Response to Comments on the Notice of Intent to List Perfluorooctanoic Acid (PFOA) and Perfluorooctane Sulfonate (PFOS) as Causing Reproductive Toxicity under Proposition 65

Office of Environmental Health Hazard Assessment
California Environmental Protection Agency

November 2017

On September 16, 2016, the Office of Environmental Health Hazard Assessment (OEHHA) issued a Notice of Intent to List[1] Perfluorooctanoic Acid (PFOA) and Perfluorooctane Sulfonate (PFOS), under Proposition 65[2] as chemicals known to the state to cause reproductive toxicity (developmental endpoint). The action was based on Proposition 65 statutory requirements[3] and on the authoritative bodies provision[4] of the Proposition 65 implementing regulations[5]. OEHHA found that PFOA and PFOS meet the criteria for listing via this mechanism based on:

- Conclusions by the US Environmental Protection Agency (US EPA) in several documents that PFOA and PFOS cause adverse developmental effects (US EPA 2016a,b,c,d)[6].
- US EPA's adoption of reference doses based on developmental endpoints. (US EPA 2016a,b,c,d)
- The scientific evidence relied upon by US EPA.

[1] Notice of Intent to List: Perfluorooctanoic Acid (PFOA) and Perfluorooctane Sulfonate (PFOS). Available at https://oehha.ca.gov/proposition-65/crnr/notice-intent-list-perfluorooctanoic-acid-pfoa-and-perfluorooctane-sulfonate

[2] The Safe Drinking Water and Toxic Enforcement Act of 1986 (codified at Health and Safety Code section 25249.5 *et seq*.), hereinafter referred to as Proposition 65 or the Act.

[3] Health and Safety Code section 25249.8(b)

[4] Title 27, Cal. Code of Regulations, section 25306.

[5] All further references are to sections of Title 27, California Code of Regulations unless indicated otherwise.

[6] US EPA (2016a). Drinking Water Health Advisory for Perfluorooctanoic Acid (PFOA). EPA Document Number: 822-R-16-005. May 2016. Available at: https://www.epa.gov/sites/production/files/2016-05/documents/pfoa_health_advisory_final-plain.pdf
US EPA (2016b). Health Effects Support Document for Perfluorooctanoic Acid (PFOA). EPA Document Number: 822-R-16-003. May 2016. Available at: https://www.epa.gov/sites/production/files/2016-05/documents/pfoa_hesd_final-plain.pdf
US EPA (2016c). Drinking Water Health Advisory for Perfluorooctane Sulfonate (PFOS). EPA Document Number: 822-R-16-004. May 2016. Available at: https://www.epa.gov/sites/production/files/2016-05/documents/pfos_health_advisory_final-plain.pdf
US EPA (2016d). Health Effects Support Document for Perfluorooctane Sulfonate (PFOS). EPA Document Number: 822-R-16-002. May 2016. Available at: https://www.epa.gov/sites/production/files/2016-05/documents/hesd_pfos_final-plain.pdf

This document responds to public comments received on the Notice of Intent to List PFOA and PFOS under Proposition 65.

Under Section 25306, a chemical is identified as causing reproductive toxicity, including developmental toxicity, if it has been "formally identified" by an authoritative body as causing reproductive toxicity. A chemical has been "formally identified" pursuant to Section 25306 if it has been included in a list of chemicals causing reproductive toxicity published by the authoritative body; is the subject of a report which is published by the authoritative body and which concludes that the chemical causes reproductive toxicity; or has been "otherwise identified" as causing reproductive toxicity by the authoritative body in a document that indicates that the identification is a final action, and if the list, report, or document meets specified criteria in Section 25306(d)(2). US EPA is designated as an authoritative body for purposes of listing chemicals as causing reproductive toxicity pursuant to Section 25306.

OEHHA has reviewed the conclusions and statements in US EPA documents from 2016 (a,b,c,d) and determined that these conclusions and statements satisfy the requirements of Section 25306(d)(1) in that PFOA and PFOS are the subjects of reports published by the authoritative body that conclude that PFOA and PFOS cause reproductive toxicity. The authoritative body has also "otherwise identified" PFOA and PFOS as causing reproductive toxicity in documents that indicate that such identification is a final action, specifically: US EPA issued lifetime drinking water Health Advisories (HA) for PFOA, based on a reference dose (RfD) derived from a developmental toxicity study in mice, and PFOS, based on a RfD derived from a developmental toxicity study in rats. OEHHA has further determined that each of the documents satisfies one or more of the Section 25306(d)(2) criteria by having been:

- "published by the authoritative body in a publication, such as, but not limited to, the federal register…" (US EPA, 2016a,b,c,d);
- "reviewed by an advisory committee in a public meeting, if a public meeting is required" (US EPA, 2016b,d); and
- "made subject to public review and comment prior to its issuance" (US EPA, 2016b,d), thus satisfying the formal identification criteria in the Proposition 65 regulations.

Pertinent statements in the US EPA reports documenting the Agency's conclusions about developmental toxicity include the following:

Drinking Water Health Advisory for Perfluorooctanoic Acid (US EPA, 2016a):

- "The US Environmental Protection Agency (EPA) is issuing a lifetime drinking water Health Advisory (HA) for PFOA of 0.07 micrograms per liter (µg/L) based on a reference dose (RfD) derived from a developmental toxicity study in mice; the critical effects included reduced ossification in proximal phalanges and

accelerated puberty in male pups following exposure during gestation and lactation." (p. 9)

- "For PFOA, ...studies report developmental effects (survival, body weight changes, reduced ossification, delays in eye opening, altered puberty, and retarded mammary gland development) … Overall, the toxicity studies available for PFOA demonstrate that the developing fetus is particularly sensitive to PFOA-induced toxicity." (p. 9)
- "The effects that serve as the basis for the RfDs for both PFOA and PFOS are developmental endpoints (reduced ossification and accelerated puberty in males for PFOA and decreased pup weight for PFOS)." (p. 55)
- "The animal toxicology studies were used in the dose-response assessment for PFOA. These studies demonstrated dose-related effects on systemic and developmental endpoints in multiple species (monkeys, rats, mice) …" (p. 33)
- "There are extensive human data from epidemiological data from the general population as well as worker cohorts. The epidemiology data provide strong support for the identification of hazards observed following exposure to PFOA in the laboratory animal studies and human relevance." (p. 51)
- "Based on the consistency of the responses across the chronic studies and those for reproductive and developmental endpoints, and with recognition of the use of developmental toxicity as the most sensitive endpoint, 0.00002 mg/kg/day was selected as the RfD for PFOA. This value is based on the HED [Human Equivalent Dose] for developmental effects (reduced ossification in male and female pups and accelerated puberty in male pups) from the Lau et al. (2006) study." (p. 54)
- "The lifetime HA for PFOA is based on effects (reduced ossification in male and female pups and accelerated puberty in male pups) on the developing fetus resulting from exposures that occur during gestation and lactation. These developmental endpoints are the most protective for the population at large and are effects that can carry lifetime consequences for a less than lifetime exposure." (p. 55)
- "EPA's risk assessment guidelines reflect that, as a general matter, a single exposure to a developmental toxin at a critical time in development can produce an adverse effect (US EPA 1991). In addition, short-term exposure to PFASs [perfluoroalkyl substances] can result in a body burden that persists for years and can increase with additional exposures. Thus, EPA recommends that the lifetime HA for PFOA of 0.07 µg/L apply to both short-term (i.e., weeks to months) scenarios during pregnancy and lactation, as well as to lifetime-exposure scenarios." (p. 10)

Health Effects Support Document for Perfluorooctanoic Acid (US EPA, 2016b):

- "Developmental effects observed in animals include decreased survival, delayed eye opening and reduced ossification, skeletal defects, …" (p. ES-2)
- "Overall, the developmental and reproductive toxicity studies available for PFOA demonstrate that the developing fetus is particularly sensitive to PFOA-induced toxicity." (p. ES-3)

Drinking Water Health Advisory for Perfluorooctane Sulfonate (PFOS) (US EPA, 2016c):

- "The US Environmental Protection Agency (EPA) is issuing a lifetime drinking water health advisory (HA) for PFOS of 0.07 micrograms per liter (µg/L) based on a reference dose (RfD) derived from a developmental toxicity study in rats; the critical effect was decreased pup body weight following exposure during gestation and lactation." (p. 10)
- "For PFOS, … studies report developmental effects (decreased body weight, survival, and increased serum glucose levels and insulin resistance in adult offspring) … Overall, the toxicity studies available for PFOS demonstrate that the developing fetus is particularly sensitive to PFOS induced toxicity." (p. 10)
- "Adverse effects observed following exposures to PFOA and PFOS are the same or similar, and include effects on lipids, birth weight, and antibodies in humans …The effects serving as the basis for the RfDs for both PFOA and PFOS are developmental endpoints (e.g., reduced ossification and accelerated puberty in males for PFOA and decreased birth weight for PFOS …)" (p.51)
- "EPA believes the uncertainty in the chosen POD *[point of departure]* and the reliance on studies with serum data is minimized because of the large and extensive database examining hazard, and the selection of pup body weight as the critical effect with lifetime implications at a NOAEL (0.1 mg/kg/day) from the low end of the range of values evaluated." (p. 51)
- "The RfD is based on the HED derived from serum levels at the NOAEL from a developmental study in rats (Luebker et al. 2005b). …The selected RfD is based on the most sensitive endpoint, developmental effects (e.g., decreased pup body weight), to provide protection to the general population and sensitive life stages." (p. 52)
- "EPA's risk assessment guidelines reflect that, as a general matter, a single exposure to a developmental toxin, at a critical time in development can produce an adverse effect (US EPA 1991). In addition, short-term exposure to PFASs *[perfluoroalkyl substances]* can result in a body burden that persists for years and can increase with additional exposures. Thus, EPA recommends that the lifetime HA for PFOS of 0.07 µg/L apply to both short-term (i.e., weeks to months) scenarios during pregnancy and lactation, as well as to lifetime-exposure scenarios." (p. 11)

Health Effects Support Document for Perfluorooctane Sulfonate (PFOS) (US EPA, 2016d):

- "EPA derived a reference dose (RfD) for PFOS…based on decreased neonatal rat body weight from the two-generation study by Luebker et al. (2005b). …The HED for effects on pup body weight in the two generation study is supported by comparable values derived from the lowest observed adverse effect level for the same effect in the one-generation study and the NOAEL for effects seen in a developmental neurotoxicity study." (p. ES-2)

- "At 3.2 mg/kg/day *[PFOS, oral dose in rats]*, there were significant decreases in gestation length and number of implantation sites, and reductions in litter size." (p. 3-63)
- "For pups only exposed prenatally, mortality was 9% compared to 1.1% for those exposed during lactation only. Reductions in pup body weights on LD 1 were observed in groups exposed both gestationally and lactationally and in those with gestational exposure only." (p. 3-64)
- "Based on the consistency of the response and of the use of the most sensitive endpoint, developmental toxicity, as the critical effect, the RfD of 0.00002 mg/kg/day from Luebker et al. (2005a) is selected as the RfD for PFOS. This RfD is derived from reduced pup body weight in the two-generation study in rats." (p. 4-16)

OEHHA has reviewed the studies cited or study descriptions provided by US EPA (2016a,b,c,d) in support of its formal identification of PFOA and PFOS as causing reproductive toxicity (developmental endpoint) relative to the criteria in Section 25306(g) (Table 1). Based on the PFOA HA (US EPA, 2016a) and PFOS HA (US EPA, 2016c) the supporting documents for PFOA and PFOS (US EPA, 2016b,d respectively), and the studies cited in those documents, OEHHA finds the criteria for listing PFOA and PFOS through the authoritative bodies mechanism as causing reproductive toxicity (developmental endpoint) have been met. Specifically, OEHHA has concluded that there are sufficient data, taking into account the adequacy of the experimental design and other parameters such as, but not limited to, route of administration, frequency and duration of exposure, numbers of test animals, choice of species, choice of dosage levels, and consideration of maternal toxicity, indicating that an association between the adverse reproductive effects in humans and the toxic agent in question is biologically plausible, thus meeting the sufficiency of evidence criteria in Section 25306.

Table 1. Studies Cited by US EPA Supporting Formal Identification of PFOA and PFOS as Causing Reproductive Toxicity.

Abbott BD, Wolf CJ, Schmid JE, Das KP, Zehr RD, Helfant L, Nakayama S, Lindstrom AB, Strynar MJ and Lau C (2007). Perfluorooctanoic Acid Induced Developmental Toxicity in the Mouse is Dependent on Expression of Peroxisome Proliferator Activated Receptor-alpha. *Toxicol Sci* **98**(2): 571-581.
Albrecht PP, Torsell NE, Krishnan P, Ehresman DJ, Frame SR, Chang SC, Butenhoff JL, Kennedy GL, Gonzalez FJ and Peters JM (2013). A species difference in the peroxisome proliferator-activated receptor alpha-dependent response to the developmental effects of perfluorooctanoic acid. *Toxicol Sci* **131**(2): 568-582.

