalkyl Chemicals and Human Fetal Development: An Epidemiologic Review with Clinical and Toxicological Perspectives*, 27 *Reproductive Toxicology* 212 (2009).
[7] M.P. Velez et al., *Maternal Exposure to Perfluorinated Chemicals and Reduced Fecundity: The MIREC study*, 30 *Human Reproductivity* 701 (2015).
[8] K.W. Whitworth et al., *Perfluorinated Compounds and Subfecundity in Pregnant Women*, 23 *Epidemiology* 257 (2012).
[9] M. W. Dzierlenga et al., *Birth Weight and Perfluorooctane Sulfonic Acid: A Random-Effects Meta-Regression Analysis*, 4 *Env't Epidemiology* e095 (2020).
[10] Kyle Steenland et al., *Serum Perfluorooctanoic Acid and Birthweight: An Updated Meta-analysis With Bias Analysis*, 29 *Epidemiology* 765 (2018).
[11] M.A. Verner et al., *Associations of Perfluoroalkyl Substances (PFAS) with Lower Birth Weight: An Evaluation of Potential Confounding by Glomerular Filtration Rate Using a Physiologically Based Pharmacokinetic Model (PBPK)*, 123 *Env't Health Perspectives* 1317 (2015).
[12] H. M. Vesterinen et al., *Fetal Growth and Maternal Glomerular Filtration Rate: A Systematic Review*, 28 *J. of Maternal Fetal Neonatal Med.* 2176 (2015).
[13] M. J. Lopez-Espinosa et al., *Association of Perfluorooctanoic Acid (PFOA) and Perfluorooctane Sulfonate (PFOS) with Age of Puberty Among Children Living Near a Chemical Plant*, 45 *Env't Sci. Tech.* 8160 (2011).
[14] H. Wu et al., *Can the Observed Association Between Serum Perfluoroalkyl Substances and Delayed Menarche Be Explained on the Basis of Puberty-Related Changes in Physiology and Pharmacokinetics?* 82 *Env't Int'l* 61 (2015).
[15] S. Knox et al., *Implications of Early Menopause in Women Exposed to Perfluorocarbons*, 96 *J. of Clinical Endocrinology & Metabolism* 1747 (2011).
[16] C. Ruark et al., *Quantitative Bias Analysis for Epidemiological Associations of Perfluoroalkyl Substance Serum Concentrations and Early Onset of Menopause*, 99 *Env't Int'l* 245 (2017).
[17] K. Taylor et al., *Polyfluoroalkyl Chemicals and Menopause among Women 20-65 Years of Age (NHANES)*, 122 *Env't Health Perspectives* 145 (2014).

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EXHIBIT A

Oyebode A. Taiwo
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November 16, 2020

VIA ELECTRONIC SUBMISSION

Dr. Ulrike Luderer, Chair
Developmental and Reproductive Toxicant Identification Committee Members
California Environmental Protection Agency
Office of Environmental Health Hazard Assessment
Developmental and Reproductive Toxicant Identification Committee

Dr. Martha Sandy, Branch Chief
Reproductive and Cancer Hazard Assessment Branch
California Environmental Protection Agency
Office of Environmental Health Hazard Assessment

3M Comments on Prioritization of Perfluorohexanesulfonic Acid (PFHxS)

Dear Dr. Luderer, DARTIC Members, and Dr. Sandy:

The 3M Company (3M) is pleased to submit the attached comments on the proposed prioritization of perfluorohexanesulfonic acid (PFHxS) for potential listing under Proposition 65 as a reproductive toxicant. As a science-based company with substantial experience, expertise and product stewardship of these chemicals, 3M is well-positioned to support the efforts of the Developmental and Reproductive Toxicant Identification Committee (DARTIC) and the Office of Environmental Health Hazard Assessment (OEHHA) in this proceeding.

As a preliminary matter, 3M wishes to emphasize that the body of scientific evidence amassed to date has failed to show that PFHxS causes adverse health effects in humans at the currently low and declining exposure levels found in the blood. This has been recently acknowledged in a study of perfluoroalkyl substances including PFHxS by the U.S. federal Agency for Toxic Substances and Disease Registry (ATSDR) and by the Expert Health Panel assembled to advise the Australian federal government (discussed in further detail in the comments attached).

Up until 3M began its voluntary phase-out of PFHxS and related chemistries over 20 years ago, 3M was one of the main manufacturers of PFHxS in the United States. 3M has worked closely with the United States Environmental Protection Agency (US EPA) on regulatory measures restricting these chemicals' manufacture, import and use. Over the years, the company has also invested substantial resources to understand the effects of these chemistries on human health. The attached comments reflect the in-depth analysis of these chemicals by the company's experts.

Pursuant to Proposition 65's "State's Qualified Experts" listing mechanism, a chemical is known to the state to cause reproductive toxicity if in the opinion of the DARTIC it has been "clearly shown through scientifically valid testing according to generally accepted principles" to cause reproductive toxicity.[1] We understand the prioritization process for this listing mechanism to embody a qualitative approach to ascertaining whether a particular chemical should undergo the next regulatory step, OEHHA's resource-intensive process of developing hazard identification materials. The goal of the prioritization process is to focus the DARTIC's efforts on "chemicals that may pose *significant hazards* to Californians."[2]

As discussed in more detail in the attached comments, PFHxS should not be designated as a high priority for further evaluation under Proposition 65 because:

- 3M was one of the main manufacturers of PFHxS and PFHxS-precursor products in the United States. In 2000, 3M announced the phase out of those chemicals. Shortly thereafter, US EPA promulgated regulations that effectively prohibit the manufacture, importation, or use of PFHxS for all but three highly-specialized uses that California consumers do not come into contact with. Accordingly, serum concentrations of PFHxS in the U.S. general population have been declining in the last decade, further evidencing the lack of consumer exposure to PFHxS from the environment and goods.
- The overall weight of the evidence with respect to PFHxS fails to clearly show that this chemical causes reproductive toxicity in humans or animals. More specifically, the reported epidemiological associations between PFHxS and reproductive toxicity in humans is based on measuring PFHxS in studies of the general population which had, for the most part, very low exposure contrasts. Some of the study outcomes may have been confounded by the underlying pharmacokinetics of PFHxS (as has been reported for PFOA and PFOS). In addition, there is no compelling animal data to suggest that PFHxS affects the functional aspects of reproduction or development in laboratory rodents.
- Even if PFHxS was a strong candidate for listing (which is not supported by the data), the levels of PFHxS reached in the laboratory animals that showed no reproductive or developmental effect in rodents were at least *3 to 4 orders of magnitude* higher than the levels reported at the 95th percentile of PFHxS measured in the general population. This demonstrates an ample margin of safety.

The well-documented diminishing exposure to this chemical, alone, is sufficient to find against designation as high priority. For this and further reasons detailed in the attached comments, we respectfully submit that prioritizing PFHxS will not achieve the process' goal of focusing the DARTIC's efforts on chemicals that may pose *significant* hazards to Californians.

[1] Cal. Health & Safety Code § 25249.8(b).
[2] Process for Prioritizing Chemicals for Consideration under Proposition 65 By The "State's Qualified Experts" https://oehha.ca.gov/media/downloads/proposition-65/document/finalpriordoc.pdf, (December 2004) (emphasis added).

