



January 14, 2022

Dr. Suhair Shallal, Designated Federal Officer (DFO)
Science Advisory Board
Environmental Protection Agency
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Submitted via email: shallal.suhair@epa.gov

Re: Comments on Meeting Materials for Public Meetings of the Science Advisory Board Per- and Polyfluoroalkyl Substances (PFAS) Review Panel

The 3M Company (“3M”) writes to follow up on a submission by the California Environmental Protection Agency’s Office of Environmental Health Hazard Assessment (“OEHHA”) in response to the meeting materials published in advance of the Environmental Protection Agency (“EPA” or the “Agency”) Science Advisory Board’s (“SAB”) public meetings to review data and analysis prepared by EPA as it considers setting Maximum Contaminant Level Goals (“MCLGs”) and National Primary Drinking Water Regulations (“NPDWR”) for Perfluorooctanoic Acid (“PFOA”) and Perfluorooctanesulfonic Acid (“PFOS”).

OEHHA’s submission references Proposed Public Health Goals (PHGs) in California, as well as an OEHHA document entitled “Evidence on the Carcinogenicity of Perfluorooctane Sulfonic Acid (PFOS) and Its Salts and Transformation and Degradation Precursors.” OEHHA did not identify how these documents are relevant to the SAB’s evaluation of the draft MCLG documents, but if SAB intends to consider these documents, it should be aware that extensive technical comments were submitted by 3M and others regarding the science supporting OEHHA’s conclusions. 3M has attached here its comments on both documents in case SAB intends to consider the OEHHA documents.

3M still intends to provide supplemental technical comments on the meeting materials, as indicated in 3M’s December 30, 2021 submission. Thank you for your consideration.



November 8, 2021

VIA ELECTRONIC SUBMISSION

Dr. Thomas Mack, Chair
Carcinogen Identification Committee Members
California Environmental Protection Agency
Office of Environmental Health Hazard Assessment
Carcinogen Identification Committee

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

3M Comments on Hazard Identification Materials and Potential Listing of Perfluorooctane Sulfonate (PFOS) and Its Salts and Transformation and Degradation Precursors

Dear Dr. Mack, CIC Members, and Dr. Sandy:

The 3M Company (3M) appreciates the opportunity to respond to the California Environmental Protection Agency's Office of Environmental Health Hazard Assessment's (OEHHA) request for public comment on the Notice of Availability of Hazard Identification Materials for Perfluorooctane Sulfonate (PFOS) and Its Salts and Transformation and Degradation Precursors (PFOS and its salts and precursors). As a science-based company with substantial experience, expertise and product stewardship of PFOS and related chemistries, 3M remains well positioned to contribute to the upcoming meeting of the Carcinogen Identification Committee (CIC) on the potential listing of PFOS and its salts and precursors.

As a preliminary matter, 3M reiterates and emphasizes that the body of scientific evidence amassed to date has failed to show that PFOS causes adverse health effects in humans at the currently low and declining exposure levels found in the blood. 3M specifically incorporates by reference the scientific data cited and discussed in the company's May 10, 2021 and October 19, 2020 comment submissions relating to PFOS and its salts and precursors (attached hereto as Exhibit A). Several regulatory bodies have reached similar conclusions, including the U.S. Environmental Protection Agency, Health Canada, and the European Food Safety Authority.

In further response, the enclosed comments provide several critical clarifications of and additions to the scientific literature referenced in OEHHA's "Evidence on the Carcinogenicity of Perfluorooctane Sulfonic Acid (PFOS) and Its Salts and Transformation and Degradation Precursors" publication (OEHHA's evidence document). In evaluating the ten "key characteristics" of carcinogens, as described in OEHHA's evidence document, 3M underscores

the importance of applying and integrating these concepts into the context of biological relevance. More specifically, in reaching its conclusion that there were some and/or suggestive evidence for eight of the ten key characteristics, OEHHA appears to have ignored or overlooked other compelling supporting data that do not support such characterization. Such data, when given proper weight, establish that PFOS is not “clearly shown” to cause cancer as required under Health & Safety Code Section 25249.8(b).

3M also cautions OEHHA that a listing of PFOS that purports to include PFOS salts and transformation and degradation precursors, and particularly OEHHA’s reference to a “non-exhaustive” set of precursors in the evidence document, lacks sufficient specificity to be reasonably understood by the majority of the regulated community. As set forth in greater detail in the enclosed comments, such action may be subject to challenge under the California Administrative Procedure Act and may have the unintended result of contributing to over-warning or unnecessary enforcement actions.

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

Regards,

A solid black rectangular box used to redact the signature of Oyeboode A. Taiwo.

Oyeboode A. Taiwo, MD, MP

Epidemiology Comments

First, while OEHHA appears to be aware of the Shearer et al.¹ matched case-control study of renal cell cancer (published in JNCI) in relation to measured single serum concentrations of PFOA, OEHHA did not mention the fact that Shearer et al. also measured serum concentrations of PFOS, MeFOSAA, and EtFOSAA. Adjusting for several potential confounders as well as PFOA, Shearer et al. did *not* conclude there was an association with renal cell carcinoma and PFOS, MeFOSAA, and EtFOSAA. Provided below are the data from the Shearer et al. report for these three analytes.

Odds Ratio and 95% CI for PFOS, MeFOSAA, and EtFOSAA serum concentrations for renal cell carcinoma in the PLCO cancer screening trial. See Table 2 from Shearer et al. JNCI 2021, Vol 113, No. 5.

ug/L	OR (95% CI)	P ^a _{trend}	OR (95% CI)	P ^b _{trend}
PFOS				
≤ 26.3	1.00 (reference)	0.009	1.00 (reference)	0.64
>26.3 - 38.4	1.67 (0.84 to 3.30)		1.24 (0.59 to 2.57)	
>38.4 - 49.9	0.92 (0.45 to 1.88)		0.53 (0.22 to 1.24)	
>49.9 - 154.2	2.51 (1.28 to 4.92)		1.14 (0.45 to 2.88)	
Continuous ^c	1.39 (1.04 to 1.86)		0.92 (0.60 to 1.42)	
MeFOSAA				
≤ 0.9	1.00 (reference)	0.86	1.00 (reference)	0.31
>0.9 - 1.4	1.00 (0.53 to 1.89)		0.77 0.40 to 1.50)	
>1.4 - 2.1	1.38 (0.73 to 2.63)		1.00 (0.50 to 2.01)	
>2.1 - 8.2	0.92 (0.48 to 1.76)		0.65 (0.32 to 1.33)	
Continuous ^c	1.01 (0.80 to 1.29)		0.86 (0.66 to 1.12)	
EtFOSAA				
≤ 0.7	1.00 (reference)	0.74	1.00 (reference)	0.63
>0.7 - 1.2	1.54 (0.83 to 2.88)		1.37 (0.72 to 2.63)	
>1.2 - 2.4	1.69 (0.91 to 3.14)		1.33 (0.69 to 2.58)	
>2.4 - 60.4	1.41 (0.71 to 2.81)		1.04 (0.49 to 2.20)	
Continuous ^c	1.07 (0.90 to 1.27)		0.97 (0.79 to 1.18)	

- Adjusted for BMI (4 categories), smoking status (3 categories), history of hypertension (yes, no), est GFR (continuous), previous freeze-thaws cycle, and calendar year of blood draw (3 categories)
- Further adjusted for other PFAS (i.e., log-transformed concentrations of PFOA, PFOS (except for PFOS), and PFHxS)
- Continuous odds ratio for renal cell carcinoma risk in relation to a 1-unit increase in serum PFAS concentration on the log base 2 scale, corresponding to an approximate doubling in analyte levels.

¹ Shearer et al. 2021 J Natl Cancer Inst 113 580-587

Second, OEHHA should be aware of the recently published study by Li et al. (2021)² with results regarding cancer incidence data pertaining to the Ronneby, Sweden area where Aqueous Film Forming Foam use from an airport had infiltrated one of the municipal wells. The predominant exposures were to PFOS and PFHxS, and much less to PFOA, but the latter exposure was still above general population levels. Exposure-specific analyses to these PFAS were not done.

Finally, based on the available research data using various models and with an understanding of biological plausibility, a quantitative assessment for PFOS carcinogenicity is not supported.

Toxicology Comments

PFOS should not be considered a carcinogenic agent based on liver tumors observed in rats.

As part of its draft Public Health Goals technical document,³ OEHHA relied upon the study data by Butenhoff et al. (2012)⁴ as evidence demonstrating an association between PFOS and liver cancer in rats. Based on the differences in species-specific mechanisms between humans and rodents, however, 3M finds that the Butenhoff study and the other publications do *not* support the conclusion that PFOS is carcinogenic to humans. In the only 2-year cancer bioassay for PFOS, Butenhoff et al. reported that PFOS treatment was related to an increase in benign hepatocellular adenomas in Sprague Dawley rats. The US Environmental Protection Agency and National Toxicology Program (NTP) have issued cautionary guidance for making conclusions about carcinogenicity in humans based on evidence in laboratory animals. There are differences in the mechanism of action (MOA) between animals and humans.⁵ For example, NTP states:

*[c]onclusions regarding carcinogenicity in humans or experimental animals are based on scientific judgment, with consideration given to all relevant information. Relevant information includes, but is not limited to, dose response, route of exposure, chemical structure, metabolism, pharmacokinetics, sensitive sub-populations, genetic effects, or other data relating to mechanism of action or factors that may be unique to a given substance. For example, there may be substances for which there is evidence of carcinogenicity in laboratory animals, but there are compelling data indicating that the agent acts through mechanisms which do not operate in humans and would therefore not reasonably be anticipated to cause cancer in humans.*⁶

² Li et al. 2021 Environ Res Oct 15:112217

³ Proposed Public Health Goals for Perfluorooctanoic Acid and Perfluorooctane Sulfonic Acid in Drinking Water, Office of Environmental Health Hazard Assessment at 153 (July 2021).

⁴ Butenhoff et al. 2012 Toxicology 293 1-15

⁵ Proposed OPPTS science policy: PPARα-mediated hepatocarcinogenesis in rodents and relevance to human health risk assessments, USEPA, 2003.

⁶ <https://ntp.niehs.nih.gov/whatwestudy/assessments/cancer/criteria/index.html>, accessed 22 August 2021

This standard is consistent with the Proposition 65 requirement that a “biologically plausible association” exist between the chemical being evaluated for listing and the adverse effect. *See* Final Statement of Reasons, Section 12306 – Authoritative Bodies (February 1, 1990) at 22 (“[B]iological plausibility is the standard *applied by the Panel when it determines on a chemical-by-chemical basis* that a chemical has been clearly shown through scientifically valid testing according to generally accepted principles”) (emphasis added).

3M’s review of the established mechanistic data does not lead to the conclusion that PFOS is likely to cause liver cancer in humans. The mechanistic research shows that liver tumors in rats with exposures to PFOS are explained by the activation of several hepatic xenosensor nuclear receptors, such as peroxisome proliferator-activated receptor α (PPAR α), constitutive androstane receptor (CAR), and pregnane X receptor (PXR).^{7,8,9,10,11}

The qualitative differences between humans and rodents in the susceptibility of the xenosensor nuclear receptor activation brings into question the relevance of rodent liver tumor response and biological significance, if any, to humans, as it relates to PFOS exposure. OEHHA acknowledged “there is substantial debate about whether hepatic effects of PPAR α -activating compounds in rodents are relevant to humans due to interspecies differences in activation characteristics.”¹² However, OEHHA ignored these interspecies differences in activation characteristics for CAR and PXR, noting that the uncertainty about whether hepatic tumors are caused “solely” by activation of PPAR α means that evidence of liver tumors in rodents should not be dismissed “due to the assumption that it lacks human relevance.”¹³

OEHHA’s conclusion is *not* supported by the available scientific data because similar to PPAR α , detailed mechanistic studies in regards to the hyperplastic responses have also shown a species-specific difference in the functions of CAR and PXR between rodents (more susceptible) and humans (less sensitive).^{14,15,16,17,18,19}

The significance of the above-mentioned mechanistic data demonstrating the additional non-PPAR α nuclear receptor activation by CAR and PXR in rodents is two-fold:

- 1) It provides the direct evidence of a plausible biological mechanism in rodents, and
- 2) It also illustrates a species-specific difference in the functions of these xenosensor nuclear receptors that likely explain why humans are considerably less sensitive to the

⁷ Bjork et al. 2011 Toxicology 288 8-17

⁸ Bjork and Wallace 2009 Toxicol Sci 111 89-99

⁹ Elcombe et al. 2012 Toxicology 293 16-29

¹⁰ Elcombe et al. 2012 Toxicology 293 30-40

¹¹ Vanden Heuvel et al. 2006 Toxicol Sci 92 476-489

¹² Proposed Public Health Goals for Perfluorooctanoic Acid and Perfluorooctane Sulfonic Acid in Drinking Water, Office of Environmental Health Hazard Assessment at 153 (July 2021).

¹³ Proposed Public Health Goals for Perfluorooctanoic Acid and Perfluorooctane Sulfonic Acid in Drinking Water, Office of Environmental Health Hazard Assessment at 159 (July 2021).