Butenhoff JL, Ehresman DJ, Chang SC, Parker GA and Stump DG (2009). Gestational and lactational exposure to potassium perfluorooctanesulfonate (K+PFOS) in rats: developmental neurotoxicity. *Reprod Toxicol* **27**(3-4): 319-330.

Butenhoff JL, Kennedy GL, Jr., Frame SR, O'Connor JC and York RG (2004a). The reproductive toxicology of ammonium perfluorooctanoate (APFO) in the rat. *Toxicology* **196**(1-2): 95-116.

Chen MH, Ha EH, Wen TW, Su YN, Lien GW, Chen CY, Chen PC and Hsieh WS (2012). Perfluorinated compounds in umbilical cord blood and adverse birth outcomes. *PloS one* **7**(8): e42474.

Fei C, McLaughlin JK, Tarone RE and Olsen J (2007). Perfluorinated chemicals and fetal growth: a study within the Danish National Birth Cohort. *Environ Health Perspect* **115**(11): 1677-1682.

Hinderliter PM, Mylchreest E, Gannon SA, Butenhoff JL and Kennedy GL, Jr. (2005). Perfluorooctanoate: Placental and lactational transport pharmacokinetics in rats. *Toxicology* **211**(1-2): 139-148.

Johnson PI, Sutton P, Atchley DS, Koustas E, Lam J, Sen S, Robinson KA, Axelrad DA and Woodruff TJ (2014). The Navigation Guide - evidence-based medicine meets environmental health: systematic review of human evidence for PFOA effects on fetal growth. *Environ Health Perspect* **122**(10): 1028-1039.

Koustas E, Lam J, Sutton P, Johnson PI, Atchley DS, Sen S, Robinson KA, Axelrad DA and Woodruff TJ (2014). The Navigation Guide - evidence-based medicine meets environmental health: systematic review of nonhuman evidence for PFOA effects on fetal growth. *Environ Health Perspect* **122**(10): 1015-1027.

Lau C, Thibodeaux JR, Hanson RG, Narotsky MG, Rogers JM, Lindstrom AB and Strynar MJ (2006). Effects of perfluorooctanoic acid exposure during pregnancy in the mouse. *Toxicol Sci* **90**(2): 510-518.

Lau C, Thibodeaux JR, Hanson RG, Rogers JM, Grey BE, Stanton ME, Butenhoff JL and Stevenson LA (2003). Exposure to perfluorooctane sulfonate during pregnancy in rat and mouse. II: postnatal evaluation. *Toxicol Sci* **74**(2): 382-392.

Lu Y, Luo B, Li J and Dai J (2016). Perfluorooctanoic acid disrupts the blood-testis barrier and activates the TNFalpha/p38 MAPK signaling pathway in vivo and in vitro. *Arch Toxicol* **90**(4): 971-983.

Luebker DJ, Case MT, York RG, Moore JA, Hansen KJ and Butenhoff JL (2005b). Two-generation reproduction and cross-foster studies of perfluorooctanesulfonate (PFOS) in rats. *Toxicology* **215**(1-2): 126-148.

Luebker DJ, Hansen KJ, Bass NM, Butenhoff JL and Seacat AM (2002). Interactions of fluorochemicals with rat liver fatty acid-binding protein. *Toxicology* **176**(3): 175-185.

Luebker DJ, York RG, Hansen KJ, Moore JA and Butenhoff JL (2005a). Neonatal mortality from in utero exposure to perfluorooctanesulfonate (PFOS) in Sprague-Dawley rats: dose-response, and biochemical and pharamacokinetic parameters. *Toxicology* **215**(1-2): 149-169.

Macon MB, Villanueva LR, Tatum-Gibbs K, Zehr RD, Strynar MJ, Stanko JP, White SS, Helfant L and Fenton SE (2011). Prenatal perfluorooctanoic acid exposure in CD-1 mice: low-dose developmental effects and internal dosimetry. *Toxicol Sci* **122**(1): 134-145.

Morken NH, Travlos GS, Wilson RE, Eggesbo M and Longnecker MP (2014). Maternal glomerular filtration rate in pregnancy and fetal size. *PloS one* **9**(7): e101897.

Mylchreest E (2003). Haskell Laboratory for Health and Environmental Sciences. PFOA: Lactational and Placental Transport Pharmacokinetic Study in Rats. Study No. DuPont-13309. December 19, 2003.

Onishchenko N, Fischer C, Wan Ibrahim WN, Negri S, Spulber S, Cottica D and Ceccatelli S (2011). Prenatal exposure to PFOS or PFOA alters motor function in mice in a sex-related manner. *Neurotox Res* **19**(3): 452-461.

Savitz DA, Stein CR, Bartell SM, Elston B, Gong J, Shin HM and Wellenius GA (2012). Perfluorooctanoic acid exposure and pregnancy outcome in a highly exposed community. *Epidemiology* **23**(3): 386-392.

Thibodeaux JR, Hanson RG, Rogers JM, Grey BE, Barbee BD, Richards JH, Butenhoff JL, Stevenson LA and Lau C (2003). Exposure to perfluorooctane sulfonate during pregnancy in rat and mouse. I: maternal and prenatal evaluations. *Toxicol Sci* **74**(2): 369-381.

Tucker DK, Macon MB, Strynar MJ, Dagnino S, Andersen E and Fenton SE (2015). The mammary gland is a sensitive pubertal target in CD-1 and C57Bl/6 mice following perinatal perfluorooctanoic acid (PFOA) exposure. *Reprod Toxicol* **54**: 26-36.

Verner MA, Loccisano AE, Morken NH, Yoon M, Wu H, McDougall R, Maisonet M, Marcus M, Kishi R, Miyashita C, Chen MH, Hsieh WS, Andersen ME, Clewell HJ, 3rd and Longnecker MP (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**(12): 1317-1324.

White SS, Kato K, Jia LT, Basden BJ, Calafat AM, Hines EP, Stanko JP, Wolf CJ, Abbott BD and Fenton SE (2009). Effects of perfluorooctanoic acid on mouse mammary

gland development and differentiation resulting from cross-foster and restricted gestational exposures. *Reprod Toxicol* **27**(3-4): 289-298.

White SS, Stanko JP, Kato K, Calafat AM, Hines EP and Fenton SE (2011). Gestational and chronic low-dose PFOA exposures and mammary gland growth and differentiation in three generations of CD-1 mice. *Environ Health Perspect* **119**(8): 1070-1076.

Wolf CJ, Fenton SE, Schmid JE, Calafat AM, Kuklenyik Z, Bryant XA, Thibodeaux J, Das KP, White SS, Lau CS and Abbott BD (2007). Developmental toxicity of perfluorooctanoic acid in the CD-1 mouse after cross-foster and restricted gestational exposures. *Toxicol Sci* **95**(2): 462-473.

York RG, Kennedy GL, Jr., Olsen GW and Butenhoff JL (2010). Male reproductive system parameters in a two-generation reproduction study of ammonium perfluorooctanoate in rats and human relevance. *Toxicology* **271**(1-2): 64-72.

OEHHA held a public comment period on the Notice of Intent to List from September 16 to November 16, 2016. Comments were submitted by:

1. Arlene Blum, PhD, Executive Director; Avery E. Lindeman, MSc, Deputy Director. Green Science Policy Institute (GSPI)
2. Avinash Kar, Senior Attorney. Natural Resources Defense Council (NRDC)
3. Kevin Dixon
4. Ann G. Grimaldi, Counsel for 3M Company (3M)
5. Tim Shestek, Senior Director. American Chemistry Council (ACC)
6. Hardy B. Poole, Vice President, Regulatory and Technical Affairs. National Council of Textile Organizations (NCTO)

OEHHA reviewed all of the comments and accompanying materials submitted in the context of the regulatory criteria for listing chemicals under the authoritative bodies mechanism in Section 25306.

Comments from the individuals and groups listed above are grouped and numbered by topic, and responses follow below.

1. Comments in Support of Listing

1.1 Comment:

1. Three commenters: GSPI, NRDC, and Kevin Dixon, expressed support for the listing of PFOA and PFOS.

Response:
OEHHA acknowledges the comments.

2. Comments on Formal Identification by US EPA of PFOA and PFOS as Causing Reproductive Toxicity

Two commenters (3M, ACC) objected to the listing of PFOA and PFOS based on the authoritative bodies mechanism because, for the reasons itemized below, they argue that US EPA did not formally identify PFOA and/or PFOS as causing reproductive toxicity.

Comment 2.1
3M:

- "…these documents do not meet the procedural criteria…set forth in Title 27, …Section 25306(d) because EPA did not "formally identify" PFO[A][S][7] as a reproductive toxicant." … The EPA PFO[A][S] Documents neither conclude that PFO[A][S] is a reproductive toxicant, nor indicate that EPA has taken final action…"
- "… EPA acknowledges the advisory is to provide information and is non-enforceable and non-regulatory… EPA admits that they are continuing to monitor the chemicals… EPA has admitted that they are still evaluating PFO[A][S] and that they have not established national primary drinking water regulations for PFO[A][S] because the chemical has not met the minimal requirements for regulation. Therefore, final action, in the usual legal sense, has not taken place"
- "OEHHA relies on EPA PFO[A][S] Documents. However, those materials do not meet the procedural criteria set forth in Section 25306(d). Therefore, PFO[A][S] was not "formally identified" as a reproductive toxicant – and cannot be deemed to be "known to the State" to cause reproductive toxicity" (3M comments: PFOA pp. 1,2,4,9; PFOS pp. 1,2,4,10).

ACC:

- "…EPA documents are non-regulatory technical guidance and subject to revision, and, therefore, do not represent a "conclusion" or "final action" of the Agency, they do not meet the requirements of the authoritative bodies listing mechanism."….[EPA] has not formally identified either PFOA or PFOS as causing reproductive toxicity."
- "According to EPA, however, "EPA's health advisories are *non-enforceable* and *non-regulatory* and provide technical information to state agencies and other public health officials on health effects…"

[7] PFO[A][S]: the letters in brackets are used to indicate that the same comment was made by the commenter for both chemicals, i.e., PFOA and PFOS

Response 2.1:

Proposition 65 provides that "[a] chemical is known to the state to cause … reproductive toxicity within the meaning of this chapter if … a body considered to be authoritative by [the state's qualified] experts has formally identified it as causing … reproductive toxicity".[8] Section 25306(d) of the implementing regulations define what constitutes formal identification by an authoritative body as causing reproductive toxicity:

> "For purposes of this section a chemical is 'formally identified' by an authoritative body when the lead agency determines that:
>
> (1) the chemical has been included on a list of chemicals causing …reproductive toxicity issued by the authoritative body; or is the subject of a report which is published by the authoritative body and which concludes that the chemical causes … reproductive toxicity; or has otherwise been identified as causing … reproductive toxicity by the authoritative body in a document that indicates that such identification is a final action, and"
> (2) the list, report, or document specifically and accurately identifies the chemical, and has been:
>
> (A) Reviewed by an advisory committee in a public meeting, if a public meeting is required, or
> (B) Made subject to public review and comment prior to its issuance, or
> (C) Published by the authoritative body in a publication, such as, but not limited to, the federal register for an authoritative body which is a federal agency, or
> (D) Signed, where required, by the chief administrative officer of the authoritative body or a designee, or
> (E) Adopted as a final rule by the authoritative body, or
> (F) Otherwise set forth in an official document utilized by the authoritative body for regulatory purposes."

As stated earlier, OEHHA has reviewed the conclusions and statements in US EPA documents from 2016 (a,b,c,d) and determined that these conclusions and statements satisfy the requirements of Section 25306(d)(1) in that PFOA and PFOS are the subjects of reports published by the authoritative body that conclude that PFOA and PFOS cause reproductive toxicity, and because PFOA and PFOS have otherwise been identified as causing reproductive toxicity by the authoritative body in documents that indicate that such identification is a final action. The latter criterion is met by the development by US EPA of lifetime drinking water HAs for PFOA (based on a RfD derived from developmental toxicity in mice) and PFOS (based on a RfD derived from developmental toxicity in rats). OEHHA has also determined that each of the documents satisfies one or more of the Section 25306(d)(2) criteria (the report or document has been "published by the authoritative body in a publication, such as, but not limited to, the federal register…" (US EPA, 2016a,b,c,d); "reviewed by an advisory committee in a public meeting, if a public meeting is required" (US EPA, 2016b,d);

[8] Health and Safety Code section 25249.8(b).

"made subject to public review and comment prior to its issuance" (US EPA, 2016b,d)), thus satisfying the formal identification criteria in the Proposition 65 regulations.

The Final Statement of Reasons (FSOR)[9] accompanying Section 25306 specifies the intent of the language incorporated into the regulation. The FSOR states:

> "The Agency recognizes that many organizations which may be considered authoritative do not treat the identification of chemical hazards as a regulatory endpoint. For them, the regulatory endpoint is the adoption of an exposure or discharge limit for a chemical, once it has been determined that the chemical poses a hazard. Hazard identification is simply one step toward the ultimate determination of a regulatory exposure limit, tolerance, level, etc. Documents explaining or noticing the progression of an exposure or discharge limit, tolerance or other standard through the regulatory process will likely identify a chemical as a cancer or reproductive hazard with finality long before the standard is finally adopted. *It is the intention of the Agency that such an identification will be sufficient indication of a 'final action' on the issue of hazard identification to conclude that the chemical has been 'formally identified.'*
>
> The words 'indicates that such identification is a final action' are intended to prevent the listing of chemicals on the basis of preliminary discussions as to whether a chemical should be considered a cancer or a reproductive hazard, or draft documents dealing with the identification of a chemical hazard." (Emphasis added.)