3M appreciates the opportunity to provide these comments. Thank you for your consideration.

Regards,

Oyebode A. Taiwo, MD, MPH

I. The Relevant Toxicity Data and Potential for Exposure Do Not Support DARTIC Prioritization of PFHxS.

The Office of Environmental Health Hazard Assessment (OEHHA) of the California Environmental Protection Agency is soliciting public comments relating to the potential designation of twenty-two chemicals as reproductive toxicants pursuant to Proposition 65. Perfluorohexanesulfonic acid (PFHxS) is included among the twenty-two chemicals proposed for further consideration by the Developmental and Reproductive Toxicant Identification Committee (DARTIC) in OEHHA's Prioritization Notice and Prioritization Document.[3]

In evaluating potential recommendations to OEHHA, the DARTIC relies on the "prioritization process endorsed by the DARTIC and adopted by OEHHA in 2004."[4] That process, the "Process for Prioritizing Chemicals for Consideration Under Proposition 65 by the 'State Qualified Experts'" ("Process"), "is designed to ensure that the efforts of these committees are focused on chemicals that may pose significant hazards to Californians."[5] The Process was requested by the DARTIC (along with the state's Carcinogen Identification Committee or CIC) "as an alternative to the random prioritization process that had been in use since 1997."[6] The DARTIC and CIC "specifically asked for an alternative process that could *better take into account the level of exposure in California*, the population affected by various chemicals being reviewed by OEHHA, as well as the *degree and extent of potential harm* posed by the Chemical."[7]

The Process that the DARTIC endorsed is consistent with the goal of focusing OEHHA's, the DARTIC's, and stakeholders' resources on chemicals that a meaningful number of consumers in California actually encounter for which they should receive a warning under Proposition 65. Staying focused on this goal is critical to preserving the integrity of Proposition 65. And, more so today than ever, protecting the integrity of Proposition 65 is crucial; over-warning is prevalent and the news media's coverage of Proposition 65 abuse by plaintiff's lawyers (so-called "bounty hunters") grows.[8]

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[3] OEHHA Prioritization: Chemicals Identified for Consultation with the Developmental and Reproductive Toxicant Identification Committee (October 2020) (hereinafter "Prioritization Document"), *available at* https://oehha.ca.gov/media/downloads/crnr/dartprioritization100120.pdf.

[4] *Id.* at 1.

[5] California Environmental Protection Agency, Office of Environmental Health Hazard Assessment, Process For Prioritizing Chemicals For Consideration Under Proposition 65 by the "State's Qualified Experts," https://oehha.ca.gov/media/downloads/proposition-65/document/finalpriordoc.pdf (December 2004) (hereinafter "Process").

[6] *Id.*

[7] *Id.* (emphasis added).

[8] *E.g.*, Jim Conran, For Proposition 65 bounty hunters, time to tame them, North Bay Business Journal (2011), https://www.northbaybusinessjournal.com/article/industry-news/for-proposition-65-bounty-hunters-time-to-tame-them/ (Aug. 8, 2011) ("Unless it is reformed, Proposition 65's enforcement mechanism will continue to shortchange the state while creating grotesque profits for a handful of trial lawyers at the expense of our small businesses."); Geoffrey Mohan, You see the warnings everywhere. But does Prop. 65 really protect you? (2020), https://www.latimes.com/business/story/2020-07-23/prop-65-product-warnings (July 23, 2020) ("That profusion of warnings has subverted Proposition 65 and left Californians, and increasingly anyone who shops online, overwarned, underinformed and potentially unprotected, a Times investigation has found. And it has funneled hundreds of millions of dollars to a handful of attorneys and their repeat clients.").

Accordingly, OEHHA is obligated under the Process to investigate "the existence of relevant toxicity data *and* the potential for human exposure," *before referral of a chemical to the DARTIC as a candidate for prioritization*.[9] OEHHA should, in turn, only refer a chemical to the DARTIC after OEHHA's actual investigation and conclusion that the data suggests a chemical can "*cause reproductive toxicity… and have exposure potential in California*."[10] OEHHA, like any public entity in California, is bound to follow its published procedures including these mandatory aspects of the Process.[11]

Pursuant to the Process, OEHHA must screen chemicals for reproductive effects based on human epidemiological and laboratory experimental data. The overall evidence of reproductive toxicity of the chemical is to be considered, including epidemiologic, animal bioassay, and other relevant information, as appropriate. Although the prioritization process evaluates chemicals in a qualitative manner, the evaluation of studies against Proposition 65 listing criteria is a useful measure of how a chemical should be prioritized. To be ultimately listed as a chemical "known to the state to cause reproductive toxicity," a chemical must be "*clearly shown* through scientifically valid testing according to generally accepted principles to cause reproductive toxicity".[12] In other words, using a weight-of-evidence approach, it must be clearly shown to be toxic, i.e., to cause adverse effects on the products of conception, adverse effects on male or female reproductive structure or function, or impair male or female reproductive performance.[13]

As detailed below, the Process and the considerations it entails do not support the DARTIC prioritization of PFHxS for the following separate and independent reasons: (1) there is minimal PFHxS exposure potential in the United States and in California; and (2) the weight of the scientific evidence does not support the conclusion that PFHxS is a reproductive toxicant in humans.

II. Prioritization of PFHxS for Potential Listing as a Reproductive Toxicant Is Unwarranted Based the Absence of Exposure Potential in California.

The DARTIC should not prioritize PFHxS becausethere is no evidence of Proposition-65 regulatable discharges or exposures in California. 3M began its voluntary phase out of PFHxS in 2000, and in 2007 US EPA promulgated regulations that effectively prohibit the manufacture, importation, or use of PFHxS. This phase out is further demonstrated by declining, residual PFHxS serum levels in California and nationwide.

[9] Process at 3.
[10] *Id.* (emphasis added).
[11] *E.g.*, *Galzinski v. Somers*, 2 Cal. App. 5th 1164, 1170-74 (2016) (recognizing court may issue writ to require agency to comply with its rules, policies, and procedures; *Pozar v. Department of Transportation*, 145 Cal. App. 3d 269, 270-72 (1983) (same).
[12] Cal. Health & Safety Code § 25249.8(b).
[13] Guidance Criteria for Identifying Chemicals for Listing as "Known to the State to Cause Reproductive Toxicity," https://oehha.ca.gov/media/downloads/proposition-65/proposition-65/dartcriterianov1993.pdf.

A. PFHxS Has Been Effectively Phased Out in the United States.

From the early 1960s until 2000, PFHxS and PFHxS precursors were used in various products. In late 1990s, PFHxS was identified in the blood of the general population at levels measured in very low parts per billion, ng/mL, and this work was later published by Hansen et al. (2001). In May 2000, over 20 years ago, 3M announced that it was voluntarily phasing out of production of certain perfluorooctanyl materials including PFHxS.