¹⁴ Corton et al. 2014 Crit Rev Toxicol 44 1-49

¹⁵ Elcombe et al. 2014 Crit Rev Toxicol 44 64-82

¹⁶ Gonzales and Shah 2008 Toxicology 246 2-8

¹⁷ Klaunig et al. 2012 Reprod Toxicol 33 410-418

¹⁸ Lake 2009 Xenobiotica 39 582-596

¹⁹ Ross et al. 2010 Toxicol Sci 116 452-466

pleiotrophic effects of CAR and PXR activation than rodents, similar to what PPAR α MOA data have shown.

Overall, because PFOS is neither genotoxic nor mutagenic and it does not metabolize,²⁰ the known species differences between rodent and human strongly support that PFOS-induced hepatic tumors in rodents are unlikely to occur in humans. This is further substantiated by the lack of epidemiological evidence for liver tumors in highly-exposed populations.²¹ Therefore, the qualitative differences in the susceptibility of the xenosensor nuclear receptor activation undermine OHHEA's conclusion that PFOS presents a biologically plausible carcinogenic hazard to humans, and establish that PFOS is not "clearly shown" to cause cancer.

PFOS should not be considered a carcinogenic agent based on pancreatic islet cell tumor observed in male rats.

PFOS should also not be considered as a carcinogenic agent to humans based on pancreatic islet cell tumor observed in rats. In the same 2-year cancer bioassay for PFOS by Butenhoff et al.,²² the authors did NOT find a statistically significant PFOS treatment-related relationship between PFOS ingestion and pancreatic islet cell carcinoma in male Sprague Dawley rats. The original study (referenced as Thomford 2002 by the OEHHHA) also did not find a statistically significant increasing trend in pancreatic islet adenoma, carcinoma, or combined adenoma and carcinoma. The reason OEHHHA concluded "[a]n increase in pancreatic islet cell carcinoma (by trend) was also observed in male rats[,]” was solely due to a different method of calculating the tumor incidence rate.

The table below summarizes the difference of the two analyses. As shown, Thomford 2002 calculated the total tumor incidence rate based on the total number of the tissues examined per specific dose group. OEHHHA calculated the tumor incidence rate based on the number of animals alive at the time of first occurrence of the tumor.

From Thomford 2002 (Text Table 5)			From OEHHHA (Table 5.7.7)		
K ⁺ PFOS concentration in feed (ppm)	Total # of tissues examined	Pancreas Islet cell carcinoma, Total incidence (Rate)	K ⁺ PFOS concentration in feed (ppm)	Total # of tissue examined (<u>per number of animals alive at the time of first occurrence of the tumor</u>)	Pancreas Islet cell carcinoma, Total incidence (Rate)
0	60	1 (1/60=0.017)	0	38	1 (1/38=0.026)
0.5	49	2 (2/49=0.041)	0.5	41	2 (2/41=0.049)
2	50	2 (2/50=0.040)	2	44	2 (2/44=0.045)
5	50	5 (5/50=0.100)	5	44	5 (5/44=0.113)
20	60	5 (5/60=0.083)	20	40	5 (5/40=0.125)
Trend test		p = 0.0681	Trend test		p < 0.05

²⁰ https://www.epa.gov/sites/production/files/2016-05/documents/pfos_hesd_final_508.pdf, accessed 22 August 2021

²¹ Alexander et al. 2003 Occ Env Med 60 722-729

²² Butenhoff et al. 2012 Toxicology 293 1-15

The relationship between pancreatic islet cell tumors and PFOS is further called into question because these tumors are one of the common spontaneous tumor types documented in aged Sprague Dawley rats.^{23,24} While the specific mechanisms are not fully understood, scientists believe that genetic and environmental factors could be involved in tumor growth. For instance, increased dietary calories (i.e., via *ad libitum* food consumption) could contribute to the development of spontaneous age-related tumors in Sprague Dawley rats such as chronic nephropathy, exocrine pancreatic atrophy and fibrosis, pancreatic islet hyperplasia and fibrosis, and the early development of potentially lethal tumors in the pituitary and mammary glands.

In the 2-year cancer bioassay study for PFOS where food was given *ad libitum*, Butenhoff et al. 2012²⁵ reported that the control and K⁺PFOS-treated male rats had generally similar food consumption rates. However, there were intermittent lower body weights observed in the 20 ppm-treated group animals. While the actual metabolic caloric balance was not evaluated in that study, it is possible that the subtle difference in food consumption per body weight may have, in part, contributed to the observation of intermittent lower body weights.

In addition, the pancreatic islet cell tumor type (endocrine-based) should not be confused with the pancreatic acinar cell tumor (exocrine-based) that has been reported in rats with exposure to PFOA.^{18,26,27} The MOA of the pancreatic acinar cell tumors in the rats exposed to PFOA is likely through increased cholecystikinin (“CCK”) as a consequence of cholestasis. While CCK promotes acinar cell hyperplasia in the rats, this MOA is not considered to be relevant to human risk and therefore is not biologically plausible. In humans, the causal mechanism in the development of the human pancreatic (ductule) adenocarcinomas is neurogenically dependent, rather than the CCK pathway, as observed in rodents.²⁸

Collectively, these data, clearly illustrating why PFOS should not be considered a carcinogenic agent based on either liver tumor or pancreatic islet cell tumor observed in rats, establish that PFOS is not “clearly shown” to cause cancer. Several regulatory bodies have also reached similar conclusions, including:

USEPA, 2016²⁹

In the case of PFOS, the existing evidence does not support a strong correlation between the tumor incidence and dose to justify a quantitative assessment.

Health Canada, 2018³⁰

²³ Suzuki et al. 1979 J Cancer Res Clin Oncol 95 187-196

²⁴ Dillberger 1994 Toxicol Path 22 48-55

²⁵ Butenhoff et al. 2012 Toxicology 293 1-15

²⁶ Butenhoff et al. 2012 Toxicology 298 1-13

²⁷ Biegel et al. 2001 Toxicol Sci 60 44-55

²⁸ Myer et al. 2014 Toxicol Pathol 42 260-274.

²⁹ https://www.epa.gov/sites/production/files/2016-05/documents/pfos_hesd_final_508.pdf, accessed 22 October 2021

³⁰ <https://www.canada.ca/en/health-canada/services/publications/healthy-living/guidelines-canadian-drinking-water-quality-guideline-technical-document-perfluorooctane-sulfonate/document.html>, accessed 23 October 2021

Some associations between PFOS and risk of cancer... were observed; however, the evidence does not support the carcinogenicity of PFOS.

EFSA, 2020³¹

In the Opinion on PFOS and PFOA (EFSA CONTAM Panel, 2018), a number of studies on cancer incidence or cancer mortality at occupational or environmental exposure were reviewed. In summary, those studies provided insufficient support for carcinogenicity of PFOS and PFOA in humans.

Inclusion of “Transformation and Degradation Precursors” in the Listing

OEHHA is proposing to include “Transformation and Degradation Precursors” in the listing. While this term may be quite clear to chemists, it is more than likely beyond the understanding of most of the Proposition 65 regulated community. Given that Proposition 65 is enforced against companies with as few as 10 employees, with little resources to devote to retain chemists to assist in the most fundamental question regarding chemical identity, this term is particularly problematic.

An unclear regulation may rise to the level of an arbitrary and capricious act by an agency where the regulation violates due process by being too vague to provide adequate notice of the conduct proscribed or prescribed. If OEHHA were to list this category of chemicals, the listing decision, which is a regulation governed by the California Administrative Procedure Act (APA), would be so unclear to those being charged with complying with Proposition 65 that it rises to failure to substantially comply with the APA. This may be the case for including “transformation and degradation precursors” in the listing.

There is a practical concern to be addressed here as well: manufacturers, distributors and retailers of products must have a sufficient basis to make inquiries of their respective suppliers regarding the chemical makeup of the products they sell. The responses to those inquiries are the first step for a business to begin to understand its obligations, if any, under Proposition 65. A reference to “transformation and degradation precursors,” which cannot be fully understood without retaining – and paying for – a chemist, fails to provide a reasonable basis from which these inquiries can be made. OEHHA has stated repeatedly that “over-warning” does not serve the public interest. Yet, the consequence of this listing, if it proceeds under this proposal, likely will be unnecessary warnings due to the regulated community’s lack of understanding of what that phrase means. Such a vague and ambiguous listing also may result in unnecessary enforcement actions – again, because of misunderstandings of what that term means.

3M notes, too, that OEHHA has never identified such a broad listing of “transformation and degradation precursors.” It should refrain from doing so here.

³¹ Schrenk et al. 2020 EFSA J 18 e06223

EXHIBIT A



May 10, 2021

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

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

Re: Response to Request for Relevant Information on the Carcinogenic Hazard of Perfluorooctane Sulfonate (PFOS) and Its Salts and Transformation and Degradation

Dear Mr. Saechao:

The 3M Company ("3M") appreciates the opportunity to respond to the California Environmental Protection Agency's Office of Environmental Health Hazard Assessment's ("OEHHA") March 26, 2021 information request, "Chemical Selected for Consideration for Listing by the Carcinogen Identification Committee and Request for Relevant Information on the Carcinogenic Hazard of: Perfluorooctane Sulfonate (PFOS) and Its Salts and Transformation and Degradation" (the "Information Request").

In response, 3M first reiterates and highlights the scientific data cited and discussed in its October 19, 2020 submission to the Carcinogen Identification Committee (the "CIC") for its November 17, 2020 Prioritization Meeting. Though that meeting related to various chemicals, 3M submitted comments related only to PFOS and its salts and its transformation and degradation precursors (collectively, "PFOS and its salts"). 3M specifically incorporates by reference the data and discussion at 7-14 of its October 19, 2020 submission, attached hereto as Exhibit A.

In further response, 3M notes that the CIC suggested during its November 17 Prioritization Meeting that there is an association between breast cancer and exposure to PFOS, purportedly based on several epidemiological studies. But, as detailed below, 3M respectfully disagrees with the conclusion reached by the CIC. This is because, though there is no known mechanism, CIC speculated that it can be attributed by the receptor-mediated effects as well as a possible result of immunosuppression. In the following sections, 3M presents evidence that illustrates why insufficient evidence of carcinogenicity exists in studies to warrant listing PFOS as causing cancer under Proposition 65. 3M respectfully submits that this information is responsive to the Information Request and should be considered dispositive in deciding the issue of whether to list PFOS as a carcinogen under Proposition 65.



Epidemiology Comments

In September 2020, OEHHA issued its documentation on its screening of the epidemiology studies for PFOS prioritization for consultation with the CIC. A total of seven published papers were cited for its review of PFOS and breast cancer: Mancini et al. (2020);¹ Tsai et al. (2020);² Cohn et al. (2019);³ Ghisari et al. (2017);⁴ Wielsøe et al. (2017);⁵ Bonefeld-Jorgensen et al. (2014);⁶ and Bonefeld-Jorgensen et al. (2011).⁷ As noted by OEHHA, there was some case participant overlap between Wielsøe et al. (2017) and Bonefeld-Jorgensen et al. (2011) for breast cancer cases diagnosed during the 2000-2003 time period.

In October 2020, 3M provided public comments to OEHHA regarding these studies. In particular, 3M wrote that OEHHA did not cite in its epidemiology screening process the findings from the large nested case-control study of breast cancer diagnosed in California female public school professionals by Hurley et al. (2018).⁸ This study did not show an association between breast cancer and measured PFOS or MeFOSAA, a compound that can metabolize to PFOS. The Hurley et al. study continued not to be identified in the comments that were provided to the CIC by one of its members (see Dr. Mariana Stern's comments on pages 106 – 113).⁹ 3M is puzzled why the study by Hurley et al. was not identified by the CIC at its November 2020 meeting. 3M reiterates the need for the CIC to include the findings from this large nested case-control study in its deliberations related to PFOS and breast cancer.

Hurley et al. (2018)⁸

This nested case-control study examined invasive breast cancer risk in 902 cases and 858 controls obtained from the California Teachers Study (CTS), a cohort of 133,479 female public school teachers, established in 1995-1996, primarily designed to study breast cancer. Breast

¹ Francesca Roman Mancini et al., *Perfluorinated Alkylated Substances Serum Concentration and Breast Cancer Risk: Evidence from a Nested Case-Control Study in the French E3N Cohort*, 146 *Int'l J. of Cancer* 917 (2020), <https://pubmed.ncbi.nlm.nih.gov/31008526/>.

² Meng-Shan Tsai et al., *A Case-Control Study of Perfluoroalkyl Substances and the Risk of Breast Cancer in Taiwanese Women*, 142 *Env't Int'l* 105850 (2020), <https://pubmed.ncbi.nlm.nih.gov/32580117/>.

³ Barbara Cohn et al., *In Utero Exposure to Poly- and Perfluoroalkyl Substances (PFASs) and Subsequent Breast Cancer*, 92 *Reproductive Toxicology* 112 (2020), <https://www.sciencedirect.com/science/article/abs/pii/S0890623818304866>.