Thus, the FSOR clearly contemplates exactly the situation that is presented here, where an identified authoritative body does not necessarily make determinations in a manner identical to Proposition 65. Many scientific organizations, including US EPA, often are focused on determining endpoints of toxicity and developing what they believe to be appropriate exposure limits or tolerances for a chemical based on those endpoints. When the endpoints identified as providing the appropriately protective exposure limits or tolerances are the result of reproductive toxicity, US EPA must first "identify a chemical as a …. reproductive hazard with finality," i.e., it must determine the "regulatory endpoint" that is at issue, and that "identification will be sufficient indication of a 'final action' on the issue of hazard identification to conclude that the chemical has been 'formally identified'."[10] Thus, under Proposition 65, US EPA's statements of its conclusions about reproductive and developmental harm caused by PFOA and PFOS, and its identification of developmental endpoints as the basis for setting lifetime drinking water HAs for PFOA and PFOS, constitute a hazard identification that represents the "formal identification" of these chemicals as causing reproductive toxicity (developmental endpoint).

[9] Final Statement of Reasons for Section 25306 (formerly 12306), page 25
[10] *Ibid*.

As discussed above, the quoted statements by US EPA that PFOA and PFOS cause developmental toxicity constitute the conclusions of the authoritative body that the chemical causes reproductive toxicity. For example, the statements "The lifetime HA for PFOA is based on effects (reduced ossification in male and female pups and accelerated puberty in male pups) on the developing fetus resulting from exposures that occur during gestation and lactation…", and "Based on the consistency of the response and of the use of the most sensitive endpoint, developmental toxicity, as the critical effect, the RfD of 0.00002 mg/kg/day from Luebker et al. (2005a) is selected as the RfD for PFOS…", are clearly conclusions that these chemicals cause developmental toxicity, even if the term "conclusion" is not explicitly used. Further, US EPA's decision to rely on certain developmental endpoints as a basis for adopting RfDs for PFOA and PFOS as a final action further demonstrates that these two chemicals have been "otherwise identified" by the authoritative body as causing developmental toxicity.

OEHHA has determined that US EPA has concluded that PFOA and PFOS cause developmental toxicity and has "otherwise identified" these chemicals "as causing reproductive [including developmental] toxicity", as those terms are used in the regulations[11]. OEHHA has further determined that the adoption by US EPA of standards (RfDs and drinking water HAs) based on developmental endpoints of toxicity constitutes, for purposes of Proposition 65, identification by US EPA of the chemicals as causing those endpoints. Finally, OEHHA has reviewed the US EPA documents cited above and the scientific literature and record before the US EPA and has concluded that the US EPA's determinations meet the criteria set out in Section 25306 of the regulations.

Comment 2.2:
3M:
The commenter argues that the US EPA documents (US EPA 2016 a,b,c,d) were not subject to peer review and public comment: "EPA did not make the 2016 EPA PFO[A][S] Documents available for public review and comment before they were issued. Nor were the 2016 EPA PFO[A][S] Documents reviewed by an advisory committee" (3M, PFOA, PFOS comments p. 2).

Response 2.2:
The 2016 US EPA documents of PFOA and PFOS resulted from a process started several years before that included peer review and public comment on drafts of the documents. In its published response to public comments, US EPA stated that "the purpose of the peer review was to provide a documented, independent, and critical review of the draft health effects documents, and identify any necessary improvements to the documents prior to being finalized and published"[12]. Among the 20 public

[11] Title 27, Cal Code of Regs, section 25306(d)(1)
[12] US EPA (2016). EPA Response to External Peer Review Comments on EPA Draft Documents: Health Effects Support Document for Perfluorooctanoic Acid (PFOA) and Health Effects Support Document for Perfluorooctane Sulfonate (PFOS) May 2016. Available at: https://www.regulations.gov/document?D=EPA-HQ-OW-2014-0138-0042

comments submitted in 2014 on the US EPA PFOA/PFOS draft documents[13], five were directly from 3M or from consultants on behalf of the 3M Company[14]. US EPA also formed a Peer Review Committee to review the draft documents and recommend revisions. The US EPA posted in its web page:

> "…The U.S. Environmental Protection Agency (EPA) announced a public comment period for the draft documents entitled, "Health Effects Document for Perfluorooctanoic Acid" and "Health Effects Document for Perfluorooctane Sulfonate."
>
> "The draft documents and charge questions were prepared in order to support potential future regulatory evaluations and decisions. EPA is releasing these draft documents for purposes of public comment (scientific views) and peer review."
>
> "All comments received during the public comment period will be made publically available on the EPA docket. In addition, comments will be made available to the peer reviewers for consideration in their review. Oral or written comments will not be accepted during the external peer review meeting, so it is important that all comments be submitted during the public comment period."
>
> "Persons interested in commenting on the documents may submit their comments electronically via www.regulations.gov, by email, by mail, or by hand delivery/courier."[15]

Following this open, public process, and taking into account recommendations made by the Peer Review Committee, the final documents were issued by US EPA in 2016.

Comment 2.3:
3M:
The commenter argues that since developmental effects were not discussed in the draft document on PFOA, and since the draft document on PFOS focused on a different developmental endpoint (neurodevelopmental delay in pups) from a different study, the conclusions in the 2016 US EPA documents should be considered preliminary and that there was no final action by US EPA:

[13] Health Advisories and Health Effects Support documents for PFOA and PFOS, available at: https://www.regulations.gov/docketBrowser?rpp=25&so=ASC&sb=organization&po=0&dct=PS&D=EPA-HQ-OW-2014-0138
[14] Comment submitted by Carol A. Ley, Vice President & Medical Director, 3M Company (PFOS); Comment submitted by A. R. Scialli; Comment submitted by John L. Butenhoff, Senior Scientific Advisor, Medical Department, 3M Company and Donald G. Stump, Vice President, Nonclinical Safety Science, U.S., WIL Research; Comment submitted by Carol A. Ley, Vice President & Medical Director, 3M Company (PFOA); Comment submitted by Gradient on behalf of 3M.
[15] From US EPA web page retrieved March 2017, available at: https://peerreview.versar.com/epa/pfoa/public-comment.html

> "The 2016 EPA PFOA documents raised, for the first time, developmental effects in a regulatory process which denied input… EPA's conclusions are properly deemed "preliminary discussions." Therefore, no "final action" exists to meet this prong of Section 25306(d)(1)." (3M, PFOA comments p. 5).
>
> "In the 2014 proceeding and draft documents, EPA focused on the Butenhoff et al. (2009) study and the developmental endpoint of neurodevelopmental delay in pups. The 2016 EPA PFOS Documents focused on the Luebker et al. (2005) study and the developmental endpoint of decreased pup weight in a regulatory process which denied input… EPA's conclusions are properly deemed "preliminary discussions." Therefore, no "final action" exists to meet this prong of Section 25306(d)(1)." (3M, PFOS comments p. 5).

Response 2.3:

This comment is inaccurate with regard to PFOA, since developmental effects were identified in the 2014 PFOA Draft document[16]:

> "In most animal studies, short-term and chronic exposure to PFOA resulted in an increase in liver weight as at least one of the critical effects. Co-occurring effects in these studies included changes in spleen, thymus, liver **and/or developmental endpoints**. " (emphasis added).
>
> "U.S. EPA has selected 0.00002 mg/kg/day as the RfD for PFOA based on the consistency of the response and with recognition of the use of liver weight as a common denominator for loss of homeostasis **and protection against co-occurring adverse effects**. This value is the outcome for modeled serum values from three rat studies and one mouse study. **In two of the rat studies, liver effects were accompanied by developmental effects"** (emphasis added).

US EPA also discussed the available data on PFOA and reproductive and developmental outcomes from studies in humans in the 2014 PFOA Draft document.

For these reasons, 3M is not correct in saying that "developmental effects" for PFOA were raised "for the first time" in the US EPA 2016 document.

As noted by the commenter with regard to PFOS, developmental effects were identified together with liver weight in the 2014 US EPA PFOS draft[17] as the basis for establishing an RfD. In the draft document, US EPA stated:

> "Based on the consistency of the response and **with recognition of the use of developmental toxicity as the sensitive endpoint**, the 0.00003 mg/kg/day outcome is selected as the RfD for PFOS. This value is the outcome for the

[16] US EPA (2014b). Health Effects Document for Perfluorooctanoic Acid (PFOA)
[17] US EPA (2014a). Health Effects Document for Perfluorooctane Sulfonate (PFOS) February 2014

> modeled rat serum for developmental neurotoxicity (Butenhoff et al., 2009) and supported by the slightly higher 0.00005 and 0.00006 mg/kg/day values for increases in liver weight and other developmental effects. Thus, co-occurring critical endpoints are protected by the chosen RfD." (emphasis added) (US EPA 2014a, pp. 5-26)

Decreased pup birthweight in rats identified in two studies by Luebker et al. in 2005 were among the other developmental effects identified by US EPA in that document.

In the 2016 Drinking Water Health Advisory for PFOS, US EPA stated that:

> "The RfD of 0.00002 mg/kg/day calculated from HED average serum values from Luebker et al. (2005b) was selected. This RfD is derived from reduced pup body weight in the two-generation study in rats. The POD for the derivation of the RfD for PFOS is the HED of 0.00051 mg/kg/day that corresponds to a NOAEL that represents approximately 30% of steady-state concentration. A UF of 30 (10 UFH and 3 UFA) was applied to the HED NOAEL to derive an RfD of 0.00002 mg/kg/day. This is supported by the 0.00002 mg/kg/day value derived from the LOAEL for the same effect in the one-generation Luebker et al. (2005a) study and the 0.00003 mg/kg/day value for neonatal neurodevelopmental effects in the Butenhoff et al. (2009) study."

Thus, the final action by US EPA in identifying the appropriate RfD for PFOS based on developmental toxicity was based on the same body of data as identified in the 2014 US EPA PFOS draft, and differed only minimally from the RfD based on the Butenhoff et al. (2009) study which was the subject of comments submitted to US EPA on the PFOS document by Gradient on behalf of 3M[18].

3. Comments that the human and animal data cited by US EPA do not meet the requirements of Title 27, Cal Code of Regs., section 25306(g)

Several comments by 3M questioned whether the sufficiency of evidence criteria in Section 25306(g) were met.

Comment 3.1:
"…the proposed listing does not meet the substantive criteria for listing reproductive toxicants under the authoritative bodies mechanism set forth in Section 25306(g)." "This section requires that studies in humans indicate that there is a causal relationship…, or that studies in experimental animals provide sufficient data to support the biological plausibility of an association between adverse reproductive effects in humans and the toxic agent."

[18] Comment submitted by Gradient on behalf of 3M (p.8-10), available at: https://www.regulations.gov/document?D=EPA-HQ-OW-2014-0138-0015

“EPA PFO[A][S] Documents merely summarize associations, not causal relationships supported by sufficient evidence, in human epidemiology studies between PFO[A][S] and reproductive toxicity. …. Developmental observations in laboratory rodents… are not appropriate for hazard assessment of the developmental toxicity in humans for various reasons, including differences in mode of action across species.”

In a section titled “Studies In Humans Indicate That There Is No Causal Relationship Between The Chemical And Reproductive Toxicity”, the commenter states for PFOS that:
“EPA has been unable to establish a causal relationship between PFOS and reproductive toxicity in humans. EPA issued its LHA for PFOS based on a RfD derived from a developmental toxicity study in rats. The PFOS RfDs are based on laboratory experiments on animals. RfDs can also be based on human data, where such data are adequate. The peer review and public comments include suggestions to use human data in the RfD development. In the peer review, ‘[a]ll reviewers generally agreed that the rationales provided for the exclusion of the human data were not actually appropriate’ and opinions varied regarding whether or not human data would be useful. In particular, Matthew P. Longnecker and William L. Hayton of the peer review panel expressed support for the use of human health data.15 In its public comments, Gradient (2014) noted that ‘[t]here are many well-conducted PFOA and PFOS human studies available. Occupational cohorts have been followed since the 1970s with exposures well above those of the general population with no evidence of adverse effects. Overall, these studies do not provide evidence of adverse effects in humans.’ The peer review and public comments on the 2014 draft had pointed out that the draft could benefit from considering published epidemiology data.”