After 3M ceased the manufacture of PFHxS, the US EPA promulgated federal regulations in 2007 that prevent other manufactures (as well as 3M) by law from manufacturing or importing PFHxS or PFHxS precursors, subject to a handful of very narrow critical use exceptions with limited exposure potential approved by EPA.[14] EPA's rules allowed the continuation of a few specifically limited, highly technical uses of these chemicals for which no alternatives were available, and which were characterized by very low volume, low exposure and low releases.[15] Any other uses of these chemicals would require prior notice to and review by the Agency. These actions effectively phased out these chemicals in the United States.[16] In other words, California citizens' exposure to PFHxS from Proposition 65-regulatable discharges and exposures is essentially non-existent. This fact is confirmed by the *declining* residual levels of PFHxS in nationwide and California citizens' blood levels.

B. Residual Levels of PFHxS in Blood in the United States General Population Have Declined and Continue to Consistently Decline Since Production Ceased. Similar Very Low Concentrations Have Been Reported in California.

According to the National Health and Nutrition Examination Survey (United States Centers for Disease Control (CDC) National Center for Environmental Health), which is a nationally representative sample of the U.S. population (non-institutionalized), the concentration of PFHxS in the serum (blood) of the general population has *declined by nearly fifty percent* since the phase-out of production activities as reported for the geometric mean and the 95th

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[14] 40 C.F.R. § 721.9582(a)(1), Table 3 (listing PFHxS precursors that cannot be manufactured or imported without EPA permission, and the permissible uses approved by EPA via its Significant New User Rule (SNUR)); *see* Perfluoroalkyl Sulfonates; Significant New Use Rule, 72 Fed. Reg. 57,222 (October 9, 2007) (to be codified at 40 C.F.R. pt. 721).

[15] The three uses permitted by EPA without the cost-prohibitive SNUR review are:

(i) Use as an anti-erosion additive in fire-resistant phosphate ester aviation hydraulic fluids.

(ii) Use as a component of a photoresist substance, including a photo acid generator or surfactant, or as a component of an anti-reflective coating, used in a photomicrolithography process to produce semiconductors or similar components of electronic or other miniaturized devices.

(iii) Use in coating for surface tension, static discharge, and adhesion control for analog and digital imaging films, papers, and printing plates, or as a surfactant in mixtures used to process imaging films.

70 C.F.R. § 721.9582 (a)(1)(Table 3), (a)(2), (a)(3).

[16] Significant New Use Rules: Long-Chain Perfluoroalkyl Carboxylate and Perfluoroalkyl Sulfonate Chemical Substances, 80 Fed. Reg. 2885 (January 21, 2015) (to be codified at 40 C.F.R. pt. 721) ("The Agency previously determined that the 271 PFAS chemical substances identified in 40 CFR 721.9582(a)(1) were no longer being manufactured for any use in the United States, other than for the uses listed under 40 CFR 721.9582(a)(3), (a)(4), and (a)(5)").

percentile (see table below). This decline in PFHxS is observed across males and females, age, and race/ethnicity.[17] The data for PFHxS is excerpted in Table 1 below. The serum elimination half-life of PFHxS has been estimated to be in the 5 to 8 year range (Li et al. 2018; Olsen et al. 2007).

Table 1: Serum PFHxS Data, excerpted from CDC NHANES Fourth National Report on Human Exposure to Environmental Chemicals, Volume 1, pages 397-400

Serum Perfluorohexane sulfonic acid (PFHxS)

CAS Number 355-46-4

Geometric mean and selected percentiles of serum concentrations (in µg/L) for the U.S. population from the National Health and Nutrition Examination Survey.

Categories (Survey Years)	Geometric Mean (95% conf. interval)	50th Percentile (95% conf. interval)	75th Percentile (95% conf. interval)	90th Percentile (95% conf. interval)	95th Percentile (95% conf. interval)	Sample Size
Total population (1999 - 2000)	2.13 (1.91-2.38)	2.10 (1.80-2.30)	3.40 (3.10-4.00)	5.80 (5.20-6.90)	8.70 (7.00-10.0)	1562
Total population (2003 - 2004)	1.93 (1.73-2.16)	1.90 (1.70-2.10)	3.30 (2.80-3.90)	5.90 (4.80-7.20)	8.30 (7.10-9.70)	2094
Total population (2005 - 2006)	1.67 (1.42-1.98)	1.80 (1.50-2.10)	3.20 (2.60-4.00)	5.40 (4.40-7.10)	8.30 (5.80-11.9)	2120
Total population (2007 - 2008)	1.95 (1.76-2.17)	2.00 (1.80-2.10)	3.50 (3.10-4.00)	5.90 (4.90-8.30)	9.80 (6.10-15.2)	2100
Total population (2009 - 2010)	1.66 (1.51-1.82)	1.70 (1.50-1.90)	3.00 (2.60-3.30)	4.80 (4.40-5.30)	6.90 (5.90-7.60)	2233
Total population (2011 - 2012)	1.28 (1.15-1.43)	1.27 (1.11-1.45)	2.26 (2.01-2.61)	3.85 (3.28-4.61)	5.44 (4.61-6.82)	1904
Total population (2013 - 2014)	1.35 (1.20-1.52)	1.40 (1.20-1.60)	2.40 (2.20-2.70)	4.10 (3.60-4.80)	5.60 (4.70-7.10)	2168
Total population (2015 - 2016)	1.18 (1.08-1.30)	1.20 (1.10-1.40)	2.10 (1.80-2.30)	3.40 (3.00-3.90)	4.90 (4.10-5.80)	1993

In addition to NHANES data, non-randomized cross-sectional biomonitoring studies have also been done, including analyses from six American Red Cross blood donation centers that have been collected periodically since 2000-2001 through 2015 (Olsen et al. 2017). These studies have shown the same trends as NHANES. One of these blood donation centers was the American Red Cross Southern California Region located in Los Angeles. The adjusted geometric mean concentration declined from approximately 2.2 ng/mL (2000 - 2001) to 1.0 ng/mL (2015) for this blood donation center.

The Biomonitoring California project has presented geometric mean serum PFHxS concentrations (ng/mL) results from nine studies, and Table 2 below sets forth the data extracted from the Biomonitoring California website. We note that the geometric means (95% CI) are also presented as Table 5 in OEHHA's Prioritization Document.[18] These geometric mean concentrations (ng/mL) and 95th percentiles are similar to the most recent NHANES and the American Red Cross data. However, unlike Table 5 in the Prioritization Document, Table 2 below also includes measured PFHxS concentrations in these nine California studies reported at different percentiles, including the 95th percentile. The mean of the 95th percentile reported in the California Biomonitoring studies is 4.32 ng/mL (sample year collected between 2010 – 2018)

[17] This data can be found in the Fourth National Report on Human Exposure to Environmental Chemicals, Volume 1, pages 397-400. *See* https://www.cdc.gov/exposurereport/index.html, accessed November 11, 2020.

[18] *See* Prioritization Document at 140.

and it is similar to the NHANES 2015-2016 95th percentile (4.9 ng/mL). The 95th percentile of PFHxS of the largest California Biomonitoring study (California Teachers Study), whose samples were collected in 2011, was 6.24 ng/mL and is similar to the upper confidence limit of 5.80 ng/mL reported for the 95th percentile in the 2015-2016 NHANES analyses. Both of these estimates were considered to reflect the highest serum PFHxS concentrations likely to be measured in the California general population today and used to calculate Margins of Exposure (MOE) as shown in Table 4 of Section IV below. This assumption is further strengthened by the two California Biomonitoring regional exposure studies whose samples were collected in 2017 and 2018 (see last two studies in table below).