⁴ Mandana Ghisari et al., *Polymorphism in Xenobiotic and Estrogen Metabolizing Genes, Exposure to Perfluorinated Compounds and Subsequent Breast Cancer Risk: A Nested Case-Control Study in the Danish National Birth Cohort*, 154 *Env't Rsch.* 325 (2017), <https://www.sciencedirect.com/science/article/abs/pii/S0013935116305266>.

⁵ M. Wielsøe et al., *Serum Levels of Environmental Pollutants is a Risk Factor for Breast Cancer in Inuit: A Case Control Study*, 16 *Environ Health* 56 (June 2017).

⁶ Eva Bonefeld-Jorgensen et al., *Breast Cancer Risk After Exposure to Perfluorinated Compounds in Danish Women: A Case-Control Study Nested in the Danish National Birth Cohort*, 25 *Cancer Causes Control* 1439 (2014), <https://link.springer.com/content/pdf/10.1007%2Fs10552-014-0446-7.pdf>.

⁷ Eva Bonefeld-Jorgensen et al., *Perfluorinated Compounds Are Related to Breast Cancer Risk in Greenlandic Inuit: A Case Control Study*, 10 *Env't Health* 88 (2011), <https://ehjournal.biomedcentral.com/articles/10.1186/1476-069X-10-88#citeas>.

⁸ Susan Hurley et al., *Breast Cancer Risk and Serum Levels of Per- and Poly-fluoroalkyl Substances: A Case-Control Study Nested in the California Teachers Study*, 17 *Env't Health* 83 (2018), <https://doi.org/10.1186/s12940-018-0426-6>.

⁹ <https://oehha.ca.gov/media/downloads/proposition-65/transcript/cicmeetingtranscript111720.pdf>



cancer cases were obtained through the California Cancer Registry where the ascertainment is estimated to be 99% complete with 99% of breast cancer tumors pathologically confirmed. Case selection included those individuals diagnosed with breast cancer between January 1, 2006 and August 1, 2014, under 80 years old at diagnosis, no prior history of invasive or *in situ* breast cancer at cohort entry, and being a continuous resident of California from cohort entry until time of diagnosis. Controls were obtained from a probability sample of at-risk CTS cohort members frequency matched to cases by age at baseline, race, ethnicity, and regional residence.

Because control serum samples were collected more frequently in the early course of the conduct of this study, which is a time of national downward trends of PFOS (and PFOA), a decision was made by Hurley et al. to minimize this bias by excluding participants who provided serum samples prior to October 2011. The last date of blood collection was August 2015. Blood samples were, therefore, collected an average of 35 months after case diagnosis (range 9 months to 8.5 years). Covariate information was derived from a series of surveys beginning at the initiation of the cohort in 1995-1996 followed by a series of follow-up surveys. The final set of covariates that were considered for adjusted odds ratios were age at baseline enrollment, race/ethnicity, region of residence, date of blood draw, season of blood draw, total smoking pack-years, BMI, family history of breast cancer, age at first full-term pregnancy, menopausal status at blood draw, and pork consumption.

Hurley et al. examined selected subsets of breast cancer that included: pre/perimenopausal versus post-menopausal cases and cases with tumors that were hormonally responsive (ER+ or PR+) and non-hormonally responsive (ER-/PR-) tumors.

Median serum PFOS concentrations among cases and controls were reported as 6.695 ng/mL and 6.950 ng/mL, respectively. The range of values went from LOD to 39.4 ng/mL (cases) and 99.8 ng/mL (controls). Analyzed as tertiles of PFOS (serum) concentration (low, medium, and high), the adjusted odds ratio for invasive breast cancer were 1.00 (reference), 0.883 (95% CI 0.691, 1.129), and 0.889 (95% CI 0.695, 1.161). The p-value for the linear trend was 0.41. The log odds ratios for a unit increase in PFOS was 0.934 (95% CI 0.83, 1.277; p-value 0.67). Stratified by menopausal status, the adjusted odds ratios by tertiles were: postmenopausal 1.00, 0.843, 0.860; p-value trend 0.26 and pre- or peri-menopausal 1.00, 1.796, 1.297; p-value trend 0.57. Adjusted log (PFOS, ng/mL) odds ratios were 0.885 (95% CI 0.641, 1.223) and 0.900 (95% CI 1.66, 4.876) for postmenopausal and pre- or peri-menopausal status, respectively. By hormonal receptor status, the adjusted odds ratio by tertiles were: ER+ or PR+ 1.00, 0.937, 0.967 (p-value trend 0.81) and ER- and PR- 1.00, 0.628, and 0.615 (p-value trend 0.06). Adjusted log (PFOS, ng/mL) odds ratios were 1.054 (95% CI 0.744, 1.493; p-value 0.77) and 0.573 (95% CI 0.323 1.016; p-value 0.06), respectively, for ER+ or PR+ and ER- and PR- hormonal receptor status tumors.

Hurley et al. did not report statistically significant associations between MeFOSAA, a compound that can metabolize to PFOS, and breast cancer. These null findings can be found in the published paper. To avoid potential bias in imputing more than 5% of their values below the detection level, EtFOSAA and PFOSA (two other compounds that can metabolize to PFOS) were excluded from risk analyses.



Hurley et al. concluded that their results did not support an association between serum PFOS and risk of breast cancer. They highlighted the important study strengths and weaknesses with the latter including the collection of serum samples post-diagnosis. The extent of PFOS change that may be affected by the onset and/or treatment of breast cancer was not known. Nevertheless, because of the long serum elimination half-life of PFOS, it still suggested to these authors that their findings were in the null direction. Hurley et al. remained cautious about the potential of the endocrine-disrupting properties, which 3M discusses further in the toxicology comments that follow.

Two other studies have also not been reviewed by the CIC related to PFOS and breast cancer. One study was mentioned in 3M's October 2020 comments (Ghisari et al. 2014). The other study that was more recent (Omoike et al. 2020) was published six days before 3M's October 2020 comments submission; thus, 3M was not aware of the existence of this publication at that time.

Ghisari et al. (2014)¹⁰

The Ghisari et al. (2014) published study was not included among the epidemiology studies cited in OEHHHA's Prioritization Document. Ghisari et al. is a follow-up study to Bonefeld-Jørgensen et al. (2011), which examined breast cancer risk in Inuit women in a hospital-based case-control study of 31 cases and 115 controls. (Note: Wilsøe et al. was the additional case-control study that included those subjects from Bonefeld-Jørgensen et al. (2011)). Ghisari et al. conducted phenotyping for CYP1A1, CYP1B1, COMT, CYP17A1, and CYP19A1 genes and the Greenlandic founder mutation BRCA1. Ghisari et al. reported an increased breast cancer risk with women who had high PFOS and PFOA and carriers of at least one CYP1A1 variant allele (OR = 2.63, 95% CI 1.46, 4.75) one variant COMT Met allele (OR = 2.65, 95% CI 1.44, 4.89) or the common CYP17A1 A1A2+A2A2 allele (OR = 2.21, 95% CI 1.19, 4.12). See Supplemental Table 2 in Ghisari et al (2014). No combined effects were seen between PFOS/PFOA exposure and CYP1B1 and CYP19 polymorphisms. As would be expected, the frequency of the BRCA1 mutation was higher in the cases than controls. As noted by the OEHHHA screening process, in a subsequent study by Ghisari et al. (2017) in a much larger studied population of 178 breast cancer cases and 233 controls from the Danish National Birth Cohort, they found no significant association between the same investigated polymorphisms and the risk of breast cancer with PFOS (or PFOA). Ghisari et al. (2017) did find an association with PFOSA (perfluorooctane sulfonamide); however, these blood samples were taken between 1996-2002. According to CDC NHANES, the last time PFOSA was detected at the 95th percentile in the United States population was in the 2005-2006 time period. Because of this lack of detection, NHANES even ceased analyzing for PFOSA starting in the 2013-2014 time period. The conclusion from both Ghisari et al. studies (2014; 2017) should be that the reported association with breast cancer risk and PFOS

¹⁰ Mandan Ghisari et al., *Polymorphisms in Phase I and Phase II Genes and Breast Cancer Risk and Relations to Persistent Organic Pollutant Exposure: A Case-Control Study in Inuit Women*, 13 *Env't Health* 19 (2014), <https://www.ehjjournal.net/content/13/1/19>.



cannot be isolated from confounding factors such as the variant alleles of the patients in the studied population.

Omoike et al. (2020)¹¹

Using data from NHANES collected between 2005-2012, Omoike et al. conducted a cross-sectional study of 11,631 participants for four cancers that they considered related to the “deregulation of estrogen receptors” (ovarian, prostate, breast, and uterine cancers). The NHANES questionnaire only inquired about whether the individual had ever been told they had each of these cancers; there was no recorded date of diagnosis nor was medical validation done. No information was obtained related to hormone receptor status. The mean concentration of PFOS was 11.4 ng/mL (25th percentile 6.45, ng/mL and 75th percentile 19.68 ng/mL). Adjusted odds ratios by quartiles of exposure for breast cancer were 1.00 (reference); 0.87 (95% CI 0.87, 0.89); 1.06 (1.05, 1.06); and 1.47 (1.46, 1.48). For ovarian cancer, Omoike et al. reported the following adjusted odds ratios by quartiles of exposure: 1.00 (reference); 0.08 (95% CI 0.08, 0.084); 1.64 (95% CI 1.62, 1.66); and 2.25 (95% CI 2.22, 2.28).

Toxicology Comments

I. Are there laboratory animal data to support mammary gland tumor finding with chronic administration of PFOS?

While CIC had suggested an association between breast cancer and exposure to PFOS based on several epidemiological studies, interestingly, this association was not supported by the laboratory animal data.

To date, among the available chronic bioassay studies in Sprague Dawley rats for either PFOS¹² or N-EtFOSE^{13,14} (a compound that ultimately metabolizes to PFOS), mammary gland was not a target organ. In fact, statistically significant decreasing trends in mammary gland tumor were observed.^{12,14}

II. Are there data to support hormone receptor-mediated effects with PFOS in laboratory animals?

The absence of the mammary gland-related findings in rats under chronic administration of PFOS condition corroborated with a lack PFOS treatment-related effects on estrous cycles.

¹¹ Ogbebor Omoike et al., *A Cross-Sectional Study of the Association Between Perfluorinated Chemical Exposure and Cancers Related to Deregulation of Estrogen Receptors*, *Env't Rsch.* 110329 (2020), <https://pubmed.ncbi.nlm.nih.gov/33068574/>.

¹² John Butenhoff et al., *Chronic Dietary Toxicity and Carcinogenicity Study with Potassium Perfluorooctanesulfonate in Sprague Dawley Rats*, 293 *Toxicology* 1 (2012), <https://pubmed.ncbi.nlm.nih.gov/22266392/>.

¹³ Riker, *Two-Year Oral (Diet) Toxicity/carcinogenicity Study of Fluorochemical FM-3924 in Rats*, Riker Laboratories, Inc., Experiment No. 0281CR0012 (May 1983), USPEA AR-226-0257 through AR-226-0262.

¹⁴ Covance Study No. 6329-212, 2001, USEPA AR226-1051a



In a two-generation study in Sprague Dawley rats,¹⁵ PFOS had no significant effects on estrous cycles. In gestational developmental studies with Sprague Dawley rats and CD-1 mice,¹⁶ PFOS did not affect estrous cycles. Furthermore, PFOS has not been shown to activate human estrogen receptor α (*hER* α) or human estrogen receptor β (*hER* β).¹⁷

In addition, there was no evidence to support a finding that thyroid homeostasis was interrupted in either rats or monkeys following PFOS treatment. In a long-term serum clinical chemistry evaluation in monkeys after PFOS exposures,¹⁸ there were no changes in thyroid hormone parameters (TSH and FT4). While detailed investigations of thyroid hormone measurement issues in laboratory rats treated with PFOS revealed a known negative bias observed with conventional immunoassay measurement on FT4,^{19,20} no effects on TSH or thyroid pathology were observed.^{21,22,23}

III. Are there data to support PFOS cause chronic immunosuppression in laboratory animals?

While the OEHHHA cited several short-term studies as evidence of “induced chronic inflammation,” they were not representative of chronic exposure by study design. Studies by Qazi et al. (2009a,²⁴ 2009b²⁵) were only 10 days in exposure duration and the other three studies (Sørli

¹⁵ Deanna Luebker et al., *Neonatal Mortality from In Utero Exposure to Perfluorooctanesulfonate (PFOS) in Sprague–Dawley Rats: Dose-Response, and Biochemical and Pharmacokinetic Parameters*, 215 *Toxicology* 149 (2005), <https://www.sciencedirect.com/science/article/abs/pii/S0300483X05003471>.

¹⁶ Christopher Lau et al., *Exposure to Perfluorooctane Sulfonate during Pregnancy in Rat and Mouse. II: Postnatal Evaluation*, 74 *Toxicological Sciences*, Issue 2 (August 2003)382-392.

¹⁷ H. Ishibashi et al., *Estrogenic Effects of Fluorotelomer Alcohols for Human Estrogen Receptor Isoforms Alpha and Beta In Vitro*, 30 *Biological & Pharm.Bulletin* 1358 (2007).