In the corresponding section in the PFOA comments, the commenter states that:
“EPA has been unable to establish a causal relationship between PFOA and reproductive toxicity in humans. EPA issued its LHA for PFOA based on a RfD derived from a developmental toxicity study in mice. The PFOA RfDs are based on laboratory experiments on animals. RfDs can also be based on human data, where such data are adequate. The peer review and public comments include suggestions to use human data in the RfD development. In the peer review, ‘[a]ll reviewers generally agreed that the rationales provided for the exclusion of the human data were not actually appropriate” and opinions varied regarding whether or not human data would be useful. In particular, Matthew P. Longnecker and William L. Hayton of the peer review panel expressed support for the use of human health data.12 Public comments submitted by Gradient in April 2014 noted that “[t]here are many well-conducted PFOA and PFOS human studies available. Occupational cohorts have been followed since the 1970s with exposures well above those of the general population with no evidence of adverse effects. Overall, these studies do not provide evidence of adverse effects in humans.’ The peer review and public comments on the 2014 draft had pointed out that the draft could benefit from considering published epidemiology data.”
(3M, PFOA, PFOS comments pp. 1,2,3,10).

Response 3.1:
The regulations governing the Proposition 65 authoritative bodies listing mechanism provide the following criteria for "as causing reproductive toxicity" in Section 25306(g):

> (g) "For purposes of this section, "as causing reproductive toxicity" means that either of the following criteria has been satisfied:
> (1) Studies in humans indicate that there is a causal relationship between the chemical and reproductive toxicity, *or*
> (2) Studies in experimental animals indicate that there are sufficient data, taking into account the adequacy of the experimental design and other parameters such as, but not limited to, route of administration, frequency and duration of exposure, numbers of test animals, choice of species, choice of dosage levels, and consideration of maternal toxicity, indicating that an association between adverse reproductive effects in humans and the toxic agent in question is biologically plausible."[19]

However, the chemical is not listed if scientifically valid data which were not considered by the authoritative body clearly establish that the sufficiency of evidence criteria were not met (Section 25306(h)).

OEHHA has reviewed the numerous animal studies cited (see Table 1 above) or study descriptions provided by US EPA (2016a,b,c,d) in support of its formal identification of PFOA and PFOS as causing reproductive toxicity (developmental endpoint), and has determined that these data satisfy the criteria in Section 25306(g)(2),As required by the regulation, OEHHA has determined that an association between adverse reproductive effects in humans and the toxic agent in question is biologically plausible. This is consistent with US EPA's conclusion that adverse reproductive effects are possible in humans.

The title statement that "Studies In Humans Indicate That There Is No Causal Relationship Between The Chemical And Reproductive Toxicity" is not consistent with the text that follows. The statement that "EPA has been unable to establish a causal relationship between PFO[A][S] and reproductive toxicity in humans" is accurate, but is not equivalent to a determination that there is no causal relationship. If the data in humans had shown conclusively that PFO[A][S] causes reproductive toxicity, a RfD could have been based on those human data. In this case, where data in humans clearly demonstrate neither reproductive toxicity nor a lack of reproductive toxicity for the chemicals, US EPA followed the accepted procedure of basing the RfD on clear effects in animal models.

Comment 3.2:
The commenter states that the co-occurrence of maternal toxicity could explain the developmental toxicity effects observed in several studies of PFOA and PFOS:

[19] Title 27, Cal Code of Regs., section 25306(g)

> "…rodent studies referenced by EPA provide strong evidence that many of the developmental outcomes reported are the consequence of maternal toxicity as opposed to developmental toxicity of PFO[A][S]. Additionally, PFO[A][S] levels in rodents were several orders of magnitude higher than PFO[A][S] levels in the general human population and are, therefore, of limited relevance to humans." "The EPA PFO[A][S] Documents do not properly address these issues." (3M comments: PFOA pp. 2,4 and Exhibit A, pp.1,6,15,17; PFOS, pp. 2,4,11 and Exhibit A, pp. 1,6,14,15)

Response 3.2:

The commenter describes co-occurrence of maternal and developmental toxicity in several studies of PFOA and PFOS, but provides no explanation for the conclusion that "many of the developmental outcomes reported are the consequence of maternal toxicity as opposed to developmental toxicity". It is a generally accepted scientific principle in developmental toxicology that the co-occurrence of maternal and developmental toxicity is not, in and of itself, a basis for discounting adverse developmental effects. This is clearly stated by US EPA in the Agency's Guidelines for Developmental Toxicity Risk Assessment:

> "Agents that produce developmental toxicity at a dose that is not toxic to the maternal animal are especially of concern because the developing organism is affected but toxicity is not apparent in the adult. However, the more common situation is when adverse developmental effects are produced only at doses that cause minimal maternal toxicity; in these cases, the developmental effects are still considered to represent developmental toxicity and should not be discounted as being secondary to maternal toxicity. At doses causing excessive maternal toxicity (that is, significantly greater than the minimal toxic dose [defined elsewhere in the guidelines to be marginal but significantly reduced body weight, reduced weight gain, or specific organ toxicity, and at the most no more than 10% mortality]), information on developmental effects may be difficult to interpret and of limited value. Current information is inadequate to assume that developmental effects at maternally toxic doses result only from maternal toxicity; rather, when the LOAEL is the same for the adult and developing organisms, it may simply indicate that both are sensitive to that dose level. Moreover, whether developmental effects are secondary to maternal toxicity or not, the maternal effects may be reversible while effects on the offspring may be permanent." (US EPA, 1991)[20].

The same scientific principle has been adopted by other regulatory bodies and is supported by publications in peer-reviewed scientific literature. Examples include:

> "Developmental effects, which occur even in the presence of maternal toxicity are considered to be evidence of developmental toxicity, unless it can be

[20] US EPA (1991). Guidelines for Developmental Toxicity Risk Assessment, EPA/600/FR-91/001, December 1991, Available at https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=23162

> unequivocally demonstrated on a case by case basis that the developmental effects are secondary to maternal toxicity." (United Nations Economic Commission for Europe Globally Harmonized System of Classification and Labeling of Chemicals, 2011, Section 3.7.2.4.2)[21]
>
> "There currently remains a considerable burden of proof lying with the investigator if developmental effects are suspected to be secondary to altered maternal physiology. This burden is justifiable in that maternal toxicity is not always associated with developmental toxicity. Thus a cause and effect relationship between the two is not automatic." (Carney, 1997)[22]

OEHHA has reviewed the sufficiency of evidence for PFOA and PFOS, including "consideration of maternal toxicity" according to these generally accepted scientific principles, and has determined that the maternal toxicity occurring in these cases is not sufficient to discount the chemicals' effects on the fetus.

OEHHA is required by the regulations and case law to accept the scientific judgment of the authoritative body unless there is factual information which demonstrates that the regulatory criteria have not been met.[23]

The comments provide no factual support for the commenter's assertions that levels of PFOA and PFOS in rodents were several orders of magnitude higher than PFOA or PFOS levels in the general human population and were therefore of limited relevance to humans, and that the US EPA documents did not properly address this issue. It is a well established scientific principle that levels of exposure to a chemical that cause adverse developmental effects in experimental animals may be substantially higher than the levels of exposure to that chemical that cause comparable effects in humans. This position was clearly stated by US EPA in the Agency's Guidelines for Developmental Toxicity Risk Assessment:

> "[A]gents causing human developmental toxicity in almost all cases were found to produce effects in experimental animal studies and, in at least one species tested, types of effects similar to those in humans were generally seen. This information provides a strong basis for the use of animal data in conducting human health risk assessments. On the other hand, a number of agents found to cause developmental toxicity in experimental animal studies have not shown clear evidence of hazard in humans, but the available human data are often too limited to evaluate a cause-and-effect relationship. The comparison of dose-

[21] UN (2011). Economic Commission for Europe Globally Harmonized System of Classification and Labeling of Chemicals, Part 3, Health Hazards, section 3.7.2.4.2. p. 176, also available online at: http://www.unece.org/fileadmin/DAM/trans/danger/publi/ghs/ghs_rev04/English/ST-SG-AC10-30-Rev4e.pdf

[22] Carney EW (1997). Maternal Physiological Disruption. In: *Drug Toxicity in Embryonic Development I: Advances in Understanding Mechanisms of Birth Defects: Morphogenesis and Processes at Risk*. Kavlock, RJ and Daston, GP (Eds.). Berlin, Heidelberg: Springer Berlin Heidelberg, pp. 573-594.

[23] Section 25306(f); Exxon Mobil Corporation v OEHHA (2009)169 Cal.App.4th 1264

response relationships is hampered by differences in route, timing, and duration of exposure. When careful comparisons have been done taking these factors into account, the minimally effective dose for the most sensitive animal species was generally higher than that for humans, usually within 10-fold of the human effective dose, but sometimes was 100 times or more higher."[24]

Comment 3.3:
The commenter states that "with respect to PFOA, findings from animal studies do not indicate that an association between PFOA and reproductive effects is biologically plausible. Reasons include evidence of maternal toxicity in the rodent studies, the presence of species-specific differences in response due to differences in nuclear receptors between humans and rodents, and the large difference between exposure levels in rodents treated with PFOA and human exposures to PFOA." (3M PFOA p. 10).

The commenter also states that "mode-of-action data suggest that rodents are not the most appropriate species for the hazard assessment of PFOA[S] toxicity in humans" and that "[t]here are many well-conducted PFOA and PFOS human studies available" (3M PFO[A][S] p. 2 and 10, respectively)

Response 3.3:
The issue of maternal toxicity in rodent studies was discussed in the response to comment 3.2.

Although the basis for the Proposition 65 listings is the developmental toxicity of PFO[A][S], the comments on nuclear receptors as the mode of action (MOA) focus on non-reproductive effects:

> "In toxicology studies, liver is the primary target organ when the laboratory animals were exposed to PFOS and mechanistic research has shown that many intermediary metabolic effects can be explained by the activation of xenosensor nuclear receptors such as PPARα, constitutive androstane receptor (CAR), and pregnane X receptor (PXR) in the liver (Elcombe et al. 2012a; Elcombe et al. 2012b)" (see 3M PFOS comments Exhibit A p. 15)

The commenter also notes that developmental toxicity occurred even when PPARα activation was eliminated as a possible mechanism of action, and that the role of other nuclear receptors in developmental toxicity of PFO[A][S] is unknown:

> "Even though study [sic] with PFOS using PPARα knockout mice did not completely attenuate the developmental effects compared to the wildtype, the % neonatal survival did improve (Abbott et al. 2009). The roles of other nuclear

[24] US EPA (1991). Guidelines for Developmental Toxicity Risk Assessment, EPA/600/FR-91/001, December 1991, Available at https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=23162

> receptors such as CAR and PXR and developmental toxicity in rodents is not known at present time." (see 3M PFOS comments Exhibit A p. 15)

US EPA considered the potential MOA of PFOA through nuclear receptors, especially the PPARα receptor, and determined that this may not be the only MOA pathway for PFOA and that the specific MOA for developmental toxicity effects is not yet clear:

> "The MOA for decreased pup body weight observed in the animal studies is unknown (Butenhoff et al. 2004a; White et al. 2009; Wolf et al. 2007).[25] The observed effects on birth weight in animals are supported by evidence of an association between PFOA and low birth weight in humans (Johnson et al. 2014). Receptor-activated changes in metabolism, hormonal perturbations, and impeded intercellular communication could play a role in this effect" (US EPA 2016a, p. 43)

US EPA also stated that PFOA activates the PPARα receptor in both rodents and humans, and noted that the response through the PPARα receptor is greater in rodents than in humans, citing two studies by Wolf et al. (2008b and 2012)[26]:

> "…the mouse PPARα was more reactive than the human PPARα." (US EPA 2016b, p. 3-139)".

Thus, although data suggest that there is a different sensitivity in PPARα activation by PFOA between human and rodent receptors, this issue was considered by US EPA and no data were identified that would satisfy the regulatory criterion that "…scientifically valid data which were not considered by the authoritative body clearly establish that the chemical does not satisfy the criteria of subsection (g)"[27].

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[25] Butenhoff JL, Kennedy GL, Jr., Frame SR, O'Connor JC and York RG (2004a). The reproductive toxicology of ammonium perfluorooctanoate (APFO) in the rat. *Toxicology* **196**(1-2): 95-116.

White SS, Kato K, Jia LT, Basden BJ, Calafat AM, Hines EP, Stanko JP, Wolf CJ, Abbott BD and Fenton SE (2009). Effects of perfluorooctanoic acid on mouse mammary gland development and differentiation resulting from cross-foster and restricted gestational exposures. *Reprod Toxicol* **27**(3-4): 289-298.

White SS, Kato K, Jia LT, Basden BJ, Calafat AM, Hines EP, Stanko JP, Wolf CJ, Abbott BD and Fenton SE (2009). Effects of perfluorooctanoic acid on mouse mammary gland development and differentiation resulting from cross-foster and restricted gestational exposures. *Reprod Toxicol* **27**(3-4): 289-298.

Wolf CJ, Fenton SE, Schmid JE, Calafat AM, Kuklenyik Z, Bryant XA, Thibodeaux J, Das KP, White SS, Lau CS and Abbott BD (2007). Developmental toxicity of perfluorooctanoic acid in the CD-1 mouse after cross-foster and restricted gestational exposures. *Toxicol Sci* **95**(2): 462-473.

