

Developmental and Reproductive Toxicants Identification Committee, c/o Michelle Robinson
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Submitted via email: P65Public.Comments@oehha.ca.gov

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RE: Prioritization: Chemicals for Consultation by the Developmental and Reproductive Toxicants Identification Committee

Dear Members of the Developmental and Reproductive Toxicants (DART) Identification Committee,

The following comments are submitted on behalf of the undersigned individuals and organizations, none of whom have any financial interest in the topic of these comments. We urge the DART to recommend that perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS) be prioritized for the further development of hazard identification materials.

Since the Office of Environmental Health Hazard (OEHHA) last reviewed PFOA and PFOS in 2007, the scientific evidence linking these chemicals to adverse human health effects has grown substantially as noted in OEHHA's August 2015 report *Prioritization: Chemicals Identified for Consultation with the Developmental and Reproductive Toxicant Identification Committee*. The evidence comes from epidemiological studies, animal studies and other relevant information as outlined in OEHHA's document describing the process for prioritization of chemicals¹.

Among the particularly compelling studies published in the last eight years are three systematic reviews on PFOA, from 2014, which evaluated the published scientific literature using objective and transparent criteria (see Appendix). The authors concluded that developmental exposure to PFOA adversely affects human health based on sufficient evidence of decreased fetal growth in both human and nonhuman mammalian species.

A) Epidemiological data shows strong evidence associating PFOA and PFOS with adverse reproductive and developmental outcomes

The broad literature search conducted by OEHHA yielded a significant number of high quality epidemiological studies finding evidence of adverse health effects caused by these chemicals. 20 analytical epidemiologic studies that meet the study quality criteria were identified as reporting association between exposure to PFOA and increased risk of adverse developmental or reproductive health effects. Similarly, fifteen studies were identified for PFOS.

¹Process for prioritizing chemicals for consideration under Proposition 65 by the "State's Qualified Experts."
Available at http://oehha.ca.gov/prop65/CRNR_notices/state_listing/pdf/finalPriordoc.pdf

The Johnson, et al systematic review of human epidemiological evidence concluded that **there is sufficient human evidence that developmental exposure to PFOA reduces fetal growth.**² This systematic review included 18 human studies, nine of which were combined through meta-analysis. The meta-analysis was used to estimate the increase in PFOA serum concentration associated with decreased birth weight.

But decreased birth weight is not the only adverse health impact of concern. Particularly troublesome are the associations identified in epidemiological studies between prenatal exposures to PFOA, PFOS, or both and devastating diseases or disorders in children. From birth defects³ to congenital cerebral palsy,⁴ altered behavior and motor development,⁵ reduced immune response to vaccines⁶ and overweight,⁷ to name just a few, these studies inject a sense of urgency into the DART's consideration of these chemicals.

Considering that these persistent, bioaccumulative perfluorinated compounds have been on the market for decades, it is likely many of these studies show the effects on a second generation of exposed children. Effects in adults, especially women, are also of great concern. These range from disruption of thyroid hormones⁸ and reproductive function,⁹ to polycystic ovary syndrome,¹⁰ and early menopause.¹¹

Without a doubt, there is very strong epidemiological data to substantiate a further hazard analysis.

B) Strong toxicological evidence that PFOA and PFOS cause developmental and reproductive toxicity

Findings from animal toxicology and mechanistic studies correlate with epidemiology study outcomes. Studies considering motor function,¹² developmental effects,¹³ immunopathologies,¹⁴ reproductive

²Johnson PI et al. The Navigation Guide—Evidence-Based Medicine Meets Environmental Health: Systematic Review of Human Evidence for PFOA Effects on Fetal Growth. 2014. *Environmental Health Perspectives* 122:1028-1039.

³Stein CR et al. Perfluorooctanoate exposure and major birth defects. 2014. *Reproductive Toxicology* 47:15-20

⁴Liew Z et al. Prenatal exposure to perfluoroalkyl substances and the risk of congenital cerebral palsy in children. 2014. *American Journal of Epidemiology* 180:574-581

⁵Hoyer BB et al. Pregnancy serum concentrations of perfluorinated alkyl substances and offspring behavior and motor development at age 5-9 years—a prospective study. 2015. *Environmental Health* 14:2

⁶Granum B et al. Pre-natal exposure to perfluoroalkyl substances may be associated with altered vaccine antibody levels and immune-related health outcomes in early childhood. 2013. *Journal of Immunology* 10:373-379

⁷Halldorsson TI et al. Prenatal exposure to perfluorooctanoate and risk of overweight at 20 years of age: a prospective study. 2012. *Environmental Health Perspectives* 120:668-673