Table 2: Studies from Biomonitoring California website[19]

Project	Study Group	Geometric mean	95% CI lower	95% CI upper	25th	50th	75th	90th	95th	Number tested
California Teachers Study (CTS)	All	1.62	1.56	1.68	1.04	1.58	2.5		6.24	1759
Firefighter Occupational Exposures (FOX) Project	Firefighters	2.26	2	2.54	1.61	2.27	3.13		4.64	101
Measuring Analytes in Maternal Archived Samples (MAMAS)	Pregnant women	0.904	0.818	0.998	0.558	0.861	1.43		2.83	200
Biomonitoring Exposures Study (BEST) - 1.Pilot	All	1.43	1.19	1.73	0.917	1.52	2.43		6.87	110
Biomonitoring Exposures Study (BEST) - 2.Expanded	All	1.03	0.937	1.13	0.615	1.12	1.78		3.57	337
Asian/Pacific Islander Community Exposures (ACE) Project - ACE 1	All	0.767	0.66	0.891	0.432	0.789	1.41	1.81		96
Asian/Pacific Islander Community Exposures (ACE) Project - ACE 2	All	1.29	1.14	1.45	0.787	1.21	1.81	3.05		99
California Regional Exposure Study, Los Angeles County (CARE-LA)	Adults	0.613	0.559	0.672	0.373	0.68	1.13		2.33	425
California Regional Exposure Study, Region 2 (CARE-2)	All	0.784	0.703	0.874	0.46	0.839	1.57		3.79	358

Accordingly, further review of PFHxS is not necessary to accomplish the goals of Proposition 65, because there is no showing of any present or foreseeable water discharge or California citizens' exposure to PFHxS.

III. Prioritization of PFHxS for Potential Listing as a Reproductive Toxicant Is Unwarranted Based on the Weight of Scientific Evidence.

A. Recent Comprehensive Assessments of the Potential Health Effects of Perfluoroalkyls (including PFHxS) by Key National and International Organizations Have Found Insufficient Evidence of Reproductive Toxicity in Humans.

The U.S. Agency for Toxic Substances and Disease Registry (ATSDR) is directed by congressional mandate to perform specific functions concerning the effect on public health of substances of concern in the environment. In its Toxicological Profile for Perfluoroalkyls, ATSDR characterized the toxicologic and adverse health effects information for perfluoroalkyls

[19] *See* https://biomonitoring.ca.gov/results/chemical/all?field_chemical_name_target_id_selective%5B0%5D=161. Accessed November 11, 2020.

including PFHxS based on "all relevant toxicologic testing and information that has been peer-reviewed," reflecting data from hundreds of studies. ATSDR concluded: "The available human studies have identified some potential targets of toxicity; however, *cause and effect relationships have not been established for any of the effects, and the effects have not been consistently found in all studies*" (emphasis added).[20]

The Expert Health Panel for per- and poly-fluoroalkyl substances (PFAS) was established to advise the Australian Government on the evidence for potential health impacts associated with PFAS exposure. In its 2018 assessment of the latest available systematic reviews of human epidemiological studies and national/international governmental studies on various PFAS compounds including several on PFHxS, the Panel considered, among other health effects, reproductive effects including altered levels of thyroid hormones and sex hormones; later age for starting menstruation (periods) in girls, and earlier menopause; and lower birth weight in babies. With respect to all of the health effects, the Panel concluded "there is mostly limited or no evidence for any link with human disease" and that "there is no current evidence that supports a large impact on a person's health…."[21] Like ATSDR, the Australian Expert Health Panel analyzed hundreds of studies in reaching this overarching conclusion, many of which are also cited in OEHHA's Prioritization Document.

For reproductive health outcomes in particular, the Panel concluded "the rationale and evidence is deficient in most respects." According to the Panel: "Studies have generally compared average values or out-of-range values in those with higher or lower measured PFAS. While this approach works for some outcomes where it is clear what is 'normal' and desirable, studies of human reproductive function are more difficult to do well. This is an extremely complex and variable area of human biology and people's reproductive capacity is expected to vary greatly over time due to many other factors (e.g. age, diet, alcohol consumption, contraceptive use and obesity). Further, interpretation of laboratory results often requires both knowledge of the reproductive stage of the individual and simultaneous interpretation of several tests, to determine what is abnormal and important and what might be contributing to them."[22]

B. The Data from Human Studies Does Not Support a Causal Relationship Between PFHxS and Reproductive Toxicity in Humans.

OEHHA presented 24 epidemiology studies (the 25th study was a duplicate Zhang et al. 2018) in its Prioritization Document. Based on 3M's review of these studies, the evidence does not support a causal relationship between PFHxS and reproductive toxicity in humans. The studies have minimum exposure response contrasts with PFHxS as they are based on general populations. The data from these studies is briefly discussed below, and illustrates the challenges of interpreting the existing epidemiology literature regarding PFHxS. Whether confounding factors, bias, and effect modifiers have been *properly controlled* in these

[20] Agency for Toxic Substances and Disease Registry (ATSDR). 2018. Toxicological profile for Perfluoroalkyls. (Draft for Public Comment), https://www.atsdr.cdc.gov/toxprofiles/tp200.pdf. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service.
[21] Australian Government, Department of Health. 2018. Expert Health Panel for PFAS Report, https://www1.health.gov.au/internet/main/publishing.nsf/Content/ohp-pfas-expert-panel.htm.
[22] *Id.* at 257.

epidemiologic associations is a critical component of a proper evaluation of these studies for prioritization of PFHxS.

The 24 studies were subdivided into seven major categories: 1) Indicators of fetal growth; 2) Neurodevelopmental effects; 3) Anogenital distance, prenatal exposure; 4) Endocrine effects; 5) Female reproductive effects; 6) Male reproductive effects; and 7) Other effects (which was further subdivided into atopic dermatitis, germ cell tumors, metabolic effects, and puberty). For each study cited, OEHHA provides one or two sentence descriptive summaries of the findings of the study. Unfortunately, not provided by OEHHA were any descriptions of the study size, the PFHxS concentrations measured in these studies (e.g., mean, geometric mean, range of values), or estimates of risk (e.g., odds ratios, hazard ratios).

Provided in Table 3 are some measures of central tendency of PFHxS concentration reported in these 24 studies. Most of these studies reported average PFHxS concentrations as either a geometric mean or median value. These geometric mean/median concentrations ranged between 0.16 ng/mL to 1.94 ng/mL. The majority of these studies were essentially based on serum concentrations found in general populations. Therefore, there were minimum exposure contrasts within these 24 studies. Only 4 of these 24 studies reported a maximum PFHxS value greater than 3.87 ng/mL. These maximum PFHxS values in the 4 studies were: 43 ng/mL (Hamm et al. 2010); 22.48 ng/mL (Skogheim et al. 2020); 25 ng/mL (Velez et al. 2015); and 19.71 ng/mL (Jorgensen et al. 2014).