¹⁸ S. Chang et al., *Evaluation of Serum Lipid, Thyroid, and Hepatic Clinical Chemistries in Association with Serum Perfluorooctanesulfonate (PFOS) in Cynomolgus Monkeys after Oral Dosing with Potassium PFOS*, 156 *Toxicology Science* 387 (2017).

¹⁹ S. Chang et al. *Negative Bias from Analog Methods Used in the Analysis of Free Thyroxine in Rat Serum Containing Perfluorooctanesulfonate (PFOS)*, 234 *Toxicology* 21-33 (January 2007).

²⁰ S. Chang et al., *Thyroid Hormone Status and Pituitary Function in Adult Rats Given Oral Doses of Perfluorooctanesulfonate (PFOS)*, 243 *Toxicology* 330 (2008).

²¹ A. Seacat et al., *Subchronic Toxicity Studies on Perfluorooctanesulfonate Potassium Salt in Cynomolgus Monkeys*, 68 *Toxicol Sci* 249-264 (2002).

²² Luebker et al., *supra* note 15.

²³ S. Chang et al., *Gestational and Lactational Exposure to Potassium Perfluorooctanesulfonate (K+PFOS) in Rats: Toxicokinetics, Thyroid Hormone Status, and Related Gene Expression*, 27 *Reproduct Toxicol* 387-399 (2009).

²⁴ MR Qazi et al., *High-Dose, Short-Term Exposure of Mice to Perfluorooctanesulfonate (PFOS) or Perfluorooctanoate (PFOA) Affects the Number of Circulating Neutrophils Differently, but Enhances the Inflammatory Responses of Macrophages to Lipopolysaccharide (LPS) in a Similar Fashion*, 262 *Toxicology* 207 (2009a).

²⁵ MR Qazi et al., *The Atrophy and Changes in the Cellular Compositions of the Thymus and Spleen Observed in Mice Subjected to Short-Term Exposure to Perfluorooctanesulfonate Are High-Dose Phenomena Mediated in Part by Peroxisome Proliferator-Activated Receptor- α (PPAR α)*, 260 *Toxicology* 68 (2009b).



et al. 2020;²⁶ Giménez-Bastida et al. 2015;²⁷ and Brieger et al. 2011²⁸) were based on tissue culture (*in vitro*).

Because chronic inflammation is often being associated with detrimental effects such as increased mortality, the survival data in the long-term chronic animal study should be considered. Based on the only chronic mammalian laboratory animal data in rats that received dietary PFOS for up to two years,²⁹ there was a statistically significant decreasing trend in mortality (increasing trend in survival) in male rats and no statistically significant trends in mortality in female rats through two years.

In addition, while the studies currently cited by OEHHA appear to suggest decreased immune response in animals (based on IgM data), OEHHA should consider other studies that offer additional insights. For example, vaccine antibody titers actually represent the secondary IgG response, not IgM, and most of the studies did not appropriately address this important issue. In the studies where IgG was evaluated, they did not show suppression of the IgG response to PFOS treatments.^{30,31,32,33}

Overall, the fact that exposure to PFOS can lead to no change or an increase in IgG suggests that PFOS does not act as an immunosuppressant.

IV. Is there sufficient evidence of carcinogenicity data from studies in experimental animals with PFOS?

The only tumor-related animal findings with PFOS is hepatocellular tumors in rats; however, due to known species difference in terms of mechanism of action (between rodents and humans), federal agencies such as the U.S. EPA and the National Toxicology Program (NTP) have prescribed various framework and guidance on interpreting rodent liver tumor findings as related

²⁶ J. Sørli et al., *Per- and Polyfluoroalkyl Substances (PFASs) Modify Lung Surfactant Function and Pro-Inflammatory Responses in Human Bronchial Epithelial Cells*, 62, *Toxicology in Vitro*, 104656 (February 2020).

²⁷ J. Giménez-Bastida et al., *In Vitro Evaluation of the Cytotoxicity and Modulation of Mechanisms Associated with Inflammation Induced by Perfluorooctanesulfonate and Perfluorooctanoic Acid in Human Colon Myofibroblasts CCD-18Co*, 29 *Toxicology in Vitro*, Issue 7, 1683-1691 (October 2015).

²⁸ A. Brieger et al., *Impact of Perfluorooctanesulfonate and Perfluorooctanoic Acid on Human Peripheral Leukocytes*, 25 *Toxicology in Vitro* Issue 4, 960-968 (June 2011).

²⁹ Ibid, page 1.

³⁰ M. Peden-Adams et al., *Developmental Toxicity in White Leghorn Chickens Following in ovo Exposure to Perfluorooctane Sulfonate (PFOS)*, 27 *Reproductive Toxicology*, Issues 3-4, 307-318 (June 2009).

³¹ MR Qazi et al., *28-Day Dietary Exposure of Mice to a Low Total Dose (7mg/kg) of Perfluorooctanesulfonate (PFOS) Alters Neither the Cellular Compositions of the Thymus and Spleen nor Humoral Immune Responses: Does the Route of Administration Play a Pivotal Role in PFOS-Induced Immunotoxicity?*, 267 *Toxicology Issues* 1-3, 132-139 (January 2010).

³² L. Zheng et al., *Type 1 and Type 2 Cytokines Imbalance in Adult Male C57BL/6 Mice Following a 7-Day Oral Exposure to Perfluorooctanesulfonate (PFOS)*, 8 *Journal of Immunotoxicology* Issue 1, 30-38 (February 2011).

³³ Guang-Hui Dong et al., *Sub-Chronic Effect of Perfluorooctanesulfonate (PFOS) on the Balance of Type 1 and Type 2 Cytokine in Adult C57BL/6 Mice*, 85 *Archives of Toxicology* 1235 (2011), https://www.researchgate.net/publication/49842219_Sub-chronic_effect_of_perfluorooctanesulfonate_PFOS_on_the_balance_of_type_1_and_type_2_cytokine_in_adult_C57BL6_mice.



to human relevance³⁴ as well as carcinogen listing criteria. For example, the following narrative is from NTP:³⁵

Conclusions regarding carcinogenicity in humans or experimental animals are based on scientific judgment, with consideration given to all relevant information. Relevant information includes, but is not limited to, dose response, route of exposure, chemical structure, metabolism, pharmacokinetics, sensitive sub-populations, genetic effects, or other data relating to mechanism of action or factors that may be unique to a given substance. For example, there may be substances for which there is evidence of carcinogenicity in laboratory animals, but there are compelling data indicating that the agent acts through mechanisms which do not operate in humans and would therefore not reasonably be anticipated to cause cancer in humans.

Based on this guiding principle, 3M's review of the established mechanistic data does *not* lead to the conclusion that PFOS causes liver cancer in humans. Briefly, detailed mechanistic research has shown that liver tumor effects observed in rats with exposures to PFOS can be explained by the activation of hepatic xenosensor nuclear receptors such as peroxisome proliferator-activated receptor α (PPAR α), constitutive androstane receptor (CAR), and pregnane X receptor (PXR).^{36,37,38,39,40} These studies have identified a species difference in the functions of these xenosensor nuclear receptors that likely explains why humans are considerably less sensitive

³⁴ U.S. EPA, Proposed OPPTS Science Policy: PPAR α -Mediated Hepatocarcinogenesis in Rodents and Relevance to Human Health Risk Assessments (2003).

³⁵ National Toxicology Program, Report on Carcinogens Process & Listing Criteria (2019), <https://ntp.niehs.nih.gov/whatwestudy/assessments/cancer/criteria/index.html>.

³⁶ James Bjork et al., *Multiplicity of nuclear receptor activation by PFOA and PFOS in primary human and rodent hepatocytes*, 288 *Toxicology* 8 (2011), https://www.researchgate.net/publication/51461697_Multiplicity_of_nuclear_receptor_activation_by_PFOA_and_PFOS_in_primary_human_and_rodent_hepatocytes.

³⁷ James Bjork and Kendall Wallace, *Structure-Activity Relationships and Human Relevance for Perfluoroalkyl Acid-Induced Transcriptional Activation of Peroxisome Proliferation in Liver Cell Cultures*, 111 *Toxicological Sciences* 89 (2009), <https://pubmed.ncbi.nlm.nih.gov/19407336/>.

³⁸ Clifford Elcombe et al., *Hepatocellular hypertrophy and cell proliferation in Sprague-Dawley rats from dietary exposure to potassium perfluorooctanesulfonate results from increased expression of xenosensor nuclear receptors PPAR α and CAR/PXR*, 293 *Toxicology* 16 (2012), <https://pubmed.ncbi.nlm.nih.gov/22245121/>.

³⁹ Clifford Elcombe et al., *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*, 293 *Toxicology* 30 (2012), <https://www.sciencedirect.com/science/article/abs/pii/S0300483X11005506>.

⁴⁰ John Vanden Heuvel et al., *Differential Activation of Nuclear Receptors by Perfluorinated Fatty Acid Analogs and Natural Fatty Acids: A Comparison of Human, Mouse, and Rat Peroxisome Proliferator-Activated Receptor-Alpha, -Beta, and -Gamma, Liver X Receptor-Beta, and Retinoid X Receptor-Alpha*, 92 *Toxicology* 476 (2006), <https://pubmed.ncbi.nlm.nih.gov/16731579/>.



to the pleiotrophic effects of PPAR α or CAR/PXR activation compared to rodents.^{41,42,43,44,45,46} Therefore, the qualitative differences in the susceptibility of the xenosensor nuclear receptor activation bring into question the relevance of rodent liver tumor response and biological significance, if any, to humans, as it relates to PFOS exposure.

Overall, because PFOS is neither genotoxic nor mutagenic and does not metabolize,⁴⁷ the known species differences between rodent and human strongly support that PFOS-induced hepatic tumors in rodents are unlikely to occur in humans. This is further substantiated by the lack of epidemiological evidence for liver tumors in highly exposed populations.⁴⁸

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

Regards,



Oyebode A. Taiwo, MD, MPH

⁴¹ JC Corton et al., *Mode of Action Framework Analysis for Receptor-Mediated Toxicity: The Peroxisome Proliferator-Activated Receptor Alpha (PPAR α) as a Case Study*, 44 Critical Reviews in Toxicology Issue 1, 1-49 (2014).

⁴² C. Elcombe et al., *Mode of Action and Human Relevance Analysis for Nuclear Receptor-Mediated Liver Toxicity: A Case Study with Phenobarbital as a Model Constitutive Androstane Receptor (CAR) Activator*, 44 Critical Reviews in Toxicology, Issue 1, 64-82 (2014).

⁴³ Frank Gonzales and Yatrik Shah, *PPAR α : Mechanism of Species Differences and Hepatocarcinogenesis of Peroxisome Proliferators*, 246 Toxicology 2 (2008), <https://pubmed.ncbi.nlm.nih.gov/18006136/>.

⁴⁴ J. Klaunig et al., *Mode of Action Analysis of Perfluorooctanoic Acid (PFOA) Tumorigenicity and Human Relevance*, 33 Reproductive Toxicology Issue 4, 410-418 (July 2012).

⁴⁵ B. Lake, *Species Differences in the Hepatic Effects of Inducers of CYP2B and CYP4A Subfamily Forms: Relationship to Rodent Liver Tumour Formation*, 39 Xenobiotica 582 (2009), <https://pubmed.ncbi.nlm.nih.gov/19622001/>.

⁴⁶ J. Ross et al., *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*, 116 Toxicological Sciences 452 (2010).

⁴⁷ U.S. EPA, *Health Effects Support Document for Perfluorooctane Sulfonate (PFOS)* (2016), https://www.epa.gov/sites/production/files/2016-05/documents/pfos_hesd_final_508.pdf.

⁴⁸ B. Alexander et al., *Mortality of Employees of a Perfluorooctanesulphonyl Fluoride Manufacturing Facility*, 60 J. of Occupational & Env't Med. 722 (2003).

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EXHIBIT A



October 19, 2020

VIA ELECTRONIC SUBMISSION

Dr. Thomas Mack, Chair
Carcinogen Identification Committee Members
California Environmental Protection Agency
Office of Environmental Health Hazard Assessment
Carcinogen Identification Committee

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

3M Comments on Prioritization of Perfluorooctane Sulfonate (PFOS)

Dear Dr. Mack, CIC Members, and Dr. Sandy:

The 3M Company (3M) is pleased to submit the attached comments on the proposed prioritization of perfluorooctane sulfonate (PFOS) and its salts and transformation and degradation precursors for potential listing under Proposition 65 as a carcinogen. As a science-based company with substantial experience, expertise and product stewardship of these chemicals, 3M is well-positioned to support the efforts of the Carcinogen Identification Committee (CIC) and the Office of Environmental Health Hazard Assessment (OEHHA) in this proceeding.