⁸Webster GM et al. Associations between perfluoroalkyl acids (PFASs) and maternal thyroid hormones in early pregnancy: a population-based cohort study. *Environmental Research* 133:338-347

⁹Kristensen SL et al. Long-term effects of prenatal exposure to perfluoroalkyl substances on female reproduction. 2013. *Human Reproduction* 28:3337-3348

¹⁰Vagi SJ et al. Exploring the potential association between brominated diphenyl ethers, polychlorinated biphenyls, organochlorine pesticides, perfluorinated compounds, phthalates, and bisphenol A in polycystic ovary syndrome: a case control study. 2014. *BMC Endocrine Disorders* 14:86

¹¹Knox SS et al. Implications of early menopause in women exposed to perfluorocarbons. 2011. *Journal of Clinical Endocrinology and Metabolism* 96:1747-1753

¹²Onishchenko N et al. Prenatal exposure to PFOS or PFOA alters motor function in mice in a sex-related manner. 2011. *Neurotoxicology Research* 19:452-461

dysfunction,¹⁵ and neurobehavioral effects¹⁶ reached conclusions consistent with the epidemiology findings. Particularly relevant as well are multi-generation mouse studies demonstrating PFOA effects on the development of the mammary gland.¹⁷ Other studies find that the mammary gland is particularly sensitive to low-level prenatal PFOA exposures, regardless of the mouse strain studied.¹⁸

The Koustas, et al systematic review of non-human studies found that PFOA causes developmental and reproductive toxicity in animals.¹⁹ The authors evaluated 21 studies (15 mammalian and 6 non-mammalian) and performed a meta-analysis of 8 data sets from studies in mice, concluding that there was **sufficient evidence that fetal developmental exposure to PFOA reduces fetal growth in animals.**

C) Exposure in the general population and in Californians

The epidemiological, animal and mechanistic study findings take on greater import given the widespread exposure to these chemicals. Almost all Americans 12 years of age and older tested by the National Health and Nutrition Evaluation Survey have PFOA and PFOS in their serum.²⁰ Similarly, PFOA²¹ and PFOS²² are present in the body of 99.9% of more than 1300 Californians tested.

This widespread exposure is of high concern due to the bioaccumulation of PFOA and PFOS in the body. Because of this chemical property and ongoing exposures, it is difficult to calculate the half-life of these chemicals. A study of 26 retired fluorochemical production workers estimated the half-life of PFOA and PFOS to be 3.8 years and 5.4 years, respectively.²³

¹³Macon MB et al. Prenatal perfluorooctanoic acid exposure in CD-1 mice: low-dose developmental effects and internal dosimetry. 2011. *Toxicological Sciences* 122:134-145

¹⁴Hu Q et al. Does developmental exposure to perfluorooctanoic acid (PFOA) induce immunopathologies commonly observed in neurodevelopmental disorders? 2012. *Neurotoxicology* 33:1491-1498

¹⁵Zhang H et al. Proteomic analysis of mouse testis reveals perfluorooctanoic acid-induced reproductive dysfunction via direct disturbance of testicular steroidogenic machinery. 2014. *Journal of Proteome Research* 13:3370-3385

¹⁶Cheng J et al. Neurobehavioral effects, c-Fos/Jun expression and tissue distribution in rat offspring prenatally co-exposed to MeHg and PFOA: PFOA impairs Hg retention. 2013. *Chemosphere* 91:758-764

¹⁷White SS et al. Gestational and chronic low-dose PFOA exposures and mammary gland growth and differentiation in three generations of CD-1 mice. 2011. *Environmental Health Perspectives* 119:1070-1076

¹⁸Tucker DK et al. *Reprod Toxicol.* 2015 Jul;54:26-36. Epub 2014 Dec 12. The mammary gland is a sensitive pubertal target in CD-1 and C57Bl/6 mice following perinatal perfluorooctanoic acid (PFOA) exposure. doi: 10.1016/j.reprotox.2014.12.002.

¹⁹Koustas,E et al. The Navigation Guide—Evidence-Based Medicine Meets Environmental Health: Systematic Review of Nonhuman Evidence for PFOA Effects on Fetal Growth. 2014. *Environmental Health Perspectives* 122:1015–1027

²⁰Perfluorochemicals (PFCs) Factsheet. Centers for Disease Control and Prevention. Accessed September 17, 2015. http://www.cdc.gov/biomonitoring/PFCs_FactSheet.html

²¹PFOA Results, Biomonitoring California. Accessed September 17, 2015.