Table 3: 24 Epidemiology studies screened by OEHHA

Parameters	Studies	N	Mean (ng/mL)	Median/GM (ng/mL)	Min-Max (ng/mL)	Association	No Association
Indicators of fetal growth	Alkhalawi et al. 2016	156 pairs	**0.62**		**<0.2, 1.72**	PI	BW or height
	Callan et al. 2016	98		0.33	0.06, 3.3	optimal BW	BW, HC, PI
	Cao et al. 2018	337	0.16		0.03,0.31	BL	BW, PI
	Hamm et al. 2010	252	2.1	1.1	<LOD,43		BW, SGA
	Costa et al. 2019	1230		0.58			Fetal growth
	Shi et al. 2017	170	0.23	0.157	<LOD,3.048		BW, BL, PI
Neuro-developmental	Hoyer et al. (2018)	531		1.69	0.94, 3.87	SDQ Greenland	
		492		1.3	0.54, 2.92		SDQ Ukraine
	Skogheim et al. (2020)	944		0.79	0.06,22.48	Nonverbal working memory	ADHD, language skills, IQ
Anogenital distance (AGD)	Lind et al. 2017	649		0.3	0.2,0.4(IQR)	AGD girls	AGD boys, penile width
Endocrine effects	Inoue et al. 2019	1366		1.11		Higher TSH < GW 10;	No change PFHxS quartiles for TSH, fT4
	Jensen et al. 2018	158 High GDM risk		0.31		Increase glucose, insulin HOMA-IR	
	Yao et al. 2019	351		0.31	0.11, 1.06	Increase E2 and placental steroidgenic hormones (females)	E2 and T (males), T (females)
	Zhang et al. 2018	120 POI		0.38	0.29, 0.67 (IQR)	Increase FSH, Decrease E2 (cases vs controls)	No association prolactin, thyroid hormones
		120 Controls		0.29	0.22 ,0.37 (IQR)		
Female reproductive effects	Velez et al. 2015	1743		1.01	<LOD, 25	Decrease fecundability	Did not adjust for parity. See critique by Bach et al. 2018
	Zhou et al. 2017	950		0.69	0.45, 1.46	Increase irregular menstrual cycle, decrease menorrhagia	
	Jorgensen et al. 2014	1428		1.94	0.22, 19.71		Adjusted for parity; no association with fecundability
	Liew et al. 2020	220 cases		1.1	0.8, 1.4 (IQR)	No overall association w/ miscarriage. No trend.	
		218 controls					

Male reproductive effects	Toft et al. (2012)	588		1.1	0.7, 1.5 (33%/66%)	Adjusted 35% difference lower normal sperm T1 v T3	Adjusted trend test not significant across tertiles
Other DART effects -Atopic dermatitis	Chen et al 2018	687		0.16	0.05, 0.85	Highest quartile associated with atopic dermatitis in females. Association not seen in male children	Association not seen in males
Other DART effects – Germ cell tumors	Lin et al. 2020	42 cases		1.787	0.833, 2.473(IQR)	Association with germ cell tumors	
		42 controls		0.388	0.233, 0.553 (IQR)		
Other DART effects – Metabolic studies	Manzaono-Salgado et al. 2017	1,230		0.61	0.28, 1.39 (5%, 95%)	Positive association triglycerides at age 4	No associations LDL, HDL
	Braun et al. 2016			1.4			No association with adiposity at 8 years of age
	Hartman et al. 2017			1.6	1.3, 2.2 (IQR)		No association with % body fat
	Ernst et al. 2019	235 boys		1.1	0.6,1.7 (10%, 90%)	Associated with a lower mean age of puberty onset in boys	
		210 girls		1	0.6,1.6 (10%, 90%)	Associated with a lower mean age of puberty onset in girls	

KEY

AGD: anogenital distance; BL: birth length; BW: birthweight; E2: estradiol 2; GDM: gestational diabetes mellitus; GM: geometric mean; GW: gestational week; HC: head circumference; IC: intelligence quotient; IQR: interquartile range; HC: head circumference; N: study sample size; PI: ponderal index; POI: primary ovarian insufficiency; SDQ: strength and difficulties questionnaire; SGA: small for gestational age; T: testosterone; T1 T2 T3: Tertile 1 Tertile 2 Tertile 3.

As stated in the OEHHA criteria for recommending chemicals for listing, sufficient evidence in humans to list as "known to the state to cause reproductive toxicity" requires epidemiological studies to be scientifically valid according to generally accepted principles. This in turn requires convincing evidence to support a causal relationship between exposure and the developmental or reproductive effect in question, which depends upon accurate exposure and toxicity endpoint classification and proper control of confounding factors, bias and effect modifiers. Longnecker (2006) commented that the advent of modern analytical chemistry not only enabled lower concentrations of environmental chemicals to be biomonitored, but also allowed for a great proportion of the variation measured to be accounted for by differences in subjects' metabolism and excretion. The low concentrations measured may be a reflection of the byproduct of the underlying pharmacokinetics, systems biology, and pathogenesis. It is conceivable that some of the epidemiologic associations that have been identified as statistically significant findings in the OEHHA epidemiologic screen process may be confounded by the underlying pharmacokinetics of PFHxS as related to the pathophysiology of these outcomes. Such associations have been reported for the longer chain perfluoroalkyls PFOA or PFOS but were likely a result of confounding or toxicokinetic bias (i.e., reverse causation) when related to time to pregnancy (subfecundity) (Bach et al. 2018; Bach et al. 2015; Fei et al. 2009; Fei et al. 2012; Olsen et al. 2009; Velez et al. 2015; Whitworth et al. 2012), birth weight (Dzierlenga et al. 2020; Steenland et al. 2018; Verner et al. 2015; Vesterinen et al. 2015), delayed menarche (Lopez-Espinosa et al. 2011; Wu et al. 2015), and early onset menopause (Knox et al. 2011; Ruark et al. 2017; Taylor et al. 2014).

C. <u>The Body of Data from Animal Studies Fails to Support a Conclusion that PFHxS Causes Reproductive Toxicity in Rodents (or Humans).</u>

OEHHA's Prioritization Document identifies five additional studies under the headings "Animal studies" and "Mechanistic, in vitro, and other relevant data," but provides essentially no context or assessment of the data nor the impact of this data in the human context. Based on 3M's review of the available reproductive and developmental toxicity studies in laboratory animals, the data does not support a conclusion that PFHxS affects the functional aspects of reproduction or development in rodents. Unlike PFOS, the absence of biologically significant effects on either reproduction or development in rodents exposed to PFHxS is an important distinction when compared to the data with PFOS at similar serum levels, which are three to four orders of magnitude higher than the general population. There is no compelling animal data to suggest that PFHxS affects the functional aspects of reproduction or development in laboratory rodents, and therefore no compelling animal data to support these effects in humans.

<u>Reproduction and developmental outcomes in rodents</u>

There are several rodent reproductive and developmental toxicology studies available with repeated oral exposure to PFHxS; two were rat studies (Butenhoff et al. 2009; Ramhoj et al. 2018) and one was mouse study (Chang et al. 2018). Overall, PFHxS did not affect male or female reproductive functions in the laboratory rats or mice. These included estrous cycles, sperm parameters, mating index, fertility index, and reproductive organ morphology. There were no PFHxS treatment-related effects on post-natal survival or development hallmarks of offspring, including body weight at birth, body weight-gain, selected organ weights and histopathology, serum TSH (only mouse data available), and attainment of sexual maturation.