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

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

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

As discussed in more detail in the attached comments, PFOS and its salts and transformation and degradation precursors should not be designated as a high priority for further evaluation under Proposition 65 because:

- 3M was one of the main manufacturers of PFOS in the United States. The company initiated a voluntary phase-out of these chemicals in 2000, effectively eliminating a significant portion of the available PFOS to discharge into sources of drinking water and use in consumer and other products originating in the U.S. PFOS has not been reported to US EPA as manufactured or imported into the United States since at least 2006.³
- Countless countries have signed onto the international Stockholm Convention, including China, which now requires the elimination of PFOS in essentially all consumer and other goods originating in member countries.
- Significant federal action relating to PFOS and PFOS precursors has been underway since 2002, and US EPA has imposed and continues to ratchet up strong restrictions on the manufacture, import and use of PFOS and PFOS precursors pursuant to its Significant New Use Rule authority under the Toxic Substances Control Act, effectively eliminating any likelihood that consumer and other products originating internationally and containing PFOS will be sold in California.
- As a result of all the steps in the U.S. and internationally to eliminate PFOS, substantial evidence supports the conclusion that further PFOS regulation under Proposition 65 is unnecessary. For example, there is an unmistakable downward trend in residues of PFOS in human blood since 2000, reflecting the results of 3M's voluntary phase-out and US EPA's restrictions. And, since PFOS' listing as a reproductive toxicant under Proposition 65, there has not been a single PFOS notice of Proposition 65 violation issued alleging discharge of or exposure to PFOS.
- The overall weight of the evidence with respect to PFOS fails to clearly show that this chemical causes cancer in humans and therefore does not warrant the extensive resources necessary for the preparation of hazard identification materials.

¹ Cal. Health & Safety Code § 25249.8(b).

² Process for Prioritizing Chemicals for Consideration under Proposition 65 By The "State's Qualified Experts" <https://oehha.ca.gov/media/downloads/proposition-65/document/finalpriordoc.pdf>, (December 2004) (emphasis added).

³ <https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/fact-sheet-20102015-pfoa-stewardship-program#mfg>.

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

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

Regards,

A solid black rectangular box used to redact the signature of Oyeboode A. Taiwo.

Oyeboode A. Taiwo, MD, MPH

I. OEHHA Has Failed to Adequately Investigate Relevant Toxicity Data and Potential for Exposure before Referring PFOS to the CIC as a Candidate for Prioritization.

The Office of Environmental Health Hazard Assessment (OEHHA) of the California Environmental Protection Agency is soliciting public comments relating to the potential designation of seven chemicals or chemical groups as carcinogens pursuant to Proposition 65. Perfluorooctane sulfonate (PFOS) and its salts and transformation and degradation precursors is included among the seven chemicals or chemical groups proposed for further consideration by the Carcinogen Identification Committee (CIC) in OEHHA's Prioritization Notice and Prioritization Document.¹

In evaluating potential recommendations to OEHHA, the CIC relies on the "prioritization process endorsed by the CIC and adopted by OEHHA in 2004."² That process, the "Process for Prioritizing Chemicals for Consideration Under Proposition 65 by the 'State Qualified Experts'" ("Process"), "is designed to ensure that the efforts of these committees are focused on chemicals that may pose significant hazards to Californians."³ The Process was requested by the CIC "as an alternative to the random prioritization process that had been in use since 1997."⁴ The CIC "specifically asked for an alternative process that could *better take into account the level of exposure in California*, the population affected by various chemicals being reviewed by OEHHA, as well as the *degree and extent of potential harm* posed by the Chemical."⁵

The Process that CIC endorsed is consistent with the goal of focusing OEHHA's, the CIC's, and stakeholders' resources on chemicals that a meaningful number of consumers in California actually encounter for which they should receive a warning under Proposition 65. Staying focused on this goal is critical to preserving the integrity of Proposition 65. And, more so today than ever, protecting the integrity of Proposition 65 is crucial; over-warning is prevalent and the news media's coverage of Proposition 65 abuse by plaintiff's lawyers (so-called "bounty hunters") grows.⁶

¹ Announcement of the Carcinogen Identification Committee Meeting Scheduled for November 17, 2020, Prioritization: Chemicals for Consultation by the Carcinogen Identification Committee, <https://oehha.ca.gov/proposition-65/cnr/announcement-carcinogen-identification-committee-meeting-scheduled-november-17>; and OEHHA Prioritization: Chemicals Identified for Consultation with the Carcinogen Identification Committee (September 2020) (hereinafter "Prioritization Document"), available at <https://oehha.ca.gov/media/downloads/cnr/cicprioritization090420.pdf>.

² *Id.* at i.

³ California Environmental Protection Agency, Office of Environmental Health Hazard Assessment, Process For Prioritizing Chemicals For Consideration Under Proposition 65 by the "State's Qualified Experts," <https://oehha.ca.gov/media/downloads/proposition-65/document/finalpriordoc.pdf> (December 2004) (hereinafter "Process").

⁴ *Id.*

⁵ *Id.* (emphasis added).

⁶ E.g., Jim Conran, For Proposition 65 bounty hunters, time to tame them, North Bay Business Journal (2011), <https://www.northbaybusinessjournal.com/article/industry-news/for-proposition-65-bounty-hunters-time-to-tame-them/> (Aug. 8, 2011) ("Unless it is reformed, Proposition 65's enforcement mechanism will continue to shortchange

Accordingly, OEHHA is obligated under the Process to investigate “the existence of relevant toxicity data *and* the potential for human exposure,” *before referral of a chemical to the CIC as a candidate for prioritization*.⁷ OEHHA should, in turn, only refer a chemical to the CIC after OEHHA’s actual investigation and conclusion that the data suggests a chemical can “*cause ...cancer and have exposure potential in California*.”⁸ OEHHA, like any public entity in California, is bound to follow its published procedures including these mandatory aspects of the Process.⁹

Pursuant to the Process, OEHHA must screen chemicals for carcinogenic effects based on human epidemiological and laboratory experimental data. The overall evidence of carcinogenicity or reproductive toxicity of the chemical is to be considered, including epidemiologic, animal bioassay, and other relevant information, as appropriate. Although the prioritization process evaluates chemicals in a qualitative manner, the evaluation of studies against Proposition 65 listing criteria is a useful measure of how a chemical should be prioritized. To be ultimately listed as a chemical “known to the state to cause cancer,” a chemical must be “*clearly shown* through scientifically valid testing according to generally accepted principles to cause cancer”.¹⁰ In other words, using a weight-of-evidence approach, it must be clearly shown to cause invasive cancer in humans, or to cause invasive cancer in animals (unless the mechanism of action has been shown not to be relevant to humans).¹¹

Similarly, to effectuate the purpose of Proposition 65 and the Process, the relevant exposure potential that OEHHA and the CIC must consider are necessarily limited to exposure potential resulting from Proposition 65-regulatable discharges into sources of drinking water and consumer product, occupational, or environmental exposures. As detailed below, the absence of Proposition 65-regulatable discharges of, as well as the absence of general exposure of Californians to, PFOS render PFOS improper for prioritization. OEHHA failed to, and cannot, offer any qualitative evidence to the contrary.

the state while creating grotesque profits for a handful of trial lawyers at the expense of our small businesses.”); Geoffrey Mohan, You see the warnings everywhere. But does Prop. 65 really protect you? (2020), <https://www.latimes.com/business/story/2020-07-23/prop-65-product-warnings> (July 23, 2020) (“That profusion of warnings has subverted Proposition 65 and left Californians, and increasingly anyone who shops online, overwarned, underinformed and potentially unprotected, a Times investigation has found. And it has funneled hundreds of millions of dollars to a handful of attorneys and their repeat clients.”).

⁷ Process at 3.

⁸ *Id.* (emphasis added).

⁹ *E.g.*, *Galzinski v. Somers*, 2 Cal. App. 5th 1164, 1170-74 (2016) (recognizing court may issue writ to require agency to comply with its rules, policies, and procedures; *Pozar v. Department of Transportation*, 145 Cal. App. 3d 269, 270-72 (1983) (same).

¹⁰ Cal. Health & Safety Code § 25249.8(b).

¹¹ Guidance Criteria for Identifying Chemicals for Listing as “Known to the State to Cause Cancer,” <https://oehha.ca.gov/media/downloads/crn/revcriteria.pdf>.

II. OEHHA Has Not Offered and Cannot Offer Qualitative Evidence of California PFOS Exposures Relevant to Proposition 65.

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

1. 3M's Voluntary Efforts and Commitments.

3M was one of the main manufacturers of PFOS in the United States. In May 2000, 3M announced that it was voluntarily phasing out of production of PFOS. That phase out was largely complete in the United States by the end of 2002 – a full 18 years ago. PFOS has not been reported to US EPA as manufactured or imported into the United States by any entity since at least 2006.¹²

2. Federal Regulations.

After 3M ceased the manufacture of PFOS, US EPA promulgated federal regulations that prevent other manufacturers (as well as 3M) by law from manufacturing or importing PFOS or PFOS precursors, subject to a handful of very narrow critical use exceptions with limited exposure potential approved by US EPA.¹³ These regulations have been in place for nearly two decades. US EPA's rules allowed the continuation of a few specifically limited, highly technical uses of these chemicals for which no alternatives were available, and which were characterized by very low volume, low exposure and low releases. Any other uses of these chemicals would require prior notice to and review by US EPA.

With the launch of its Perfluoro and Polyfluoroalkyl Substances (PFAS) Action Plan in 2019, US EPA is taking a proactive, cross-agency approach to evaluating uses of PFAS (including PFOS and its salts) and potential restrictions on these uses. The agency has already taken steps towards establishing a federal maximum contaminant level for PFAS under the Safe Drinking Water Act and has already finalized guidance on soil and groundwater remediation standards for PFOS.

3. PFOS Levels in Blood Serum Confirm PFOS's Effective Phase Out in the United States.

3M acknowledges that OEHHA's generalization that "PFOS was detected in 98% of blood samples from 425 participants in the 2018 California Regional Exposure Study, Los Angeles County (CARE-LA)"¹⁴ is technically correct. But this technically correct generalization fails to provide a

¹² <https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/fact-sheet-20102015-pfoa-stewardship-program#mfg>

¹³ See 40 C.F.R. §721.9582 (listing several hundred PFOS precursors that cannot be manufactured or imported without EPA permission, and the permissible uses approved by US EPA via its Significant New Use Rule).

¹⁴ Prioritization Document at 83.

complete picture of the trend of exceptional and continual decline in PFOS in blood serum levels over the years.¹⁵

The National Health and Nutrition Examination Survey (“NHANES”) prepared by the United States Centers for Disease Control (“CDC”) National Center for Environmental Health, which is a nationally representative sample of the U.S. population (noninstitutionalized), provides data¹⁶ which demonstrates the following declines:

Serum Perfluorooctane sulfonic acid (PFOS) (1999 – 2010)						
CAS Number 1763-23-1						
Geometric mean and selected percentiles of serum concentrations (in µg/L) for the U.S. population from the National Health and Nutrition Examination Survey.						
Categories (Survey Years)	Geometric Mean (95% conf. interval)	50th Percentile (95% conf. interval)	75th Percentile (95% conf. interval)	90th Percentile (95% conf. interval)	95th Percentile (95% conf. interval)	Sample Size
Total population (1999 – 2000)	30.4 (27.1-33.9)	30.2 (27.8-33.9)	43.7 (37.5-47.3)	57.0 (50.2-71.7)	75.7 (58.1-97.5)	1562
Total population (2003 – 2004)	20.7 (19.2-22.3)	21.1 (19.8-22.4)	30.0 (27.5-33.0)	41.3 (35.6-50.0)	54.6 (44.0-66.5)	2094
Total population (2005 – 2006)	17.1 (16.0-18.2)	17.5 (16.8-18.6)	27.2 (24.9-29.6)	39.4 (34.9-43.1)	47.5 (42.7-56.8)	2120
Total population (2007 – 2008)	13.2 (12.20-14.2)	13.6 (12.8-14.7)	21.0 (18.9-23.3)	32.6 (29.4-36.3)	40.5 (35.4-47.4)	2100
Total Population (2009 – 2010)	9.32 (8.13-10.7)	9.7 (8.50-10.8)	14.8 (12.9-17.3)	23.7 (18.3-30.2)	32.0 (22.6-48.5)	2233
Total population (2011 – 2012)	6.31 (5.84-6.82)	6.53 (5.99-7.13)	10.5 (9.78-11.1)	15.7 (14.7-17.5)	21.7 (19.3-23.9)	1904
Total population (2013 – 2014)	4.99 (4.50-5.52)	5.20 (4.80-5.70)	8.70 (7.9009.40)	13.9 (11.9-15.5)	18.5 (15.4-22.0)	2165
Total population (2015 – 2016)	4.72 (4.40-5.07)	4.80 (4.40-5.30)	8.10 (7.30-9.40)	13.2 (11.4-15.6)	18.3 (15.5-22.7)	1993

The CARE-LA study confirms this declining trend, revealing that 2018 California data shows PFOS blood serum levels consistent with the averages and rate of decline of the total population documented by CDC.

Project: California Regional Exposure Study, Los Angeles County (CARE-LA)

Study Group: Adults

Sample Collection Date: 2018

					95% Confidence Interval		Selected Percentiles					
<u>Chemical measured</u>	<u>Indicates exposure to</u>	<u>Units</u>	<u>Number of people tested</u>	<u>Geometric mean</u>	<u>Lower</u>	<u>Upper</u>	<u>25th</u>	<u>50th</u>	<u>75th</u>	<u>95th</u>	<u>Detection frequency</u>	<u>Limit of Detection (LOD), wet-weight</u>
PFOS	PFOS	ng/mL	425	2.15	1.92	2.35	1.27	2.43	3.98	8.33	97.9%	0.0615

¹⁵ The mere presence of PFOS in blood serum, without a full understanding of the broader influencing factors, provides only a limited view of exposure risk. These additional factors are further discussed in the comments that follow.