[26] Wolf CJ, Takacs ML, Schmid JE, Lau C and Abbott BD (2008b). Activation of mouse and human peroxisome proliferator-activated receptor alpha by perfluoroalkyl acids of different functional groups and chain lengths. *Toxicol Sci* **106**(1): 162-171.

Wolf CJ, Schmid JE, Lau C and Abbott BD (2012). Activation of mouse and human peroxisome proliferator-activated receptor-alpha (PPARalpha) by perfluoroalkyl acids (PFAAs): further investigation of C4-C12 compounds. *Reprod Toxicol* **33**(4): 546-551.

[27] Section 25306(h)

Regarding the comment that there are many well-conducted PFOA and PFOS human studies available, OEHHA notes that human data were taken into consideration by US EPA in its formal identification of PFO[A][S] as causing developmental toxicity:

> "The human data demonstrate an association between PFOA exposure and endpoints, including effects on serum lipids, antibody responses, fetal growth and development, and the liver. They provide support for identification of hazards of PFOA exposure." (US EPA 2016a, p. 58)
>
> "The human data demonstrate an association between PFOS exposure and endpoints including effects on serum lipids, antibody responses, the thyroid, and fetal growth and development. The data provide support for identification of hazards of PFOS exposure." (US EPA 2016c, p. 52)
>
> "The observed effects on birth weight in animals are supported by evidence of an association between PFOA and low birth weight in humans (Johnson et al. 2014)[28]." (US EPA 2016a, p. 43)
>
> "An inverse association between maternal PFOA (measured during the second or third trimester) on cord blood PFOA concentrations and birth weight was seen in several studies. It has been suggested that low glomerular filtration rate (GFR) can impact fetal birth weight (Morken et al. 2014)[29]. Pharmacokinetic (PK) analyses have shown, however, that in individuals with low GFR, there are increased levels of serum PFOA and lower birth weights. Thus, the impact on body weight is likely due to a combination of the low GFR and the serum PFOA." (US EPA 2016b, p. ES-2)
>
> "A low GFR would diminish the removal of PFOS from serum for excretion by the kidney, thus increasing the serum PFOS levels." (US EPA 2016d, p. 3-11)
>
> "When low GFR was accounted for in the model simulations, the reduction in birth weight associated with increasing serum PFOS was less than that found by the author's meta-analysis of the same data. This finding suggests that a portion of the association between prenatal PFOS and birth weight could be confounded by maternal GFR differences within the populations studied." (US EPA 2016d, p. 3-21)

[28] Johnson PI, Sutton P, Atchley DS, Koustas E, Lam J, Sen S, Robinson KA, Axelrad DA and Woodruff TJ (2014). The Navigation Guide - evidence-based medicine meets environmental health: systematic review of human evidence for PFOA effects on fetal growth. *Environ Health Perspect* **122**(10): 1028-1039.

[29] Morken NH, Travlos GS, Wilson RE, Eggesbo M and Longnecker MP (2014). Maternal glomerular filtration rate in pregnancy and fetal size. *PloS one* **9**(7): e101897.

Comment 3.4:
3M asserts that there is an absence of data that supports reproductive toxicity. (3M comments, PFOA, p. 11 and Exhibit A p. 1; PFOS p. 2, and Exhibit A p. 1).

Response 3.4:
The numerous relevant studies considered by US EPA that support formal identification of PFOA and PFOS as causing reproductive toxicity are identified above in Table 1. OEHHA also reviewed the citations identified by the commenter. Of the 99 studies cited in the comments by 3M, 39 were not cited in any of the four US EPA documents that provide formal identification of PFO[A][S] as causing developmental toxicity[30]. These 39 studies are listed in Table 2. For the reasons explained in that table, the studies do not constitute "scientifically valid data which were not considered by the authoritative body [and] clearly establish that the chemical does not satisfy the criteria of subsection (g), paragraph (1) or subsection (g), paragraph (2)"[31].

Table 2. Studies identified by 3M and not considered by US EPA

Reference	Comments
1. Abbott BD (2015). Developmental Toxicity In: Toxicological effects ofperfluoroalkyl and polyfluoroalkyl substances In: *Toxicological Effects of Perfluoroalkyl and Polyfluoroalkyl Substances*. DeWitt, JC: Springer, pp. 203-218.	This chapter is a review and does not provide original data relevant to identification of developmental toxicity. As illustrated by the following quotations, the review is in general agreement with US EPA's identification of PFO[A][S] as causing developmental toxicity. "This chapter provides an overview of the developmental toxicity resulting from exposure to perfluorinated alkyl acids (PFAAs). The majority of studies of PFAA-induced developmental toxicity have examined effects of perfluorooctane sulfonate (PFOS) or perfluorooctanoic acid (PFOA)". "In general, among the PFAAs that do produce developmental toxicity in one or more laboratory species, prenatal PFAA exposure in teratology studies typically does not result in major malformations and significant findings are often limited to the higher exposure levels." "The role of peroxisome proliferator activated receptor-alpha (PPARα) in mediating developmental effects is discussed, including insights from genetically modified mice, PPARα knockout mice,

[30] See footnote 6 above
[31] Section 25306(h)

	and mice expressing the human PPARα gene. Pharmacokinetic issues are relevant to selecting an appropriate animal model for developmental studies and regarding the influence of rapid clearance on manifestation of developmental toxicity. Whether or not a particular PFAA will cause developmental toxicity depends on levels and timing of fetal exposure and is influenced by species and gender specific pharmacokinetic characteristics that impact exposure of the conceptus throughout gestation" "The expression and activation of PPARα is necessary for mediating developmental effects of PFOA…but the early postnatal deaths caused by exposure to PFOS were not dependent on expression of PPARα"
2. Bach CC, Bech BH, Brix N, Nohr EA, Bonde JP and Henriksen TB (2015). Perfluoroalkyl and polyfluoroalkyl substances and human fetal growth: a systematic review. *Crit Rev Toxicol* **45**(1): 53-67.	This review used systematic literature searches to summarize the evidence of an association between exposure to PFOS and PFOA, and human fetal growth. Again, the conclusions of the review are in general agreement with US EPA's identification of PFO[A][S] as causing developmental toxicity. "Animal studies indicate that maternal PFAS exposure is associated with reduced fetal growth. However, the results of human studies are inconsistent." *Results*: "Fourteen studies were eligible. In utero PFOA exposure was associated with decreased measures of continuous birth weight in all studies"… "the magnitude of the association differed and many results were statistically insignificant." PFOS exposure was associated with decreased birth weight in some studies, while others found no association. *"Conclusions:* Higher PFOS and PFOA concentrations were associated with decreased average birth weight in most studies, but only some results were statistically significant." It should be noted that 10 of the 14 studies used in this review were considered by US EPA in at least one of the 2016 documents.

3. Bastos Sales L, Kamstra JH, Cenijn PH, van Rijt LS, Hamers T and Legler J (2013). Effects of endocrine disrupting chemicals on in vitro global DNA methylation and adipocyte differentiation. *Toxicol In Vitro* **27**(6): 1634-1643.	This paper reports the results of an *in vitro* test of PFOA and PFOS (and other chemicals) to investigate the effects of EDCs (endocrine disrupting chemicals) with putative obesogenic properties on global DNA methylation and adipocyte differentiation in vitro. This mechanistic study provides no data relevant to reproductive toxicology.
4. Braissant O, Foufelle F, Scotto C, Dauca M and Wahli W (1996). Differential expression of peroxisome proliferator-activated receptors (PPARs): tissue distribution of PPAR-alpha, -beta, and -gamma in the adult rat. *Endocrinology* **137**(1): 354-366.	This study investigated differential expression of PPAR nuclear receptors in various tissues in the rat. The PPARs are expressed moderately in all reproductive tissues analyzed. The study notes that "the analysis of the developmental expression of PPARs will be of particular interest and will probably reveal specific and transient involvements of these receptors in many developmental and differentiation processes", but itself provides no data relevant to developmental toxicity.
5. Case MT, York RG and Christian MS (2001). Rat and rabbit oral developmental toxicology studies with two perfluorinated compounds. *Int J Toxicol* **20**(2): 101-109.	This study investigated the developmental toxicity of PFOS at dose levels of 0, 0.1, 1.0, 2.5, and 3.75 mg/kg/day by gastric gavage on GD 6-20 in rabbit. Maternal toxicity (reduced body weight gain and feed consumption) was reported at doses of 1 and 2.5 mg/kg/day (no data for 3.75). It was associated with increased abortions and reduced fetal weights. The authors stated that there were no external gross, soft tissue, or skeletal fetal malformations found. They concluded that PFOS is not a selective developmental toxicant in rabbits. However, the reported data showed: • Reduced body weight gain and **not** feed consumption in dams • The reduced body weight gain was significant at GD 7-21 and not at GD 21-29 (cesarean time) • Reduced fetal weight in the 2-highest dose groups. • Delays in ossification (sternebrae, hyoid, metacarpal, and pubic bones) in the rabbit fetuses of the highest two dose groups. These findings are consistent with US EPA's identification of developmental toxicity caused by PFOS in rodents.

6. Dixon D, Reed CE, Moore AB, Gibbs-Flournoy EA, Hines EP, Wallace EA, Stanko JP, Lu Y, Jefferson WN, Newbold RR and Fenton SE (2012). Histopathologic changes in the uterus, cervix and vagina of immature CD-1 mice exposed to low doses of perfluorooctanoic acid (PFOA) in a uterotrophic assay. *Reprod Toxicol* **33**(4): 506-512.	This study investigated estrogenic and antiestrogenic potential of PFOA in an immature mouse uterotrophic assay and by histologic evaluation of the uterus, cervix and vagina following treatment. Female offspring of CD-1 dams were weaned at 18 days old and assigned to groups of equal weight, and received 0, 0.01, 0.1, or 1 mg PFOA/kg BW/d by gavage with or without estradiol (E2), 500 µg/kg/d from post-natal day (PND)18-20 (n=8/treatment/block). At 24 hr after the third dose (PND 21), uteri were removed and weighed. Absolute and relative uterine weights were significantly increased in the 0.01 mg/kg PFOA only group. Characteristic estrogenic changes were present in all E2-treated mice; however, they were minimally visible in the 0.01 mg/kg PFOA only mice. These data suggest that at a low dose PFOA produces minimal histopathologic changes in the reproductive tract of immature female mice, and does not antagonize the cellular effects of E2. These results do not conflict with US EPA's identification of developmental toxicity caused by PFOA in rodents.
7. D'Orazio G, Asensio-Ramos M, Hernandez-Borges J, Fanali S and Rodriguez-Delgado MA (2014). Estrogenic compounds determination in water samples by dispersive liquid-liquid microextraction and micellar electrokinetic chromatography coupled to mass spectrometry. *J Chromatogr A* **1344**: 109-121.	This study provided technical data on how to analyze 12 estrogenic compounds by chromatography and mass spectrometry (MS) using ammoniumperfluorooctanoate (APFO) as a volatile BGE surfactant. This paper is not relevant to the developmental toxicity of PFOA or PFOS.
8. Du G, Huang H, Hu J, Qin Y, Wu D, Song L, Xia Y and Wang X (2013). Endocrine-related effects of perfluorooctanoic acid (PFOA) in zebrafish, H295R steroidogenesis and receptor reporter gene assays. *Chemosphere* **91**(8): 1099-1106.	This study investigated endocrine-related effects of PFOA. Lower dose effects of PFOA on development and endocrine-related gene expression were assessed in a short-term zebrafish assay in vivo. Effects of PFOA on estrogen, androgen, and thyroid hormone receptor (ER, AR, and TR respectively) activities were also assessed using reporter gene assays in a human cell line capable of steroidogenesis (H295R).

	Exposure of zebrafish embryos to PFOA resulted in higher expression of esr1, hhex and pax. In H295R cells, PFOA increased E2 production and decreased T production, and altered the expression of major steroidogenic genes and the regulator gene SF-1. The information in this paper does not conflict with US EPA's formal identification of PFOA and PFOS as causing developmental toxicity.
9. Elcombe CR, Elcombe BM, Foster JR, Chang SC, Ehresman DJ, Noker PE and Butenhoff JL (2012). Evaluation of hepatic and thyroid responses in male Sprague Dawley rats for up to eighty-four days following seven days of dietary exposure to potassium perfluorooctanesulfonate. *Toxicology* **293**(1-3): 30-40.	This study evaluated the persistence/resolution of K+PFOS-induced, liver-related effects in male Sprague Dawley rats following a 7-day dietary exposure to K+PFOS at 20 or 100 ppm. This paper is not relevant to the developmental toxicity of PFOA or PFOS.
10. Fei C, Weinberg CR and Olsen J (2012). Commentary: perfluorinated chemicals and time to pregnancy: a link based on reverse causation? *Epidemiology* **23**(2): 264-266.	This study investigated time to pregnancy following exposure to perfluorinated chemicals (PFC) and found a positive association between maternal PFC exposure and subfecundity (defined as time to pregnancy $\geq$12 months) in parous women, but no association in nulliparous women. This paper investigated a female reproductive toxicity effect and is not relevant to the developmental toxicity of PFOA or PFOS.
11. Feng X, Wang X, Cao X, Xia Y, Zhou R and Chen L (2015). Chronic Exposure of Female Mice to an Environmental Level of Perfluorooctane Sulfonate Suppresses Estrogen Synthesis Through Reduced Histone H3K14 Acetylation of the StAR Promoter Leading to Deficits in Follicular Development and Ovulation. *Toxicol Sci* **148**(2): 368-379.	This study investigated the effect of PFOS exposure on estrogen synthesis and subsequent female reproductive effects. This paper investigated female reproductive toxicity effects and is not relevant to the developmental toxicity of PFOA or PFOS.