- In Sprague Dawley rats, Butenhoff et al. (2009) observed no developmental or reproductive effects, including litter size, at parental daily oral K^+PFHxS doses up to 10 mg/kg-d. The highest maternal serum PFHxS concentration achieved was approximately 60 μg/mL at the end of gestation. The highest serum PFHxS concentration in pups was approximately 93 μg/mL at weaning.

- In a separate study using Wistar rats, Ramhoj et al. (2018) also found no developmental or reproductive effects at maternal doses up to 45 mg/kg-d when PFHxS was administered orally from gestation day 7 through postnatal day 22. At the end of lactation where the highest maternal serum PFHxS concentration approximated 174 μg/mL, no effects on maternal weight gain during pregnancy, post-implantation loss, perinatal loss, litter size, and sex-ratio were reported.

  It is worth noting that Ramhoj et al. (2018) did NOT report a decreased birth weight in male pups in their study *when PFHxS was evaluated alone*. The decreased birth weight in male pups, in which OEHHA described in the current assessment, was observed only in male pups from dams that received ED_{mix} (a mixture of 12 environmental chemicals) or PFHxS + ED_{mix}, not from dams treated with PFHxS alone.

- In CD-1 mice, Chang et al. (2018) evaluated the reproductive and developmental toxicity study with repeated oral doses of K^+PFHxS to dams at 0.3, 1.0, and 3.0 mg/kg-d for 14 days prior to mating, during mating, throughout gestation and lactation. In addition, the F_1 pups were directly dosed with K^+PFHxS starting at weaning until attainment of sexual maturation. Even though there was a slight but statistically significant decrease in mean live litter size in the 1 mg/kg-d and 3 mg/kg-d dose groups, there were no effects in other related endpoints and the toxicological significance of this finding is unclear because 1) there was a lack of a clear dose-response; 2) there was no statistically significantly difference in the number of pups born to implant ratios between control and the treated groups; and 3) there were no other negative effects on development or reproduction.

  The highest maternal serum PFHxS concentrations were approximately 111 μg/mL and 136 μg/mL at the end of gestation and lactation, respectively. The highest serum PFHxS concentrations in F_1 pups were approximately 180 μg/mL right after attainment of sexual maturation.

<u>Serum thyroxine finding in rats</u>

Study by Ramhoj et al. (2018) also reported PFHxS-related effect on serum thyroxine levels in rats and suggested endocrine disturbance potential with exposure to PFHxS. Endocrine is a very complicated system and evaluation of endocrine functions is a highly specialized field (this is especially true in human clinical medicine). Based on the data from the reproductive and developmental studies described above, PFHxS clearly did not alter the endocrine functions as the reproductive functions and performances in both males and females were normal (*vide supra*). If PFHxS is indeed an endocrine disrupting compound, such as interfering with thyroid axis, then one would expect it to directly activate human thyroid receptors. Ehresman et al. (2014) reported that PFHxS, at up to 100 μM, did not

activate human thyroid receptor *in vitro*. As a comparison and under the same study condition, triiodothyronine (T3, the active form of thyroid hormone) elicited a dose-response activation of human thyroid receptor from 0.000001 – 0.01 μM.

Studies in laboratory rats and monkeys have reported that high concentrations of perfluorooctane sulfonate in serum (PFOS, the eight-carbon congener homologue of PFHxS) can lead to hypothyroxinemia where serum total thyroxine (TT4) was decreased without a concomitant compensatory increase in TSH (Chang et al. 2017; Chang et al. 2008; Lau et al. 2003; Luebker et al. 2005; Seacat et al. 2001; Thibodeaux et al. 2003). This condition takes place when inactive protein-bound thyroxines are being displaced from binding proteins (i.e., due to competition with PFOS for binding proteins) without altering overall thyroid hormone homeostasis. To properly assess thyroid hormone status, one should consider serum TSH (the primary diagnostic index for thyroid endocrinology) and if there a need for supplementary verification, it would be appropriate to measure free thyroxine (FT4), the metabolically-active hormone (Mendel et al. 1986; Oppenheimer et al. 1995; Refetoff et al. 1970). Therefore, it is not surprising that Ramhoj et al. (2018) reported PFHxS treatments caused lower serum TT4 in Wistar rats based on the previous knowledge. However, given no other thyroid-related parameters (i.e., FT4, TSH, or thyroid histology) were evaluated, the overall thyroid homeostasis in the study by Ramhoj et al. (2018) was unclear. While Butenhoff et al. (2009) did not study serum TSH in their rat study with exposure to PFHxS, serum TSH was not affected in either dams or pups in CD-1 mice (Chang et al. 2018).

Neurodevelopmental effects

OEHHA cited a study by Lee and Viberg (2013) speculating that changes in certain neuroprotein levels in young adult mice could have been associated with changes in spontaneous behavior (locomotion, rearing, and total activity counts) when they were given a single dose of PFHxS at either 6.1 or 9.2 mg/kg on PND 10, a critical stage of brain development. There was no serum PFHxS level reported. This observation directly contradicted with the studies in rats by Butenhoff et al. (2009) and mice by Chang et al. (2018), where no abnormal activity levels or clinical behaviors were reported for these young animals. The F_1 pups from both studies were predisposed with PFHxS since birth (via *in utero* exposure) and they were continuously exposed to PFHxS during the brain growth period via lactation. Chang et al. (2018) also exposed the mouse pups directly with PFHxS for 14 days until attainment of sexual maturation.

Mechanistic, in vitro, and other relevant data

OEHHA cited the study by Kjeldsen and Bonefeld-Jorgensen (2013) where reported PFHxS antagonized the androgen receptor activity *in vitro* using Chinese hamster ovary cell line at 5×10^{-5}M or higher. Given that PFHxS is a strong surfactant, the toxicity effects reported from the mono-layered *in vitro* tissue cultured cells offered very little insight and scientific value because the data were often compromised by the surfactant-induced toxicity with likely disruption of the membrane integrity. In addition, this limited *in vitro* finding is not consistent with *in vivo* data where the functional aspects of male androgen-related

parameters (i.e., sperm concentration, sperm motility, and morphology) was not affected when male rats or mice were exposed to repeated doses of PFHxS (Butenhoff et al. 2009; Chang et al. 2018).

IV. Even If PFHxS Was Considered A Strong Candidate for Listing (which is not supported by the data), the Margins of Safety Are Large Enough That It Should Not Be Assigned A High Priority for Review By OEHHA.

For all of the reasons articulated above, we believe that PFHxS should not be considered for high prioritization for review as a reproductive toxicant by OEHHA. Moreover, and as further detailed above, the steady decline of PFHxS serum concentrations in the United States general population is a reflection of effective risk management steps taken by 3M and EPA to eliminate production and restrict almost all use of PFHxS, thereby greatly reducing exposures.