¹⁶ U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, Fourth National Report on Human Exposure to Environmental Chemicals, Updated Tables, January 2019, Volume One, https://www.cdc.gov/exposurereport/pdf/FourthReport_UpdatedTables_Volume1_Jan2019-508.pdf (January 2019).

Studies show that from 1999 to 2014, blood PFOS levels in the United States have declined by more than 80%.¹⁷ This trend of decline has occurred since the phase out of PFOS, and EPA's regulation of PFOS, detailed here.¹⁸

4. Proposition 65 Enforcement Trends Confirm the Effectiveness of PFOS's Phase Out.

Based on data available in 2015, PFOS was listed as a reproductive toxicant under Proposition 65.¹⁹ As relevant here, that listing effectively prohibited the discharge of PFOS into sources of drinking water in California, and triggered a warning obligation before exposing California consumers to PFOS. Yet, of the nearly 5,500 notices of Proposition 65 violations issued since the PFOS listing was effective under Proposition 65, 3M is not aware of a single one alleging a Proposition 65 violation based on a PFOS exposure or discharge.

Further, because PFOS has been effectively phased out in the United States and is already listed as a reproductive toxicant under Proposition 65, its regulation as a carcinogen under Proposition 65 would not impact Californians' lives or further the purpose of Proposition 65.

5. OEHHA Offers No Evidence of Ongoing Discharge of PFOS into Drinking Water.

OEHHA generalizes that PFOS "has been found in drinking water supplies in California and other parts of the US."²⁰ But this generalization does not warrant the prioritization of PFOS for two separate and independent reasons.

First, in its generalization, OEHHA fails to account for whether the presence of PFOS found in any source of drinking water in California is based on current or anticipated discharges subject to Proposition 65. Indeed, if OEHHA were to account for that factor, it would likely be forced to acknowledge that any detectable presence of PFOS in drinking water in California (if any at all) is not from present or anticipated discharges subject to Proposition 65.

Second, because PFOS is already listed under Proposition 65 as a reproductive toxicant, its discharge into sources of drinking water is already prohibited. Thus, regulatory action concerning PFOS under Proposition 65 at this juncture could not in any way serve to further reduce or eliminate any actual PFOS discharges regulatable under Proposition 65.

¹⁷ Agency for Toxic Substances and Disease Registry, PFAS in the U.S. Population, <https://www.atsdr.cdc.gov/pfas/health-effects/us-population.html> (last accessed October 16, 2020).

¹⁸ United States Environmental Protection Agency, Drinking Water Health Advisory for Perfluorooctane Sulfonate (PFOS), https://www.epa.gov/sites/production/files/2016-05/documents/pfos_health_advisory_final_508.pdf (May 2016).

¹⁹ As detailed in this Section II, substantial additional data on the impact of the PFOS phase out was not yet available in 2015.

²⁰ Prioritization Document at 83.

6. OEHHA Offers No Evidence of California Consumers' Exposure to PFOS from Foods.

FDA's research confirms that California consumers' exposure to PFOS from food, if any at all, does not warrant prioritizing PFOS's listing as a carcinogen under Proposition 65. Specifically, "[i]n 2012, [FDA] began testing for certain types of PFAS in milk and later expanded testing to seafood and cranberries. In 2019, we were able to expand and validate the testing method with a diverse group of foods including breads, cakes, fruits, dairy, vegetables, meats, poultry, fish, and bottled water for 16 types of PFAS."²¹

As of December 2019, the FDA has conducted eight surveys designed to measure certain PFAS in foods generally and from specific areas with environmental contamination. Overall, we have found that very few foods have detectable levels of certain PFAS. From our recent surveys of foods that are part of the general food supply, the results of our first round of testing showed that out of 91 foods, two samples—ground turkey and tilapia—had detectable levels of one type of PFAS called PFOS. The PFOS levels that were measured in these samples were very low and are not likely a health concern. The second round of testing included 88 foods and showed that one sample—tilapia—had a detectable level of the same type of PFAS. Again, the PFOS level found in the tilapia sample is very low and is not likely a health concern.²²

Finally, the complete lack of any Proposition 65 notices of violation relating to PFOS supports the conclusion that PFOS is not sufficiently present in the foods that Californians eat to establish an exposure potential.

B. OEHHA Did Not Offer Sufficient Qualitative Evidence of California Consumers' Exposure to PFOS From Products.

First, 3M agrees with OEHHA that the phase out and prohibition of PFOS in the United States has resulted in a lack of products manufactured domestically containing PFOS. OEHHA acknowledges that 3M, "[t]he principal US manufacturer of PFOS[,] phased out its production of the chemical in the early 2000s."²³ OEHHA emphasizes without any support, however, that "PFOS and PFOS commercial products are still manufactured in some parts of the world and may be imported to California."²⁴

But OEHHA's supposition that PFOS-containing products from abroad are being imported for sale at sufficient volumes to merit the extensive resources these and related proceedings would require is not based on any evidence at all. The facts support the opposite conclusion. First, there has not been a single Proposition 65 violation alleging a discharge or exposure to PFOS. Second, as stated in Sections II.A.1 and 2 above, 3M, one of the main manufacturers of

²¹ U.S. Food and Drug Administration, Questions and Answers on Per and Polyfluoroalkyl Substances (PFAS) in Food, <https://www.fda.gov/food/chemicals/questions-and-answers-and-polyfluoroalkyl-substances-pfas-food> (July 31, 2020).

²² *Id.*

²³ Prioritization Document at 83.

²⁴ *Id.*

PFOS in the United States, phased out its production nearly two decades ago and US EPA has strictly regulated uses and imports of PFOS. Third, other countries across the world have agreed to effectively eliminate PFOS in consumer and other products under The Stockholm Convention on Persistent Organic Pollutants (POPs), a global treaty which was adopted by the Conference of Plenipotentiaries on May 22, 2001 in Stockholm, Sweden (“Stockholm Convention”).²⁵

III. Prioritization of PFOS for Potential Listing as a Carcinogen Is Unwarranted and Would be Premature Based on the Weight of Scientific Evidence.

A. Recent Comprehensive Assessments of the Potential Health Effects of PFOS by Key National and International Organizations Have Found Insufficient Evidence of Carcinogenicity in Humans.

The U.S. Agency for Toxic Substances and Disease Registry (ATSDR) is directed by congressional mandate to perform specific functions concerning the effect on public health of substances of concern in the environment. In its Toxicological Profile for Perfluoroalkyls, ATSDR characterized the toxicologic and adverse health effects information for perfluoroalkyls including PFOS based on “all relevant toxicologic testing and information that has been peer-reviewed,” reflecting data from hundreds of studies. ATSDR concluded regarding the carcinogenicity of perfluoroalkyls: “The available human studies have identified some potential targets of toxicity; however, *cause and effect relationships have not been established for any of the effects, and the effects have not been consistently found in all studies*” (emphasis added).²⁶

The Expert Health Panel for per- and poly-fluoroalkyl substances (PFAS) was established to advise the Australian Government on the evidence for potential health impacts associated with PFAS exposure. In its 2018 assessment of the latest available systematic reviews of human epidemiological studies and national/international governmental studies on PFAS, the Panel concluded “there is mostly limited or no evidence for any link with human disease” and that “there is no current evidence that supports a large impact on a person’s health as a result of high levels of PFAS exposure.”²⁷ The Panel reviewed five key national and international reports and three systematic reviews compiling studies that analyzed human epidemiological evidence regarding exposure to PFAS (primarily PFOS and PFOA) and cancer. Like ATSDR, the Australian Expert Health Panel analyzed hundreds of studies in reaching this conclusion, many

²⁵ Among other things, the provisions of the Stockholm Convention require each party to restrict the production and use, as well as the import and export, of certain persistent organic pollutants identified in Annex B to the Convention. When PFOS was originally listed in the Stockholm Convention’s Annex B, its permitted uses were already limited. In 2019, PFOS’s listing in Annex B was amended to eliminate nearly all of the previously permitted uses. Now, only use in close-loop metal plating systems, fire-fighting foams, and insect bait for leaf-cutting ants is permitted. See Adoption of Amendments to Annexes A and B, Stockholm Convention on Persistent Organic Pollutants, Secretariat of the Stockholm Convention (Dec. 20, 2019). Notably, there are over 184 countries that are signatories to the Stockholm Convention and are bound by Annex B with respect to PFOS. Among those 184 countries are the United States’ largest consumer goods importers, including China.

²⁶ Agency for Toxic Substances and Disease Registry (ATSDR). 2018. Toxicological profile for Perfluoroalkyls. (Draft for Public Comment), <https://www.atsdr.cdc.gov/toxprofiles/tp200.pdf>. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service.

²⁷ Australian Government, Department of Health. 2018. Expert Health Panel for PFAS Report, <https://www1.health.gov.au/internet/main/publishing.nsf/Content/ohp-pfas-expert-panel.htm>.

of which are also cited in OEHHA's Prioritization Document. With respect to cancer, the Panel concluded "there is no current evidence that suggests an increase in overall cancer risk."

B. Human Studies Have Consistently Refuted Evidence of Carcinogenicity of PFOS for the Most Heavily Studied Cancer Types.

OEHHA's Prioritization Document provides fairly limited information characterizing the identified human studies pertaining to PFOS and cancer effects. However, these characterizations appear to show OEHHA's recognition that there is insufficient evidence of an association between PFOS and bladder cancer, prostate cancer, liver cancer, and certain other cancers. With respect to bladder cancer in particular, the referenced studies (and several related studies that were not referenced) collectively and consistently refute any evidence that PFOS exposure caused the observed incidences of cancer.

3M wishes to provide additional context on several epidemiologic studies included in the Prioritization Document that were conducted by 3M and/or the University of Minnesota (Alexander et al. 2003; Alexander and Olsen 2007; Olsen et al. 2004) as well as one study that OEHHA excluded (Grice et al. 2007).

- The original study by Alexander et al. reported a large, highly imprecise, but nevertheless statistically significant SMR for bladder cancer (SMR = 12.77; 95% CI 2.63 to 37.35).
- In a series of investigations that followed, Olsen et al. analyzed health claims data for the Decatur manufacturing site. They reviewed 204 inpatient and 34,053 outpatient claims for the 652 chemical plant employees and 237 inpatient and 40,174 outpatient claims for the adjacent film plant employees to ascertain any additional prevalent bladder cancer cases let alone other cancer and non-cancer claims data. No bladder cancer claims were found for workers in the chemical plant and 1 bladder cancer claim was found in the film plant.
- Another follow-up study, as reported by Alexander and Olsen (2007), examined medically validated self-reported incidence of bladder cancer of current and former Decatur employees who worked one year or longer. A total of 11 bladder cancer cases were identified (8.6 expected, SIR = 1.28 (95% CI 0.64-2.29)). The expected numbers were based on NCI SEER data. Compared with employees in the lowest cumulative exposure category, the relative risk of bladder cancer was 0.83 (95% CI 0.15-4.65), 1.92 (95% CI 0.30-12.06), and 1.52 (95% CI 0.21-10.99). Alexander and Olsen concluded these results did not confirm the high excess risk of bladder cancer that was reported in the mortality study by Alexander et al. but the possibility remained for a smaller risk in the higher exposed workers. However, the limited size of the population prohibited a conclusive exposure response analysis.
- Not cited by OEHHA was the additional analyses obtained in this research effort by Grice et al. (2007),²⁸ who reported on validated and self-reported cases in this current and former worker population (n = 1400 respondents out of a target population of 1800). The risk for melanoma (validated) was 1.01 (95% CI 0.25, 4.11) among current or former workers who were considered to have high occupational exposure to PFOS > 1 year. The

²⁸ Grice, M. M., Alexander, B. H., Hoffbeck, R., and Kampa, D. M. (2007). Self-reported medical conditions in perfluorooctanesulfonyl fluoride manufacturing workers. J Occup Environ Med 49, 722-9.

odds ratio for self-reported colon cancer for high exposure to PFOS (> 1 year) was 1.69 (95 CI 0.68, 4.17). For prostate cancer, the self-reported odds ratio for PFOS (>>1 year) was 1.91 (95% CI 0.44, 2.6).

C. The Small Number of More Recent Human Studies Fail to Demonstrate any Causal Link Between PFOS and Breast Cancer.

In determining whether to further prioritize PFOS, it would be premature to rely on the reported potential epidemiological associations between PFOS exposures and incidences of breast cancer in humans in the small number of recent studies identified in the Prioritization Document. In addition, OEHHA's Prioritization Document failed to include several other significant and recent studies with results that did not support an association between serum PFOS and risk of breast cancer.