12. Gao Y, Li X and Guo LH (2013). Assessment of estrogenic activity of perfluoroalkyl acids based on ligand-induced conformation state of human estrogen receptor. *Environ Sci Technol* **47**(1): 634-641.	This study investigated effects of PFOA and PFOS on estrogen receptor (ER) activation: "[PFOS] and [PFOA] were found to be ER agonists" but are weak binders of ER. "Overall, the two 8-carbon PFAAs were assessed as weak agonists of [human ERα] and are of potential concern." The information in this paper does not conflict with US EPA's formal identification of PFO[A][S] as causing developmental toxicity.
13. Gonzalez FJ and Shah YM (2008). PPARalpha: mechanism of species differences and hepatocarcinogenesis of peroxisome proliferators. *Toxicology* **246**(1): 2-8.	This study investigated the mode of action for hepatotoxicity including cancer in rodents and suggested that there are differences in PPARα activation in rodent and humans. This paper is not relevant to the developmental toxicity of PFOA or PFOS.
14. Gortner EG (1980). Oral teratology study ofFC-95 in rats. Experiment Number 0680TR0008. USEPA Public Docket, AR-226-0016.	This developmental toxicity study of oral administration of PFOS (as identified by the commenter, identified in the study report as FC-95) at doses of 10, 5 and 1 mg/kg/day to pregnant Sprague-Dawley rats during days 6 through 15 of gestation (period of organogenesis) resulted in fetuses with teratogenic changes in the lens of the eye. The teratogenic effect was a developmental eye abnormality which appeared to be an arrest in development of the primary lens fibers forming the embryonal lens nucleus, followed by secondary aberrations of the secondary lens fibers of the fetal nucleus. The lens abnormality occurred in all dose groups, but the proportion of fetuses with the lens changes was significantly higher than the control group only in the 10 mg/kg/day group. In addition, the number of viable fetuses in the high dose group was 23% lower than controls, although this was reported not to be statistically significant. The findings in this study are consistent with US EPA's identification of developmental toxicity caused by PFOS in rodents.
15. Gortner EG (1981). US EPA Administrative Record 226 226-0463	In this developmental toxicity study, ammonium PFOA (as identified by the commenter, identified in the study report as T-2998CoC) administered at doses of 0, 150, 50, 1.5, or 0.05 mg/kg/day to

Oral teratology study of T-2998CoC in rats. Experiment Number 0681TR0110, Safety Evaluation Laboratory and Riker Laboratories, Inc., St. Paul, MN.	pregnant Sprague-Dawley rats during days 6 through 15 of gestation, was not embryotoxic and did not affect the ovaries or reproductive tract contents of the dams. This study of the ammonium salt of PFOA may represent a PFOA exposure after dissociation to PFOA in vivo. The absence of reported developmental toxicity findings in this study does not clearly establish that PFOA does not satisfy the sufficiency of evidence criteria in Section 25306(g)(2).
16. Gortner EG (1982). USEPA Public Docket AR-226-0465. Oral teratology study of T-3141 CoC in rabbits. Experiment Number 0681 TB0398. Safety Evaluation Laboratory and Riker Laboratories.	This developmental toxicity study of ammonium PFOA (as identified by the commenter, identified in the study report as T-3141CoC) in pregnant New Zealand White/Minikin rabbits did not provide evidence of embryotoxicity or effects on the ovaries or reproductive tract contents of the does. US EPA noted that "female rats, male hamsters, and both genders of rabbits appear to be good excreters [of PFOA] based on their response to a radiolabeled dose of 10 mg/kg. Most of the dosed material is excreted within 24 hours after dosing.… The long half-lives in humans suggest that their excretion rates are more like mice or male rats." (EPA 2016b, Table 2-2, p. 2-27). Consistent with this observation, US EPA based its formal identification of PFOA on studies in rodents and not rabbits. The absence of reported developmental toxicity findings in this study does not clearly establish that PFOA does not satisfy the sufficiency of evidence criteria in Section 25306(g)(2).
17. Guizhen Du JH, Ling Song, Xinru Wang and Di Wu (2012). Neonatal Exposure to Perfluorooctane Sulfonate (PFOS) and Perfluorooctanoic Acid (PFOA) Causes Early Puberty Onset and Elevated Postpubertal Hormone Levels in Female Rats. The Endocrine Society's 94th Annual Meeting and Expo, June 23–26. Houston, TX	This study investigated the effects of PFOS and PFOA on female reproductive maturation following postnatal exposure on days 1-5. This study reported female reproductive toxicity of PFOA and PFOS resulting from postnatal exposure. These results do not conflict with US EPA's identification of developmental toxicity caused by PFOA and PFOS in rodents.

18. Helal I, Fick-Brosnahan GM, Reed-Gitomer B and Schrier RW (2012). Glomerular hyperfiltration: definitions, mechanisms and clinical implications. *Nat Rev Nephrol* **8**(5): 293-300.	This paper reviewed renal physiology and concluded that "A physiological state of glomerular hyperfiltration occurs during pregnancy". The issue of glomerular filtration during pregnancy and its relevance to PFOA and PFOS was considered by US EPA (see response to comment 3.6).
19. Ishibashi H, Ishida H, Matsuoka M, Tominaga N and Arizono K (2007). Estrogenic effects of fluorotelomer alcohols for human estrogen receptor isoforms alpha and beta in vitro. *Biol Pharm Bull* **30**(7): 1358-1359.	This study investigated the effects of fluorotelomer alcohols on estrogen receptors in vitro and found "no estrogenic effects of perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA) for these hERs [human estrogen receptor]." The information in this paper does not conflict with US EPA's formal identification of PFO[A][S] as causing developmental toxicity.
20. Kraugerud M, Zimmer KE, Ropstad E and Verhaegen S (2011). Perfluorinated compounds differentially affect steroidogenesis and viability in the human adrenocortical carcinoma (H295R) in vitro cell assay. *Toxicol Lett* **205**(1): 62-68.	This study was an in vitro assessment of the effects of PFOS on steroid metabolism in a human adrenocortical carcinoma cell line, and is not relevant to the developmental toxicity of PFOS.
21. Lake BG (2009). Species differences in the hepatic effects of inducers of CYP2B and CYP4A subfamily forms: relationship to rodent liver tumour formation. *Xenobiotica; the fate of foreign compounds in biological systems* **39**(8): 582-596.	This review of the hepatic effects of CYP2B and CYP4A inducers with respect to their established modes of action for rodent liver tumor formation provides no information on the developmental toxicity of PFOA or PFOS.
22. Lam J, Koustas E, Sutton P, Johnson PI, Atchley DS, Sen S, Robinson KA, Axelrad DA and Woodruff TJ (2014). The Navigation Guide - evidence-based medicine meets environmental health: integration of animal and human	This study used the Navigation Guide systematic review methodology and 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.

evidence for PFOA effects on fetal growth. *Environ Health Perspect* **122**(10): 1040-1051.	The conclusions in this paper are consistent with US EPA's formal identification of PFOA as causing developmental toxicity.
23. Lau C, Butenhoff JL and Rogers JM (2004). The developmental toxicity of perfluoroalkyl acids and their derivatives. *Toxicol Appl Pharmacol* **198**(2): 231-241.	This review paper by US EPA provides a brief overview of the perfluoroalkyl chemicals and a summary of the available information on the developmental toxicity of the eight-carbon compounds, PFOS and PFOA. "Although the teratological potentials of some of these chemicals had been studied in the past and the findings were generally unremarkable, results from recent postnatal studies on developmental and reproductive indices have prompted consideration of their relevance to human health risk. Based on current understanding of the developmental effects of PFOS and PFOA in rodents, several avenues of research are suggested that would further support the risk assessment of these perfluorinated organic chemicals." The findings of US EPA in this review are superseded by the more recent findings in the 2016 reports[32] that provide formal identification of PFOA and PFOS as causing developmental toxicity.
24. Lau C (2012). Perfluoroalkyl acids: recent research highlights. *Reprod Toxicol* **33**(4): 405-409.	This is an editorial paper that reviews data on reproductive toxicity of PFAAs (including PFOA and PFOS). Regarding data supporting developmental effects in animal models, the paper states that: "In a developmental toxicity study, Dixon et al. describe the histopathologic changes in the reproductive tract of weanling female mice after exposure to low doses of PFOA (0.01–1 mg/kg/d) in utero. These changes are rather small, though significant" "Evidence to support the endocrine disrupting potential of PFOA is perhaps stronger in a paper presented by Zhao et al., who examined PFOA effects on mammary gland development in the mouse. These investigators report that PFOA

[32] See footnote 6

	significantly inhibited mammary growth in Balb/c and C57Bl/6 mice, although the former strain appeared to be more sensitive to PFOA insults…. In this mouse model, PFOA also delayed onset of puberty, decreased ovarian steroid hormone synthesis, and reduced expression of estrogen or progesterone-related mammary growth factors…" The conclusions in this paper are consistent with US EPA's formal identification of PFOA and PFOS as causing developmental toxicity.
25. Lee SS, Pineau T, Drago J, Lee EJ, Owens JW, Kroetz DL, Fernandez-Salguero PM, Westphal H and Gonzalez FJ (1995). Targeted disruption of the alpha isoform of the peroxisome proliferator-activated receptor gene in mice results in abolishment of the pleiotropic effects of peroxisome proliferators. *Mol Cell Biol* **15**(6): 3012-3022.	The authors of this study reported that they had demonstrated that mice lacking expression of PPARα protein do not respond to the prototypical peroxisome proliferators, clofibrate and Wy-14,643, and lack detectable hepatomegaly, proliferation of peroxisomes, or induction of the mRNA encoding the peroxisomal and microsomal lipid-metabolizing enzymes. This mechanistic study provides no information on the developmental toxicity of PFOA or PFOS.
26. Longnecker MP (2006). Pharmacokinetic variability and the miracle of modern analytical chemistry. *Epidemiology* **17**(4): 350-351.	This paper provided a commentary on PCBs and diabetes and contained no information on PFOA or PFOS or developmental or reproductive toxicity.
27. Lopez-Doval S, Salgado R, Fernandez-Perez B and Lafuente A (2015). Possible role of serotonin and neuropeptide Y on the disruption of the reproductive axis activity by perfluorooctane sulfonate. *Toxicol Lett* **233**(2): 138-147.	This study evaluated the possible role of serotonin and neuropeptide Y (NPY) on the disruption of the hypothalamic–pituitary–testicular (HPT) axis induced by PFOS in adult male rats. This paper is not relevant to the developmental toxicity of PFOA or PFOS.
28. Olsen GW, Church TR, Miller JP, Burris JM, Hansen KJ, Lundberg JK, Armitage JB, Herron RM, Medhdizadehkashi Z, Nobiletti JB,	This study evaluated blood concentrations of PFOS and other fluorochemicals from 645 adult donor serum samples from six American Red Cross blood collection centers.