Information on margins of exposure (margins of safety) may also be informative in setting priorities. We can identify the margin of exposure between the residual serum PFHxS concentrations in people and the serum PFHxS concentrations in mice during the various key stages of reproduction and development. Because the comparison is based on measured serum concentrations, these margins already account for species differences in toxicokinetics. The table below illustrates the range of the margin using the study data from Chang et al. (2018) which reported serum PFHxS concentrations in dams prior to mating, at the end of gestation, and at the end of lactation; and for F_1 pups, serum PFHxS levels were determined at birth, at weaning (PND 21), and at attainment of sexual maturation (PND 36). It is clear that the levels of PFHxS are *three to four orders of magnitude* higher than the levels experienced by the general population, demonstrating an ample margin of safety.

Table 4: Margin of Exposure for Human Exposure Compared to Serum PFHxS Concentrations Reported in the Reproductive / Developmental Study in Mice

Human Exposure Level	Serum PFHxS Level in Mice			Margin of Exposure
6.24 ng/mL (95^{th} percentile from California Teacher's Study – sample collection year 2011)	27,000 – 179,000 ng/mL	Pre-mating	Dams	4,326 – 28,685
	16,000 – 111,000 ng/mL	Delivery		2,564 – 17,788
	21,000 – 136,000 ng/mL	End of lactation		3,365 – 21,794
	20,000 – 137,000 ng/mL	Birth	F_1 pups	3,205 – 21,955
	12,000 – 63,000 ng/mL[a]	End of lactation		1,923 – 10,096
	19,000 – 177,000 ng/mL[a]	Sexual attainment		3,044 – 28,365
5.80 ng/mL (Upper 95^{th} confidence limit of the 95^{th} percentile from 2015-2016 NHANES data)	27,000 – 179,000 ng/mL	Pre-mating	Dams	4,655 – 30,862
	16,000 – 111,000 ng/mL	Delivery		2,758 – 19,137
	21,000 – 136,000 ng/mL	End of lactation		3,620 – 23,448
	20,000 – 137,000 ng/mL	Birth	F_1 pups	3,448 – 23,620
	12,000 – 63,000 ng/mL[a]	End of lactation		2,068 – 10,862
	19,000 – 177,000 ng/mL[a]	Sexual attainment		3,275 – 30,517

[a] Average value between male and female pups

For this reason, as well as the others above, PFHxS ***should not be assigned a high priority*** for review by OEHHA.

REFERENCES

Bach, C., Matthiesen, B., Olsen, J., and Henriksen, B. (2018). Conditioning on Parity in Studies of Perfluoroalkyl Acids and Time to Pregnancy: An Example from the Danish National Birth Cohort. *Environ Health Perspect* **126**, 117003.

Bach, C. C., Bech, B. H., Brix, N., Nohr, E. A., Bonde, J. P., and Henriksen, T. B. (2015). Perfluoroalkyl and polyfluoroalkyl substances and human fetal growth: a systematic review. *Crit Rev Toxicol* **45**, 53-67.

Butenhoff, J. L., Chang, S. C., Ehresman, D. J., and York, R. G. (2009). Evaluation of potential reproductive and developmental toxicity of potassium perfluorohexanesulfonate in Sprague Dawley rats. *Reprod Toxicol* **27**, 331-341.

Chang, S., Allen, B. C., Andres, K. L., Ehresman, D. J., Falvo, R., Provencher, A., Olsen, G. W., and Butenhoff, J. L. (2017). Evaluation of Serum Lipid, Thyroid, and Hepatic Clinical Chemistries in Association With Serum Perfluorooctanesulfonate (PFOS) in Cynomolgus Monkeys After Oral Dosing With Potassium PFOS. *Toxicol Sci* **156**, 387-401.

Chang, S., Butenhoff, J. L., Parker, G. A., Coder, P. S., Zitzow, J. D., Krisko, R. M., Bjork, J. A., Wallace, K. B., and Seed, J. G. (2018). Reproductive and developmental toxicity of potassium perfluorohexanesulfonate in CD-1 mice. *Reprod Toxicol* **78**, 150-168.

Chang, S. C., Thibodeaux, J. R., Eastvold, M. L., Ehresman, D. J., Bjork, J. A., Froehlich, J. W., Lau, C., Singh, R. J., Wallace, K. B., and Butenhoff, J. L. (2008). Thyroid hormone status and pituitary function in adult rats given oral doses of perfluorooctanesulfonate (PFOS). *Toxicology* **243**, 330-9.

Dzierlenga, M. W., Crawford, L., and Longnecker, M. P. (2020). Birth weight and perfluorooctane sulfonic acid: a random-effects meta-regression analysis. *Environ Epidemiol* **4**, e095.

Ehresman, D. J., Webb, P., Ayers, S., Vanden Heuvel, J., Olsen, G. W., Chang, S. C., and Butenhoff, J. L. (2014). Effects of perfluoroalkyls on the activation of human CAR3, PXR, TRα, and TRβ in vitro (abstract 1135). *The Toxicologist* **138**, 302.

Fei, C., McLaughlin, J. K., Lipworth, L., and Olsen, J. (2009). Maternal levels of perfluorinated chemicals and subfecundity. *Hum Reprod* **24**, 1200-5.

Fei, C., Weinberg, C. R., and Olsen, J. (2012). Commentary: perfluorinated chemicals and time to pregnancy: a link based on reverse causation? *Epidemiology* **23**, 264-6.

Hamm, M. P., Cherry, N. M., Chan, E., Martin, J. W., and Burstyn, I. (2010). Maternal exposure to perfluorinated acids and fetal growth. *J Expo Sci Environ Epidemiol* **20**, 589-97.

Hansen, K. J., Clemen, L. A., Ellefson, M. E., and Johnson, H. O. (2001). Compound-specific, quantitative characterization of organic fluorochemicals in biological matrices. *Environ Sci Technol* **35**, 766-70.

Jorgensen, K. T., Specht, I. O., Lenters, V., Bach, C. C., Rylander, L., Jonsson, B. A., Lindh, C. H., Giwercman, A., Heederik, D., Toft, G., and Bonde, J. P. (2014). Perfluoroalkyl substances and time to pregnancy in couples from Greenland, Poland and Ukraine. *Environ Health* **13**, 116.

Kjeldsen, L. S., and Bonefeld-Jorgensen, E. C. (2013). Perfluorinated compounds affect the function of sex hormone receptors. *Environ Sci Pollut Res Int* **20**, 8031-44.

Knox, S. S., Jackson, T., Javins, B., Frisbee, S. J., Shankar, A., and Ducatman, A. M. (2011). Implications of early menopause in women exposed to perfluorocarbons. *J Clin Endocrinol Metab* **96**, 1747-53.

Lau, C., Thibodeaux, J. R., Hanson, R. G., Rogers, J. M., Grey, B. E., Stanton, M. E., Butenhoff, J. L., and Stevenson, L. A. (2003). Exposure to perfluorooctane sulfonate during pregnancy in rat and mouse. II: postnatal evaluation. *Toxicol Sci* **74**, 382-92.

Lee, I., and Viberg, H. (2013). A single neonatal exposure to perfluorohexane sulfonate (PFHxS) affects the levels of important neuroproteins in the developing mouse brain. *Neurotoxicology* **37**, 190-6.