Hurley et al. (2018)

First, OEHHA did not cite in its epidemiology screening process the **very large** case-control study of breast cancer diagnosed in California female public school professionals by Hurley et al. (2018).²⁹ This study examined invasive breast cancer risk in 902 cases and 858 controls obtained from the California Teachers Study (CTS), a cohort of 133,479 female public school teachers, established in 1995-1996, primarily designed to study breast cancer. Breast cancer cases are obtained through the California Cancer Registry, a legally mandated statewide population-based cancer reporting system where the ascertainment is estimated to be 99% complete with 99% of breast cancer tumors pathologically confirmed. In this particular study, case selection included those individuals diagnosed with breast cancer between January 1, 2006 and August 1, 2014, age < 80 years at diagnosis, no prior history of invasive or *in situ* breast cancer at cohort entry, and being a continuous resident of California from cohort entry until time of diagnosis. Controls were obtained from a probability sample of at-risk CTS cohort members frequency matched to cases by age at baseline, race ethnicity, and regional residence.

Because control serum samples were collected more frequently in the early course of the conduct of this study, which is a time of national downward trends of PFOS (and PFOA), the decision was made to minimize this bias, to exclude participants who provided serum samples prior to October 2011. The last date of blood collection was August 2015. Blood samples were, therefore, collected on average of 35 months after case diagnosis (range 9 months to 8.5 years). Covariate information was derived from a series of surveys beginning at the initiation of the cohort in 1995-1996 followed by a series of follow-up surveys. The final set of covariates that were considered for adjusted odds ratios were age at baseline enrollment, race/ethnicity, region of residence, date of blood draw, date of blood draw, season of blood draw, total smoking pack-years, BMI, family history of breast cancer, age at first full-term pregnancy, menopausal status at blood draw, and pork consumption.

Hurley et al. examined selected subsets of breast cancer that included: pre/perimenopausal versus post-menopausal cases and cases with tumors that were hormonally responsive (ER+/PR+) versus non-hormonally responsive (ER-/PR-).

²⁹ Hurley et al. 2018. Environmental Health 17:83 <https://doi.org/10.1186/s12940-018-0426-6>.

Median serum PFOS concentrations among cases and controls were reported as 6.695 ng/mL and 6.950 ng/mL, respectively. The range of values went from LOD to 39.4 ng/mL (cases) and 99.8 ng/mL (controls). Analyzed as tertiles of PFOS (serum) concentration (low, medium, and high), the adjusted odds ratio for invasive breast cancer were 1.00 (reference), 0.883 (95% CI 0.691, 1.129), and 0.889 (95% CI 0.695, 1.161). The p-value for the linear trend was 0.41. The log odds ratios for a unit increase in PFOS was 0.934 (95% CI 0.83, 1.277; p-value 0.67). Stratified by menopausal status, the adjusted odds ratios by tertiles were: postmenopausal 1.00, 0.843, 0.860; p-value trend 0.26) and pre- or per-menopausal 1.00, 1.796, 1.297; p-value trend 0.57). Adjusted log (PFOS, ng/mL) odds ratios were 0.885 (95% CI 0.641, 1.223) and 0.900 (95% CI 1.66, 4.876) respectively for postmenopausal and pre- or perimenopausal status. By hormonal receptor status, the adjusted odds ratio by tertiles were: ER+ or PR+ 1.00, 0.937, 0.967 (p-value trend 0.81) and ER- and PR- 1.00, 0.628 and 0.573 (p-value trend 0.06). Adjusted log (PFOS, ng/mL) odds ratios were 1.054 (95% CI 0.744, 1.493) and 0.573 (95% CI 0.323, 1.016) respectively, for ER+ or PR+ and ER- and PR- hormonal status tumors.

Hurley et al. concluded their results *did not support an association between serum PFOS and risk of breast cancer*. They highlight the important study strengths and weaknesses, the latter including the collection of serum samples post-diagnosis. However, because of the long serum elimination half-life of PFOS, this post-diagnosis collection would still provide a level of analysis although the effect of treatment regimens for breast cancer on PFOS is unknown. The Danish National Birth Cohort also found no association between breast cancer and PFOS (Bonefield-Jørgensen et al. 2014) as well in the daughters in the Child Health and Development Study pregnancy cohort (Cohn et al. 2020). Both of these studies were screened by OEHHHA.

Ghisari et al. (2014)

The Ghisari et al. (2014) published study³⁰ was not included among the epidemiology studies cited in OEHHHA's Prioritization Document. Ghisari et al. is a follow-up study to Bonefield-Jørgensen et al. (2011), which examined breast cancer risk in Inuit women in a hospital-based case-control study of 31 cases and 115 controls. (Note: Wilsøe was the additional case-control study that included those subjects from Bonefield-Jørgensen et al. (2011)). Ghisari et al. conducted phenotyping for CYP1A1, CYP1B1, COMT, CYP17A1, and CYP19A1 genes and the Greenlandic founder mutation BRCA1. Ghisari et al. reported an increased breast cancer risk with women who had high PFOS and PFOA and carriers of at least one CYP1A1 variant allele (OR = 2.63, 95% CI 1.46, 4.75) one variant COMT Met allele (OR = 2.65, 95% CI 1.44, 4.89) or the common CYP17A1 A1A2+A2A2 allele (OR = 2.21, 95% CI 1.19, 4.12). See Supplemental Table 2 in Ghisari et al (2014). No combined effects were seen between PFOS/PFOA exposure and CYP1B1 and CYP19 polymorphisms. As would be expected, the frequency of the BRCA1 mutation was higher in the cases than controls.

As noted by the OEHHHA screening process, in a subsequent study by Ghisari et al. (2017) in a much larger studied population of 178 breast cancer cases and 233 controls from the Danish National Birth Cohort, they found no significant association between the same

³⁰ Ghisari et al. 2014. Environmental Health 13:19 <https://www.ehjournal.net/content/13/1/19>.

investigated polymorphisms and the risk of breast cancer with PFOS (or PFOA). Ghisari (2017) did find an association with PFOSA (perfluorooctane sulfonamide); however, these blood samples were taken between 1996-2002. According to CDC NHANES, the last time PFOSA was detected at the 95th percentile in the United States population was in the 2005-2006 time period. Because of this lack of detection, NHANES even ceased analyzing for PFOSA starting in the 2013-2014 time period. The conclusion from both Ghisari et al. studies (2014; 2017) should be that the reported association with breast cancer risk and PFOS cannot be isolated from confounding factors such as the variant alleles of the patients in the studied population.

D. The Body of Data from Animal Studies and In Vitro Studies Fail to Support a Conclusion that PFOS Causes Cancer in Humans.

OEHHA's Prioritization Document identifies a number of additional studies under the headings "animal data" and "other relevant data," but provides essentially no context or assessment of the impact of this data in the human context. The body of data from animal studies and in vitro tissue culture cell-based studies, particularly when viewed in light of biological differences between species and other critical contextualizing information, fails to support a conclusion that PFOS causes cancer in humans.

Many in vitro tissue culture cell-based studies have been included in the Prioritization Document and the corresponding data reported are limited in that they do not fully represent the overall key events required and necessary in the tumor development process. It is imperative for OEHHA, in consultation with the CIC, to fully examine the available data and apply weight of evidence evaluation rigorously in the final assessment. Specifically, critical analysis of key events involved in the progression from a normal cell to a neoplastic cell should not be based on some isolated changes in a single gene expression noted in a tissue culture system; it should be supported by robust and consistent experimental data along with plausible biological explanation. We provide more detailed comments below regarding specific studies and OEHHA's characterizations of animal data and other relevant data in the Prioritization Document.

Under "Long-term feeding studies in rats" (pages 89 – 92)

- Given that the liver is the primary target organ of PFOS and many biological effects observed in laboratory animals are mediated by the liver, it is imperative for OEHHA to fully discern the biological differences between rodent and humans. More specifically, OEHHA should take note of the differences in terms of how the human liver and the rodent liver process and handle xenobiotics. This understanding is necessary for OEHHA, in consultation with the CIC, to ultimately properly assess the relevance of these findings in rodents as related to human health.

For example, detailed mechanistic research has shown that many metabolic effects of PFOS exposures in rodents can be explained by the activation of xenosensor nuclear receptors such as PPARa, constitutive androstane receptor (CAR), and pregnane X

receptor (PXR) in the liver.³¹ Given that humans are considerably less sensitive to the pleiotrophic effects of PPARα or CAR/PXR activation compared to rodents,³² the qualitative differences brings into question the relevance of rodent response and biological significance to humans.

- Because OEHHA categorically defines “perfluorooctane sulfonate (PFOS) and its salts and transformation and degradation precursors” in its Prioritization Document, the long-term feeding studies in rats with N-ethyl-perfluorooctanesulfonamidoethanol (N-EtFOSE) should also be included.³³
 - N-EtFOSE is the precursor molecule that metabolically degrades to form PFOS as end-stage metabolite.³⁴
 - Similar to the observation in the PFOS 2-year study in Sprague Dawley rats, increased incidence of liver adenoma was observed in rats in both studies.
 - In the first study,³⁵ there was a sporadic increase in the incidence of pituitary gland adenoma in the male rats that received N-EtFOSE; however, there was no dose-response and this finding was not observed in the female rats or in the second 2-year study. The study authors noted that “there did not appear to be any meaningful relationship of these to the dose administered”. It is worth noting that in the second study, there was a statistically significant decreasing trend in pituitary adenoma incidence in female rats.
 - In the second study,³⁶ there was a statistically significant increase in the thyroid follicular cell adenoma in male rats that received 100 ppm N-EtFOSE in the diet at the end of 2-year study. This observation lacked a clear dose-response, was not observed in female rats and was not previously observed in the first N-EtFOSE 2-year study either. The study authors specifically noted that “The relationship of this finding to treatment is questionable for several reasons: thyroid follicular cell tumors in historical controls from this laboratory are relatively common (occur with an incidence of 1%), however, no thyroid follicular cell tumors occurred in male controls from this study, there was no evidence on nonneoplastic lesions of the thyroid, the increase at 100 ppm was within the range of historical controls, and a clear dose-response was not present”.

³¹ Bjork et al. 2011 Toxicology 288 8-17; Bjork and Wallace 2009 Toxicol Sci 111 89-99; Elcombe et al. 2012 Toxicology 293 16-29; Elcombe et al. 2012 Toxicology 293 30-40; Vanden Heuvel et al. 2006 Toxicol Sci 92 476-489.

³² Corton et al. 2014 Crit Rev Toxicol 44 1-49; Elcombe et al. 2014 Crit Rev Toxicol 44 64-82; Gonzales and Shah 2008 Toxicology 246 2-8; Klaunig et al. 2012 Reprod Toxicol 33 410-418; Lake 2009 Xenobiotica 39 582-596; Ross et al. 2010 Toxicol Sci 116 452-466.

³³ Riker Laboratories Experiment No. 0281CR0012, 1983; Covance Study No. 6329-212, 2001; see also US EPA AR226-0257 and AR226-1051a, respectively.

³⁴ Xu et al. 2004 Chem Res Toxic 17 767-775.

³⁵ Riker Laboratories Experiment No. 0281CR0012, 1983; US EPA AR226-0257.

³⁶ Covance Study No. 6329-212, 2001; US EPA AR226-1051a.

- In all the 2-year bioassays in rats for either PFOS (one study) or N-EtFOSE that metabolizes to PFOS (two studies), it is worth noting that mammary gland was not a target organ. In fact, statistically significant decreasing trends in mammary gland tumor were reported in two of the studies.³⁷

Under “Is genotoxic” (pages 92 – 94)

OEHHA and the CIC should consider a series of studies that was undertaken to evaluate the mutagenicity and genotoxicity potentials of PFOS. Collectively, under these validated guideline protocols, PFOS did not elicit any positive mutagenic/genotoxic responses in any of the studies, clearly demonstrating the absence of mutagenic risk associated with PFOS. These studies included:

- *In vivo* mouse micronucleus assay³⁸;
- Chromosomal aberrations in human whole blood lymphocytes³⁹;
- Mammalian microsome reverse mutation using *Salmonella-Saccharomyces*⁴⁰;
- Mammalian microsome reverse mutation using *Salmonella- Escherichia*; and
- Unscheduled DNA synthesis in primary rat hepatocytes.⁴¹

Under “Induces chronic inflammation” (page 95)

The studies cited by OEHHA under the category for “induced chronic inflammation” were not representative of chronic exposure duration and they should not be interpreted as such.

- Studies by Qazi et al. (2009a; 2009b) were only ten days in exposure duration and the other three studies⁴² were based on tissue culture (*in vitro*).
- Because chronic inflammation is often being associated with detrimental effect such as increased mortality, the survival data in the long-term chronic animal study should be considered. Based on the only chronic mammalian laboratory animal data in rats that received dietary PFOS for up to 2 years⁴³, there was a statistically significant decreasing trend in mortality (increasing trend in survival) in male rats and no statistically significant trends in mortality in female rats through 2 years.

Under “immunosuppressive” (page 96)

OEHHA should carefully consider the weight of evidence for the proper interpretation of immune response, including assessment from the US EPA.

³⁷ Butenhoff et al. 2012 Toxicology 293 1-15; Covance Study No. 6329-212, 2001; US EPA AR226-1051a.

³⁸ Corning Hazleton study No. 17403-0-455, 1996.

³⁹ Covance study No. 20784-0-449, 1999.

⁴⁰ Covance study No. 20784-0-409, 1999.