[http://www.biomonitoring.ca.gov/results/chemical/all?field_chemical_name_target_id_selective\[0\]=165](http://www.biomonitoring.ca.gov/results/chemical/all?field_chemical_name_target_id_selective[0]=165)

²²PFOS Results, Biomonitoring California. Accessed September 17, 2015.

[http://www.biomonitoring.ca.gov/results/chemical/all?field_chemical_name_target_id_selective\[0\]=164](http://www.biomonitoring.ca.gov/results/chemical/all?field_chemical_name_target_id_selective[0]=164)

²³Olsen GW et al. Half-life of serum elimination of perfluorooctanesulfonate,perfluorohexanesulfonate, and perfluorooctanoate in retired fluorochemical production workers. 2007. *Environmental Health Perspectives* 115:1298-1305

The carcinogenic, immunotoxic and mammary gland effects at low PFOA doses are particularly of concern and point to the potential for harm at current levels of human exposure.^{24, 25, 26}

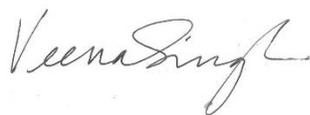
Conclusion

The collective evidence of the reproductive and developmental toxicity of these chemicals is powerful. In the Lam et al systematic review integrating the evidence from 18 human studies and 21 animal toxicology studies²⁷, the strength of evidence led to the conclusion that **“PFOA is ‘known to be toxic’ to human reproduction and development based on sufficient evidence of decreased fetal growth in both human and nonhuman mammalian species.”**

In summary, the evidence from epidemiology, animal studies and exposure studies all support the prioritization of PFOA and PFOS for the further development of hazard identification materials, and we encourage the DART to prioritize these chemicals.

Thank you for the opportunity to comment on the list of priority chemicals.

Respectfully submitted,



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²⁴Grandjean et al. Perfluorinated Alkyl Substances: Emerging Insights Into Health Risks. *New Solutions: A Journal of Environmental and Occupational Health Policy*, June 17, 2015.

²⁵Grandjean et al., Immunotoxicity of perfluorinated alkylates: calculation of benchmark doses based on serum concentrations in children. *Environmental Health*, April 19, 2013.

²⁶Post GB, et al. Perfluorooctanoic acid (PFOA), An emerging drinking water contaminant: A critical review of recent literature. *Environmental Research*, July 2012.

²⁷Lam J et al. The Navigation Guide—Evidence-Based Medicine Meets Environmental Health: Integration of Animal and Human Evidence for PFOA Effects on Fetal Growth. 2014. *Environmental Health Perspectives* 122:1040–1051; <http://dx.doi.org/10.1289/ehp.1307923>

Appendix

Abstracts from PFOA Systematic Review Studies

1. The Navigation Guide—Evidence-Based Medicine Meets Environmental Health:

Systematic Review of Human Evidence for PFOA Effects on Fetal Growth Paula I. Johnson, Patrice Sutton, Dylan S. Atchley, Erica Koustas, Juleen Lam, Saunak Sen, Karen A. Robinson, Daniel A. Axelrad, and Tracey J. Woodruff. 2014. *Environ Health Perspect* 122:1028–1039; <http://dx.doi.org/10.1289/ehp.1307893>

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

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

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

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

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

2. The Navigation Guide—Evidence-Based Medicine Meets Environmental Health:

Systematic Review of Nonhuman Evidence for PFOA Effects on Fetal Growth. Erica Koustas, Juleen Lam, Patrice Sutton, Paula I. Johnson, Dylan S. Atchley, Saunak Sen, Karen A. Robinson, Daniel A. Axelrad, and Tracey J. Woodruff. 2014 *Environ Health Perspect* 122:1015–1027; <http://dx.doi.org/10.1289/ehp.1307177>

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

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

Methods: We conducted a comprehensive search of the literature, applied prespecified criteria to the search results to identify relevant studies, extracted data from studies, obtained additional

information from study authors, conducted meta-analyses, and rated the overall quality and strength of the evidence.

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

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

3. The Navigation Guide—Evidence-Based Medicine Meets Environmental Health:

Integration of Animal and Human Evidence for PFOA Effects on Fetal Growth Juleen Lam, Erica Koustas, Patrice Sutton, Paula I. Johnson, Dylan S. Atchley, Saunak Sen, Karen A. Robinson, Daniel A. Axelrad, and Tracey J. Woodruff. 2014. *Environ Health Perspect* 122:1040–1051; <http://dx.doi.org/10.1289/ehp.1307923>

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

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

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

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

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