Li, Y., Fletcher, T., Mucs, D., Scott, K., Lindh, C. H., Tallving, P., and Jakobsson, K. (2018). Half-lives of PFOS, PFHxS and PFOA after end of exposure to contaminated drinking water. *Occup Environ Med* **75**, 46-51.

Longnecker, M. P. (2006). Pharmacokinetic variability and the miracle of modern analytical chemistry. *Epidemiology* **17**, 350-1.

Lopez-Espinosa, M. J., Fletcher, T., Armstrong, B., Genser, B., Dhatariya, K., Mondal, D., Ducatman, A., and Leonardi, G. (2011). Association of Perfluorooctanoic Acid (PFOA) and Perfluorooctane Sulfonate (PFOS) with Age of Puberty among Children Living near a Chemical Plant. *Environ. Sci. Technol.* **45**, 8160-8166.

Luebker, D. J., York, R. G., Hansen, K. J., Moore, J. A., and Butenhoff, J. L. (2005). Neonatal mortality from in utero exposure to perfluorooctanesulfonate (PFOS) in Sprague-Dawley rats: dose-response, and biochemical and pharamacokinetic parameters. *Toxicology* **215**, 149-69.

Mendel, C. M., Frost, P. H., and Cavalieri, R. R. (1986). Effect of free fatty acids on the concentration of free thyroxine in human serum: the role of albumin. *J Clin Endocrinol Metab* **63**, 1394-9.

Olsen, G. W., Burris, J. M., Ehresman, D. J., Froehlich, J. W., Seacat, A. M., Butenhoff, J. L., and Zobel, L. R. (2007). Half-life of serum elimination of perfluorooctanesulfonate,perfluorohexanesulfonate, and perfluorooctanoate in retired fluorochemical production workers. *Environ Health Perspect* **115**, 1298-305.

Olsen, G. W., Butenhoff, J. L., and Zobel, L. R. (2009). Perfluoroalkyl chemicals and human fetal development: an epidemiologic review with clinical and toxicological perspectives. *Reprod Toxicol* **27**, 212-230.

Olsen, G. W., Mair, D. C., Lange, C. C., Harrington, L. M., Church, T. R., Goldberg, C. L., Herron, R. M., Hanna, H., Nobiletti, J. B., Rios, J. A., Reagen, W. K., and Ley, C. A. (2017). Per- and polyfluoroalkyl substances (PFAS) in American Red Cross adult blood donors, 2000-2015. *Environ Res* **157**, 87-95.

Oppenheimer, J. H., Schwartz, A. L., and Strait, K. A. (1995). An integrated view of thyroid hormone actions *in vivo* (B. D. Weintraub, Ed.^ Eds.), pp. 249-65. Raven Press, Ltd., New York.

Ramhoj, L., Hass, U., Boberg, J., Scholze, M., Christiansen, S., Nielsen, F., and Axelstad, M. (2018). Perfluorohexane Sulfonate (PFHxS) and a Mixture of Endocrine Disrupters Reduce Thyroxine Levels and Cause Antiandrogenic Effects in Rats. *Toxicol Sci* **163**, 579-591.

Refetoff, S., Robin, N. I., and Fang, V. S. (1970). Parameters of thyroid function in serum of 16 selected vertebrate species: a study of PBI, serum T4, free T4, and the pattern of T4 and T3 binding to serum proteins. *Endocrinology* **86**, 793-805.

Ruark, C. D., Song, G., Yoon, M., Verner, M. A., Andersen, M. E., Clewell, H. J., 3rd, and Longnecker, M. P. (2017). Quantitative bias analysis for epidemiological associations of perfluoroalkyl substance serum concentrations and early onset of menopause. *Environ Int* **99**, 245-254.

Seacat, A. M., Butenhoff, J., Hansen, K. J., Olsen, G. W., and Thomford, P. J. (2001). Toxicity of potassium perfluorooctanesulfonate in cynomologus monkeys after twenty-six weeks of oral dosing and one year of recovery (abstract 1656). *Toxicol Sci* **60 Supplement 1**, 348.

Skogheim, T. S., Villanger, G. D., Weyde, K. V. F., Engel, S. M., Suren, P., Oie, M. G., Skogan, A. H., Biele, G., Zeiner, P., Overgaard, K. R., Haug, L. S., Sabaredzovic, A., and Aase, H. (2020). Prenatal exposure to perfluoroalkyl substances and associations with symptoms of attention-deficit/hyperactivity disorder and cognitive functions in preschool children. *Int J Hyg Environ Health* **223**, 80-92.

Steenland, K., Barry, V., and Savitz, D. (2018). Serum Perfluorooctanoic Acid and Birthweight: An Updated Meta-analysis With Bias Analysis. *Epidemiology* **29**, 765-776.

Taylor, K. W., Hoffman, K., Thayer, K. A., and Daniels, J. L. (2014). Polyfluoroalkyl Chemicals and Menopause among Women 20-65 Years of Age (NHANES). *Environ Health Perspect* **122**, 145-150.

Thibodeaux, J., Hanson, R. G., Grey, B. E., Barbee, B. D., Richards, J. H., Butenhoff, J. L., Rogers, J. M., and Lau, C. (2003). Maternal and developmental toxicity of perfluorooctane sulfonate (PFOS) in the mouse (abstract 1658). *The Toxicologist* **72** 342.

Velez, M. P., Arbuckle, T. E., and Fraser, W. D. (2015). Maternal exposure to perfluorinated chemicals and reduced fecundity: the MIREC study. *Hum Reprod* **30**, 701-9.

Verner, M. A., Loccisano, A. E., Morken, N. H., Yoon, M., Wu, H., McDougall, R., Maisonet, M., Marcus, M., Kishi, R., Miyashita, C., Chen, M. H., Hsieh, W. S., Andersen, M. E., Clewell, H. J., 3rd, and Longnecker, M. P. (2015). Associations of Perfluoroalkyl Substances (PFAS) with Lower Birth Weight: An Evaluation of Potential Confounding by Glomerular Filtration Rate Using a Physiologically Based Pharmacokinetic Model (PBPK). *Environ Health Perspect* **123**, 1317-24.

Vesterinen, H. M., Johnson, P. I., Atchley, D. S., Sutton, P., Lam, J., Zlatnik, M. G., Sen, S., and Woodruff, T. J. (2015). Fetal growth and maternal glomerular filtration rate: a systematic review. *J Matern Fetal Neonatal Med* **28**, 2176-81.

Whitworth, K. W., Haug, L. S., Baird, D. D., Becher, G., Hoppin, J. A., Skjaerven, R., Thomsen, C., Eggesbo, M., Travlos, G., Wilson, R., and Longnecker, M. P. (2012). Perfluorinated compounds and subfecundity in pregnant women. *Epidemiology* **23**, 257-63.

Wu, H., Yoon, M., Verner, M.-A., Xue, J., Luo, M., Andersen, M. E., Longnecker, M. P., and Clewell III, H. J. (2015). Can the observed association between serum perfluoroalkyl subtances and delayed menarche be explained on the basis of puberty-related changes in physiology and pharmacokinetics? *Environ Int* **82**, 61-68.