O'Neill EM, Mandel JH and Zobel LR (2003). Perfluorooctanesulfonate and other fluorochemicals in the serum of American Red Cross adult blood donors. *Environ Health Perspect* **111**(16): 1892-1901.	This paper is not relevant to the developmental toxicity of PFOA or PFOS.
29. Olsen GW, Mair DC, Church TR, Ellefson ME, Reagen WK, Boyd TM, Herron RM, Medhdizadehkashi Z, Nobiletti JB, Rios JA, Butenhoff JL and Zobel LR (2008). Decline in perfluorooctanesulfonate and other polyfluoroalkyl chemicals in American Red Cross adult blood donors, 2000-2006. *Environ Sci Technol* **42**(13): 4989-4995.	This study evaluated blood concentrations of PFOS and other polyfluoroalkyl chemicals in American Red Cross adult blood donors between 2000 – 2006. This paper is not relevant to the developmental toxicity of PFOA or PFOS.
30. Olsen GW, Lange CC, Ellefson ME, Mair DC, Church TR, Goldberg CL, Herron RM, Medhdizadehkashi Z, Nobiletti JB, Rios JA, Reagen WK and Zobel LR (2012). Temporal trends of perfluoroalkyl concentrations in American Red Cross adult blood donors, 2000-2010. *Environ Sci Technol* **46**(11): 6330-6338.	This study evaluated blood concentrations of eleven perfluorinated alkyl acids (PFAAs) including PFOS and PFOA in plasma from a total of 600 American Red Cross adult blood donors from six locations in 2010, to assess changes between 2000 – 2010. This paper is not relevant to the developmental toxicity of PFOA or PFOS.
31. Pereiro N, Moyano R, Blanco A and Lafuente A (2014). Regulation of corticosterone secretion is modified by PFOS exposure at different levels of the hypothalamic-pituitary-adrenal axis in adult male rats. *Toxicol Lett* **230**(2): 252-262.	This study evaluated the effects of PFOS exposure on the regulation of corticosterone secretion in adrenal and pituitary glands and at the hypothalamic level in adult male rats. PFOS exposure induces a global inhibition of hypothalamic–pituitary–adrenal (HPA) axis activity, and small morphological changes were observed in adrenal zona fasciculata cells. This paper is not relevant to the developmental toxicity of PFOA or PFOS.
32. Ross J, Plummer SM, Rode A, Scheer N, Bower CC, Vogel O,	This study investigated the mechanism of hepatomegaly induced in mice by phenobarbital and

Henderson CJ, Wolf CR and Elcombe CR (2010). Human constitutive androstane receptor (CAR) and pregnane X receptor (PXR) support the hypertrophic but not the hyperplastic response to the murine nongenotoxic hepatocarcinogens phenobarbital and chlordane in vivo. *Toxicol Sci* **116**(2): 452-466.	chlordane and provides no data on PFOA or PFOS, or any data on developmental toxicity.
33. Sonthithai P, Suriyo T, Thiantanawat A, Watcharasit P, Ruchirawat M and Satayavivad J (2016). Perfluorinated chemicals, PFOS and PFOA, enhance the estrogenic effects of 17beta-estradiol in T47D human breast cancer cells. *J Appl Toxicol* **36**(6): 790-801.	This was an in vitro study on the estrogenic effect of PFOA and PFOS on human breast cancer cells. This mechanistic study provides no information on the developmental toxicity of PFOA or PFOS.
34. Wang F, Liu W, Jin Y, Dai J, Zhao H, Xie Q, Liu X, Yu W and Ma J (2011). Interaction of PFOS and BDE-47 co-exposure on thyroid hormone levels and TH-related gene and protein expression in developing rat brains. *Toxicol Sci* **121**(2): 279-291.	This study investigated the developmental toxicity effects of PFOS, particularly via disruption of thyroid hormone (TH) function. Adult female Wistar rats were exposed to 3.2 and 32 mg/kg of PFOS in their diet from GD 1 to PND 14. Serum and brain tissues from both male and female neonates were collected on PNDs 1, 7, and 14 to examine TH-regulated gene and protein expression. Results: 1. On an equimolar basis, PFOS affected serum total triiodothyronine and total thyroxine differently in adults and offspring; 2. There were region-specific and exposure- and time-dependent alterations in TH concentrations and tested gene and protein expression levels; “results suggest a complex TH-mediated gene and protein response to PFOS exposure that seems little related to TH homeostasis… The underlying mechanisms remain uncertain but seem to involve more actions than just TH-regulated pathway.” The information in this paper does not conflict with US EPA’s formal identification of PFOA and PFOS as causing developmental toxicity.

35. Wens B, De Boever P, Verbeke M, Hollanders K and Schoeters G (2013). Cultured human peripheral blood mononuclear cells alter their gene expression when challenged with endocrine-disrupting chemicals. *Toxicology* **303**: 17-24.	This in vitro study investigated the effects of endocrine disrupting chemicals, including PFOA, on gene expression of mononuclear cells. This paper is not relevant to the developmental toxicity of PFOA.
36. White SS, Fenton SE and Hines EP (2011). Endocrine disrupting properties of perfluorooctanoic acid. *J Steroid Biochem Mol Biol* **127**(1-2): 16-26.	This paper reviews the existing literature on the known health effects of PFOA in animal models, focusing on sensitive developmental periods and also presents epidemiologic health data, with the caveat that these studies largely address only associations between adult exposures and outcomes, rarely focusing on endocrine-specific endpoints, susceptible subpopulations, or windows of sensitivity. The authors conclude that further research in these areas is needed. This review does not provide new data not considered by the authoritative body, but instead provides the authors' interpretation of existing data.
37. Wu H, Yoon M, Verner MA, Xue J, Luo M, Andersen ME, Longnecker MP and Clewell HJ, 3rd (2015). Can the observed association between serum perfluoroalkyl substances and delayed menarche be explained on the basis of puberty-related changes in physiology and pharmacokinetics? *Environ Int* **82**: 61-68.	This study assessed how much of the epidemiologic association between PFAS and delayed menarche can be explained by the correlation of growth and maturation with PFAS body burden. This paper investigated the association between PFAS body burden and a female reproductive toxicity effect and is not relevant to the developmental toxicity of PFOA or PFOS.
38. Yao PL, Ehresman DJ, Rae JM, Chang SC, Frame SR, Butenhoff JL, Kennedy GL and Peters JM (2014). Comparative in vivo and in vitro analysis of possible estrogenic effects of perfluorooctanoic acid. *Toxicology* **326**: 62-73.	This study investigated whether PFOA activates mouse or human estrogen receptor, and concluded that the data indicate that it does not. The information in this paper does not conflict with US EPA's formal identification of PFOA as causing developmental toxicity.

39. Zhao Y, Tan YS, Haslam SZ and Yang C (2010). Perfluorooctanoic acid effects on steroid hormone and growth factor levels mediate stimulation of peripubertal mammary gland development in C57BL/6 mice. *Toxicol Sci* **115**(1): 214-224.	This study investigated the mechanism of action of PFOA on peripubertal mammary gland development in mice. This paper is not relevant to the developmental toxicity of PFOA.

Comment 3.5:

3M resubmitted comments originally sent to OEHHA in 2015 pursuant to the prioritization of PFOA and PFOS for possible listing consideration in the future under the state's qualified experts mechanism. 3M stated that their 2015 comments "demonstrate that existing studies do not support the listing of PFO[A][S] under the authoritative bodies mechanism". In the resubmitted comments, the commenters identify three points regarding the human data that they believe do not support a conclusion that PFOA and PFOS cause reproductive toxicity:

> ***"Human Data:*** …We illustrate three examples that OEHHA will encounter as it ascertains whether there was "proper control of confounding factors." These examples are: a) PFO(A)(S) and time to pregnancy; b) PFO(A)(S) and birth weight; and c) PFO(A)(S) and delayed onset to menarche."(3M PFOA, PFOS p. 11; PFOA Exhibit A: pp. 6-14; PFOS comments, Exhibit A: pp. 6-13)."

a) PFO(A)(S) and time to pregnancy (TTP): "…women with longer TTP will have longer intervals of time between given births and therefore may reaccumulate higher PFO(A)(S) levels prior to the next pregnancy compared to women with shorter TTP. This would result in longer TTP measurements associated with higher PFO(A)(S) levels, but the direction of the causality would be backwards; it would be the longer time between births (including the TTP) that resulted in higher PFO(A)(S) concentrations."

b) PFOA and birth weight. "A set of 4 papers was published in *Environmental Health Perspectives* in October 2014 that provided a "comprehensive and transparent assessment on the nonhuman mammalian and human evidence of whether fetal growth, in particular birth weight at term, was inversely associated with exposure to PFOA or its salts" (Johnson et al. 2014; Koustas et al. 2014; Lam et al. 2014; Woodruff and Sutton 2014)."

c) PFO(A)(S) delayed onset to menarche: "PFOS (girls only) was associated with median delays of three to six months based on quartile analyses."

The commenter suggests that this association "may be due, in part, to dilution (through growth of adolescents) and excretion (via menstruation)."

Response 3.5:
In regard to point a above, US EPA concluded that PFOA and PFOS cause developmental toxicity. Time to pregnancy is a metric of female reproductive toxicity, which is not the endpoint on which the proposed listing of PFOA and PFOS is based, so the comment is not relevant to the proposed action.

In regard to point b, OEHHA reviewed the studies cited by 3M (Johnson et al. 2014; Koustas et al. 2014; Lam et al. 2014; Woodruff and Sutton 2014)[33]. All of these studies investigate the effects of PFOA on birth weight, and all except that by Lam et al. were considered by US EPA. The US EPA documents note that:

> "Meta-analyses were conducted to determine whether developmental exposure to PFOA was associated with fetal growth effects in animals (Koustas et al. 2014)[34]. Eight animal studies identified in the published literature met the criteria of the Navigation Guide systematic review methodology as developed and published by Woodruff and Sutton (2014)[35] for inclusion in the analyses. The animal data sets included mouse gavage studies with maternal PFOA doses from 0.01 to 20 mg/kg/day. The results from the meta-analysis showed that a 1 mg/kg/day increase in PFOA dose was associated with a -0.023 g (95% CI [-0.029, -0.016]) difference in pup birth weight." (US EPA 2016a, p.35; US EPA 2016b, p.3-42).

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[33] Johnson PI, Sutton P, Atchley DS, Koustas E, Lam J, Sen S, Robinson KA, Axelrad DA and Woodruff TJ (2014). The Navigation Guide - evidence-based medicine meets environmental health: systematic review of human evidence for PFOA effects on fetal growth. *Environ Health Perspect* **122**(10): 1028-1039.

Koustas E, Lam J, Sutton P, Johnson PI, Atchley DS, Sen S, Robinson KA, Axelrad DA and Woodruff TJ (2014). The Navigation Guide - evidence-based medicine meets environmental health: systematic review of nonhuman evidence for PFOA effects on fetal growth. *Environ Health Perspect* **122**(10): 1015-1027.

Lam J, Koustas E, Sutton P, Johnson PI, Atchley DS, Sen S, Robinson KA, Axelrad DA and Woodruff TJ (2014). The Navigation Guide - evidence-based medicine meets environmental health: integration of animal and human evidence for PFOA effects on fetal growth. *Environ Health Perspect* **122**(10): 1040-1051.

Woodruff TJ and Sutton P (2014). The Navigation Guide systematic review methodology: a rigorous and transparent method for translating environmental health science into better health outcomes. *Environ Health Perspect* **122**(10): 1007-1014.

[34] Koustas E, Lam J, Sutton P, Johnson PI, Atchley DS, Sen S, Robinson KA, Axelrad DA and Woodruff TJ (2014). The Navigation Guide - evidence-based medicine meets environmental health: systematic review of nonhuman evidence for PFOA effects on fetal growth. *Environ Health Perspect* **122**(10): 1015-1027.

[35] Woodruff TJ and Sutton P (2014). The Navigation Guide systematic review methodology: a rigorous and transparent method for translating environmental health science into better health outcomes. *Environ Health Perspect* **122**(10): 1007-1014.

Thus, the conclusions of these reviews are consistent with US EPA's identification of developmental toxicity of PFOA.

US EPA did not consider the publication by Lam et al. (2014). This study integrated available data from human and animal studies to determine the strength of the evidence for developmental effects of PFOA specifically on fetal growth, but did not provide any new empirical data on this outcome. The authors state in their conclusion that: "…Developmental exposure to PFOA adversely affects human health based on sufficient evidence of decreased fetal growth in both human and nonhuman mammalian species." It is therefore clear that the conclusions from this review are also consistent with US EPA's conclusion that PFOA causes developmental toxicity.

Regarding point c, although delayed menarche resulting from prenatal exposure is an endpoint relevant to identification of developmental toxicity under Proposition 65, it is not among the endpoints that formed the basis for formal identification of developmental toxicity of PFOS by US EPA. This comment is therefore not relevant to the proposed action.

Comment 3.6:

The commenter argued that there could be relevant confounders that could explain the observed reproductive toxicity of PFO[A][S], concluding that "In summary, epidemiological associations between maternal PFO[A][S] and birth weight are confounded by GFR" (3M, PFOA comments Exhibit A pp. 11-14, PFOS comments Exhibit A pp. 9,11,13).

> "Whitworth et al. (2012) suggested that, because GFR [glomerular filtration rate] is diminished in lower weight infants, this could lead to less renal elimination of PFOA".
>
> "Vesterinen et al. (2015) concluded 'the strength of the evidence of an association between fetal growth and GFR was not classifiable based on the low quality and indeterminate direction of effect of human studies and the small number and size of non-human mammalian studies which were of low quality with indeterminate direction of effect.' 'Upon their review of the literature, and concluding there was likely a true association between maternal GFR and birth weight, Verner et al. (2015) modified an existing physiologically based pharmacokinetic model (PBPK) of pregnancy and lactation and PFOA (Loccisano et al. 2012; Loccisano et al. 2013) to address how much of the PFOA and birth weight association might be attributable to GFR. Verner et al. concluded a substantial proportion of the association between maternal PFOA and birth weight may be attributable to confounding by GFR.'" "…Verner et al. reported a reduced association with birth weight in six of these seven studies. The summary metaanalysis estimate for the seven studies was -5.0 g (95% CI -8.9, -1.1) birth weight per ng/mL increase in PFOS."

"…Whitworth et al. (2012) suggested that, because GFR is diminished in lower weight infants, this could lead to less renal elimination of PFOS; thus raising the question whether the epidemiologic studies that assessed a relationship between birth weight and PFOS were confounded by not considering for GFR."

"Verner et al. (2015) had the distinct advantage of having a one critically important paper (Morken et al. 2014) that was not available to Vesterinen et al.[36] (i.e., not yet published) and they concluded "there is reason to believe a true association exists between maternal GFR during pregnancy and birth weight."

Response 3.6:

US EPA specifically evaluated the potential influence of altered GFR on developmental outcome for both PFOA (US EPA 2016a and b) [37] and PFOS (US EPA 2016d)[38], including consideration of the studies cited in the comments submitted by 3M. US EPA concluded that:

"Although some uncertainty exists in the interpretation of the observed association between PFOA and birth weight given the potential impact of low GFR, the available information indicate that the association between PFOA exposure and birth weight cannot be ruled out. In humans with low GFR (which includes women with pregnancy-induced hypertension or preeclampsia) the impact on body weight is likely due to a combination of the low GFR and the serum PFOA." (US EPA 2016a, p.42)

"While there is some uncertainty in the interpretation of the observed association between PFOS and birth weight given the potential impact of low GFR, the available information indicates that the association between PFOS exposure and birth weight for the general population cannot be ruled out." (US EPA 2016d, pp. 3-29)

Although the commenter's interpretation of the data differs from that of US EPA, OEHHA cannot substitute its scientific judgment for that of the authoritative body[39], nor can OEHHA substitute the judgment of other scientists for that of the authoritative body.

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[36] In the comments on PFOA, 3M refers in this statement to Lam et al., but it appears from the preceding text that the intention was also to refer to Vesterinen et al. as was done in the comments on PFOS.

[37] US EPA (2016a). Drinking Water Health Advisory for Perfluorooctanoic Acid (PFOA). EPA Document Number: 822-R-16-005. May 2016. Available at: https://www.epa.gov/sites/production/files/2016-05/documents/pfoa_health_advisory_final-plain.pdf US EPA (2016b). Health Effects Support Document for Perfluorooctanoic Acid (PFOA). EPA Document Number: 822-R-16-003. May 2016. Available at: https://www.epa.gov/sites/production/files/2016-05/documents/pfoa_hesd_final-plain.pdf

[38] US EPA (2016d). Health Effects Support Document for Perfluorooctane Sulfonate (PFOS). EPA Document Number: 822-R-16-002. May 2016. Available at: https://www.epa.gov/sites/production/files/2016-05/documents/hesd_pfos_final-plain.pdf

[39] Final Statement of Reasons, Title 22 [now 27], Cal. Code of Regs., sections 12701 [now section 25701], *et seq*., No Significant Risk Levels, sections 12801 [now 25801], *et seq*., No Observable Effect Levels. Available at: https://oehha.ca.gov/media/downloads/crnr/art78fsrjune1989.pdf .

Comment 3.7:
The commenter argues that the effect of PFOS on birth weight is not relevant due to the lack of consensus among the studies:

> "Based on a qualitative literature review of PFOS and birth weight, Bach et al. (2015) identified 8 epidemiologic studies (Apelberg et al. 2007; Chen et al. 2012; Darrow et al. 2013; Fei et al. 2007; Hamm et al. 2010; Inoue et al. 2004; Maisonet et al. 2012; Washino et al. 2009[40]) that examined PFOS as a continuous variable. All eight studies were from general populations. Six of these studies reported an association between PFOS and lower birth weight (Apelberg et al. 2007, Chen et al. 2012, Darrow et al. 2013, Fei et al. 2007, Maisonet et al. 2012, Washino et al. 2009) but only three (Washino et al. 2009, Chen et al. 2012, Maisonet et al. 2012) were statistically significant. Bach et al. concluded PFOS exposure was associated with decreased average birth weight but the impact on public health was not clear." (3M, PFOS comments Exhibit A p.9).

Response 3.7:
US EPA did not include the review by Bach et al. (2015)[41] in its PFO[A][S] reports (US EPA 2016a,b,c,d). However, the eight epidemiologic studies cited by the commenter as being reviewed by Bach et al (2015) were reviewed by US EPA in those documents. The review by Bach et al. therefore does not constitute "scientifically valid data which were not considered by the authoritative body". Regarding this endpoint, US EPA states:

> "Although three studies were null (Fei et al. 2008b; Hamm et al. 2010; Monroy et al. 2008)[42], birth weight deficits ranging 29–149 grams were detected in five studies (Apelberg et al. 2007; Chen et al. 2015; Darrow et al. 2013; Maisonet et al. 2012; Washino et al. 2009)[43]." (US EPA 2016d).

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[40] The commenter did not include the reference for Washino et al. 2009

[41] Bach CC, Bech BH, Brix N, Nohr EA, Bonde JP and Henriksen TB (2015). Perfluoroalkyl and polyfluoroalkyl substances and human fetal growth: a systematic review. *Crit Rev Toxicol* **45**(1): 53-67.

[42] Fei C, McLaughlin JK, Lipworth L and Olsen J (2008). Prenatal exposure to perfluorooctanoate (PFOA) and perfluorooctanesulfonate (PFOS) and maternally reported developmental milestones in infancy. *Environ Health Perspect* **116**(10): 1391-1395.

Hamm MP, Cherry NM, Chan E, Martin JW and Burstyn I (2010). Maternal exposure to perfluorinated acids and fetal growth. *J Expo Sci Environ Epidemiol* **20**(7): 589-597.

Monroy R, Morrison K, Teo K, Atkinson S, Kubwabo C, Stewart B and Foster WG (2008). Serum levels of perfluoroalkyl compounds in human maternal and umbilical cord blood samples. *Environ Res* **108**(1): 56-62.

[43] Apelberg BJ, Witter FR, Herbstman JB, Calafat AM, Halden RU, Needham LL and Goldman LR (2007). Cord serum concentrations of perfluorooctane sulfonate (PFOS) and perfluorooctanoate (PFOA) in relation to weight and size at birth. *Environ Health Perspect* **115**(11): 1670-1676.

Chen MH, Ha EH, Wen TW, Su YN, Lien GW, Chen CY, Chen PC and Hsieh WS (2012). Perfluorinated compounds in umbilical cord blood and adverse birth outcomes. *PloS one* **7**(8): e42474.

As noted in the response to Comment 3.6, OEHHA cannot substitute its scientific judgment for that of the authoritative body, nor can OEHHA substitute the judgment of other scientists for that of the authoritative body. However, in this case, the conclusion in the review by Bach et al 2015 was that "[w]hile high PFOA and PFOS exposures in pregnancy were associated with lower average birth weights in human newborns in most studies, not all results were statistically significant. The existing data is insufficient to confirm or reject a certain association between PFASs exposure and fetal growth." OEHHA notes that this conclusion does not differ from that reached by US EPA, and that based on the entire body of human and animal evidence US EPA concluded that PFOA and PFOS cause developmental toxicity.

4. Other Comments

Comment 4.1:
The commenter (3M) notes that in "October 2015, 3M submitted comments to OEHHA as OEHHA was pursuing listing PFO[A][S] as reproductive toxicants under the SQE [State's Qualified Experts] Mechanism" and states that those comments explain that the serum concentrations of PFOA[S] in the US general population have been steadily declining in the last decade, and PFOS can no longer be manufactured, imported or used without US EPA's permission in the United States. "Based on the Centers for Disease Control and Prevention ("CDCs") National Health and Nutrition Examination Survey (NHANES) data, mean blood levels of [PFOA in the general population have declined by approximately 60% between 1999-2000 and 2011-2012] [PFOS in the general population have declined by approximately 79% between 1999-2000 and 2011-2012]." (3M, PFOA and PFOS comments p. 2)

Response 4.1:
The comments of October 2015 were submitted to OEHHA during the process for prioritizing and selecting chemicals for consideration by the state's qualified experts (SQE). PFOA and PFOS are not currently under consideration for listing by that mechanism. Actual or potential human exposures to candidate chemicals are considered in *prioritizing* chemicals for consideration by the SQE, but are not a consideration in determining whether chemicals meet the criteria for addition to the Proposition 65 list by the SQE or any other listing mechanism. When a chemical is

Darrow LA, Stein CR and Steenland K (2013). Serum perfluorooctanoic acid and perfluorooctane sulfonate concentrations in relation to birth outcomes in the Mid-Ohio Valley, 2005-2010. *Environ Health Perspect* **121**(10): 1207-1213.

Maisonet M, Terrell ML, McGeehin MA, Christensen KY, Holmes A, Calafat AM and Marcus M (2012). Maternal concentrations of polyfluoroalkyl compounds during pregnancy and fetal and postnatal growth in British girls. *Environ Health Perspect* **120**(10): 1432-1437.

Washino N, Saijo Y, Sasaki S, Kato S, Ban S, Konishi K, Ito R, Nakata A, Iwasaki Y, Saito K, Nakazawa H and Kishi R (2009). Correlations between prenatal exposure to perfluorinated chemicals and reduced fetal growth. *Environ Health Perspect* **117**(4): 660-667.

listed, OEHHA can consider human exposures to the chemical in determining whether the warning requirement and discharge prohibition of the statute are applicable[44].

Comment 4.2:
3M notes that OEHHA prioritized PFO[A][S] for possible listing under the SQE mechanism and recommends that OEHHA proceed with the already-initiated SQE process and refrain from listing PFO[A][S] under the authoritative bodies mechanism. The commenter asserts that by doing so, OEHHA will preserve the integrity of its own regulatory process. The commenter's recommendation is based on the assertion that OEHHA cannot reasonably conclude that US EPA "formally identified" PFO[A][S] as a reproductive toxicant. (3M, PFOA comments p. 11, PFOS comments pp. 11-12).

Response 4.2:
Although PFO[A][S] were prioritized for consideration by the SQE, such prioritization does not require OEHHA to bring the chemicals forward for consideration for listing through that mechanism. OEHHA has concluded that the criteria for listing through the authoritative bodies mechanism have been met, for the reasons presented in the Notice of Intent to List PFOA and PFOS[45] and discussed in detail in the present document. Where a chemical meets the criteria for consideration under both the authoritative bodies and state's qualified experts mechanisms, the law does not require the use of any specific mechanism. OEHHA generally lists chemicals through whatever mechanism is the most efficient. If the criteria for listing through the authoritative bodies mechanism are met, that mechanism is usually more efficient than bringing a chemical before the SQE, which is more time and labor intensive. Since the criteria for listing through the authoritative bodies mechanism are met for PFOA and PFOS, that mechanism is being used in this instance.

Comment 4.3:
The National Council of Textile Organizations requests information regarding whether OEHHA's possible listing pertains only to PFOA and PFOS. The commenter also states the belief that the routes of exposure to PFOA and PFOS for textile consumer products is quite different from the ingestion of drinking water and is limited primarily to dermal absorption and inhalation. The commenter expresses concern about analyzing for PFOA and PFOS at parts per trillion levels cited for drinking water and notes that safe levels of exposure could be significantly different from drinking water limits. The commenter requests that dermal absorption and inhalation exposure routes be addressed separately from ingestion. The commenter also expresses concern that lack of "safe harbor" numbers could lead to excessive warnings.

The commenter expresses concern that after-market treatments with PFOA or PFOS and other potentially harmful chemicals may affect levels of PFOA and PFOS in incoming water supplies, which in turn may affect test results on finished products. The commenter requests OEHHA to provide information on qualified testing labs that can

[44] Health and Safety Code section 25249.8(b)
[45] See footnote 1.

properly conduct the necessary analysis on textiles, and on specific details of the required testing procedures.

Finally, the commenter notes several ongoing efforts to reduce exposures to PFOA and PFOS and encourages OEHHA to review the proposed limits for textile fabrics recommended by the European Chemical Agency's Registration, Evaluation, Authorization and Restriction of Chemicals (REACH) regulation in Europe. (NCTO, pp. 1-3).

Response 4.3:
Only PFOA and PFOS were identified in the Notice of Intent to List[46], and only those two chemicals are the subject of the present action.

US EPA did not limit its formal identification of PFO[A][S] to any specific route(s) of exposure. Therefore, this listing is not specific to any route of exposure. The US EPA drinking water HA values cited in the Notice of Intent to List PFOA and PFOS are relevant to listing only because they were established on the basis of developmental toxicity. Exposures that trigger the warning requirement or discharge prohibition under Proposition 65 are determined under the statutory provision exempting an "exposure [that] will have no observable effect assuming exposure at one thousand (1,000) times the level in question".[47] The applicability of the warning requirement and the discharge prohibition may vary by route of exposure. Depending on the availability of relevant data, the maximum allowable dose levels (MADLs) that meet the statutory provision can be different for each route of exposure. OEHHA generally makes an effort to propose MADLs within one year of listing a chemical. OEHHA will consider all relevant information in its efforts to establish MADLs for PFOA and PFOS.

In the absence of such "safe harbor" numbers established by OEHHA, however, it remains the responsibility of the party causing the exposure to determine if a warning is necessary or a discharge is prohibited. Regulations concerning how to calculate these levels can be found in Section 25803.

OEHHA does not identify or endorse laboratories that can provide testing for PFOA or PFOS; it is the responsibility of the party causing the potential exposure to these chemicals to appropriately determine the anticipated level of exposure in order to determine whether a warning is required. Similarly, OEHHA does not determine the appropriate testing protocols.

[46] See footnote 1.
[47] Health and Safety Code section 25249.10