⁴¹ Covance study No. 20784-0-447, 1999.

⁴² Sorli et al. 2020; Gimenez-Bastida et al. 2015; and Brieger et al. 2011.

⁴³ Butenhoff et al. 2012; see also Thomford 2001.

- In its 2016 Health Effect Document, the US EPA states that “Effects on immune response in animals are also associated with PFOS exposure; however, inconsistencies exist across the study results (Dong et al. 2009; Keil et al. 2008; Peden-Adams et al. 2008; Zheng et al. 2009) that highlight the need for additional research to confirm a LOAEL for the immunological endpoints.”⁴⁴
- In addition, while the current studies cited by OEHHHA appear to suggest decreased immune response in animals (based on IgM data), OEHHHA should consider other studies that offer additional insights. For example, vaccine antibody titers actually represent the secondary IgG response, not IgM, and most of the studies did not appropriately address this important issue. In the studies where IgG was evaluated, they did not show suppression of the IgG response to PFOS treatments.⁴⁵ Overall, the fact that exposure to PFOS can lead to no change or an increase in IgG suggests that PFOS does not act as an immunosuppressant.

Under “Modulates receptor-mediated effects” (pages 96 – 97)

The following studies should be considered for additional insights on the status of estrous cycles:

- Two-generation study in rats → no effects on estrous cycles⁴⁶; and
- Developmental studies in rats and mice → no effects on estrous cycles⁴⁷.

Finally, the following studies should be considered for additional insights on the status of thyroid hormones:

- Clinical evaluation of in monkeys after PFOS exposure → no change in thyroid hormone parameters⁴⁸; and
- Investigation of thyroid hormone measurement issues in laboratory animals exposed to PFOS → negative bias observed with conventional immunoassay measurement on FT4, no effects on TSH or thyroid pathology.⁴⁹

⁴⁴ https://www.epa.gov/sites/production/files/2016-05/documents/pfos_health_advisory_final_508.pdf.

⁴⁵ Peden-Adams et al. 2009 *Reproduct Toxicol* 27 307-318; Qazi et al. 2010 *Toxicology* 267 132-139; Zheng et al. 2011 *J Immunotoxicol* 8 30-38; Dong et al. 2011 *Arch Toxicol* 85 1235-1244.

⁴⁶ Luebker et al. 2005 *Toxicol* 215 126-148.

⁴⁷ Lau et al. 2003 *Tox Sci* 74 382-392.

⁴⁸ Chang et al. 2017 *Toxicol Sci* 156 387-401.

⁴⁹ Seacat et al. 2002 *Toxicol Sci* 68 249-264; Luebker et al. 2005 *Toxicol* 215 149-169; Chang et al. 2007 *Toxicology* 234 21-33; Chang et al. 2008 *Toxicology* 243 330-339; Chang et al. 2009 *Reproduct Toxicol* 27 387-399.



October 28, 2021

Pesticide and Environmental Toxicology Branch
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Submitted electronically via: <https://oehha.ca.gov/comments>

Re: Comments on Draft Technical Support Document for Proposed Public Health Goals and Health-Protective Concentrations for Perfluorooctanoic Acid and Perfluorooctane Sulfonic Acid in Drinking Water

The 3M Company (“3M”) appreciates the opportunity to review and comment on the Draft Technical Support Document (hereinafter the “Support Document”) issued by the Office of Environmental Health Hazard Assessment (“OEHHHA”) on July 30, 2021 to support OEHHHA’s proposed Public Health Goals (“Proposed PHGs”) and Health-Protective Concentrations (“HPCs”) for perfluorooctane sulfonic acid (“PFOS”) and perfluorooctanoic acid (“PFOA”). As a science-based company with substantial experience, expertise, and product stewardship of these chemicals, 3M is well-positioned to provide input to OEHHHA on the Support Document for the Proposed PHGs of 0.007 ppt for PFOA and 1 ppt PFOS, as well as the HPCs for PFOA and PFOS set at 3 ppt and 2 ppt respectively.

While OEHHHA explicitly notes that the Proposed PHG values are “not regulatory and represent only non-mandatory goals,” and that HPCs are “advisory,” OEHHHA nevertheless has an obligation to conduct a rigorous scientific evaluation because PHGs inform the eventual regulatory value. Indeed the California State Water Resources Board (“SWRCB”) has a statutory obligation to come as close as possible to the PHG while considering economic and technical feasibility. *See* Cal. Health & Safety C. § 116365 (“A primary drinking water standard adopted by the state board shall be set at a level that is as close as feasible to the corresponding public health goal placing primary emphasis on the protection of public health, and that, to the extent technologically and economically feasible, meets all of the following.”). The Proposed PHGs are orders of magnitude smaller than guidance and standards established by the U.S. Environmental Protection Agency (“EPA”) and by other states.¹ The Proposed PHGs and HPCs are well below any proposed or existing standards and are not based on sound science bases. In fact, the Proposed PHGs and HPCs are so low it is unlikely they could be reliably measured as regulatory standards because they are below method detection limits.² As discussed in the

¹ For example, EPA has issued Drinking Water Health Advisories for PFOA and PFOS at 70 ppt which is 10,000 times greater than the proposed PHG for PFOA.

² Indeed, OEHHHA has set notification levels 6.5 ppt for PFOS and 5.1 ppt for PFOA in drinking water which were “the lowest levels at which they can be reliably detected in drinking water using currently available and appropriate

detailed technical comments below, OEHHA should revisit the technical bases outlined in the Support Document and bring the Proposed PHGs and HPCs in line with sound science.

TECHNICAL COMMENTS

Given the extensive amount of related literature, 3M focused its technical comments primarily on the reference studies chosen by OEHHA for the derivation of the Proposed PHGs and HPCs, as well as other relevant studies that OEHHA did not consider.

A. PFOA

1. OEHHA failed to consider relevant epidemiological studies regarding the risk of kidney cancer from exposure to PFOA.

To derive the Proposed PHG for PFOA, OEHHA chose to rely on only two kidney cancer case-control studies in their risk assessment calculations: a nested case-control study by Shearer et al. (2021)³ that included 324 kidney cancer cases and matched controls, and a case-control study by Vieira et al. (2013)⁴ that included 246 kidney cancer cases (only 58 were exposed to PFOA through residential exposure) and 7,338 controls. OEHHA chose not to rely upon several relevant and important studies,⁵ including an occupational cohort mortality and cancer incidence study by Raleigh et al (2014) of 4,668 3M employees.⁶ In selecting only two studies for their PFOA PHG analysis, OEHHA dismissed other relevant studies that did not demonstrate an association between PFOA and excess kidney cancer cases.

Based on statements made by OEHHA, both in writing (*see* Support Document at 202, 214 – 216) and verbally during the public webinar, OEHHA appears to have declined to include the Raleigh et al. (2014) study because of the exposure matrix used in that study and misinformation about the data analyses. As discussed in further detail below, 3M respectfully believes OEHHA's criticisms of this study to be misguided. Raleigh et al. (2014) was a collaborative study conducted by the University of Minnesota School of Public Health Division of Environmental Health Sciences and 3M. Prior cohort mortality studies of this 3M manufacturing plant located in Cottage Grove, MN had been reported by these two institutions: Ubel et al. (1980),⁷ Gilliland and Mandel (1993)⁸, and Lundin et al. (2009)⁹. Raleigh et al. was

technologies." *See* OEHHA Announcement, "Perfluorooctanoic acid (PFOA) and Perfluorooctanesulfonic acid (PFOS)" available at https://www.waterboards.ca.gov/drinking_water/certlic/drinkingwater/PFOA_PFOS.html

³ Shearer et al. 2021 J Natl Cancer Inst 113 580-587

⁴ Vieira et al. 2013 Environ Health Perspect 121 318-323

⁵ *See* Steenland and Woskie 2012 Am J Epidemiol 176 909-917 (an occupational cohort mortality study by Steenland and Woskie (2012) of DuPont workers with PFOA exposure (n = 5,791); and PFOA was used as a processing aid in the polymerization of tetrafluoroethylene (TFE) in the production of PTFE. This cohort had a total of 12 kidney cancer deaths); Barry et al. 2013 Environ Health Perspect 121 1313-1318 (a community/worker cohort study by Barry et al. (2013) of 32,254 residents (28,285 community members and 3,713 DuPont workers with residential exposure to PFOA in their drinking water for which there were a total of 105 kidney cancer cases (87 from the community and 18 from the DuPont workers))).

⁶ Raleigh et al. 2014 Occup Environ Med 71 500-506

⁷ Ubel et al. 1980 Am Ind Hyg Assoc J 41 584-589

⁸ Gilliland and Mandel 1993 JOM 35 950-954

⁹ Lundin et al. 2009 Epidemiology 921-928

the first time the 3M Cottage Grove cohort was linked to the two relevant statewide cancer reporting systems (Minnesota and Wisconsin) that were each established in 1988 by their respective state health departments. 3M was involved with the exposure matrix construction but not in record linkage activities, which was conducted between these statewide cancer reporting systems and the University of Minnesota.

The Raleigh et al. study used two referent populations for the mortality study: 1) the state of Minnesota that used traditional summary-based Standardized Mortality Ratio (“SMR”) analyses; and 2) a 3M plant in St. Paul that manufactured tape and abrasives but was not involved with PFOA manufacturing, was the referent group used in the Cox proportional hazard models. Only the St. Paul plant was used as the referent group for the cancer incidence analyses, again, using Cox regression models. Unlike the prior mortality studies of this plant, the construction of the exposure matrix for PFOA in the Raleigh et al. study was noted as reasonable by IARC in their Monograph 110 on PFOA¹⁰ where they wrote,

“the Working Group noted the reasonable quality of the exposure data. Another strength of this study was the use of incidence data, but this analysis covered only a 20-year period, which limited the number of observed cases for some cancers.”

Likewise, Steenland and Winquist (2021)¹¹ also noted the Raleigh et al. study had “improved exposure assessment with estimation of past cumulative inhalation exposure.” In short, 3M recommends that OEHHA reevaluate its assessment of the cancer risk associated with PFOA to consider additional available data including the Raleigh et al. study. A quantitative assessment for PFOA carcinogenicity based on the epidemiological data considered cannot be supported.

Specific Responses to Criticism of Raleigh et al. in the OEHHA Support Document

3M’s responses to OEHHA’s specific criticisms of Raleigh et al. follow below.

Page 214, 3rd paragraph:

OEHHA suggests various possibilities why Raleigh et al. did not find an association with kidney cancer. Each is misguided. The first explanation offered by the OEHHA is:

“Overall, the small numbers of kidney cancer cases, and the imprecise results highlight the possibility that the Raleigh (2014) study could have missed a true association because of chance.”

OEHHA states that Raleigh et al. only had 6 kidney cancer deaths and 16 kidney cancer incident cases with only four in the highest exposure category because of chance and the

¹⁰ <https://publications.iarc.fr/Book-And-Report-Series/Iarc-Monographs-On-The-Identification-Of-Carcinogenic-Hazards-To-Humans/Some-Chemicals-Used-As-Solvents-And-In-Polymer-Manufacture-2016>, accessed 23 October 2021

¹¹ Steenland and Winquist 2021 Environ Res 194 110690

relatively small numbers of cases in the study. But OEHHA fails to acknowledge that Raleigh et al. is consistent with other studies including the occupational study by Steenland and Woskie (2012),¹² which only had 12 kidney cancer deaths through 2008 and these authors never examined for cancer incidence data. Furthermore, there were no new or additional kidney cancer deaths identified in the study by Steenland and Woskie (2012) because the prior study by Leonard et al. (2008)¹³ on the same population had already identified these 12 kidney cancer deaths by the year 2002.

Comparing the highest exposure category in the Raleigh et al. study (4 kidney cancer cases, Hazard Ratio (HR) = 0.73; 95% CI 0.21 – 2.48) to the highest quartile in Steenland and Woskie study (8 deaths, SMR = 2.66; 95% CI 1.15 – 5.24), OEHHA stated, that in their analyses, the upper quartile in the study by Raleigh et al. is not statistically significant from the SMR estimate reported by Steenland and Woskie. Rather, the OEHHA inferred it being “close ($p = 0.08$)”. OEHHA never showed their data on how this was calculated, but went on to infer that this demonstrates the study could have missed a true association by chance.

OEHHA did not mention that the 2nd highest exposure category in Raleigh et al. study also had 4 additional kidney cancer cases HR= 0.98; 95% CI 0.33 – 2.92). In addition, the OEHHA failed to mention that the 2nd highest exposure category in Steenland and Woskie study had 0 (zero) kidney cancer deaths (SMR = 0.0; 95% CI 0.0 – 1.48). Combining the upper two exposure categories, Raleigh et al. reported an HR for kidney cancer of 0.85 (95% CI 0.36 – 2.06). Steenland and Woskie did not report the combined upper two quartiles of exposure for an SMR but it can be readily calculated from Table 1 of the Steenland and Woskie study.

SMR = Observed / Expected, meant that there was a total of 9.4 expected deaths for all quartiles combined. These calculations can then be made for the 1st, 2nd, and 4th quartiles which resulted in approximately 0.9, 2.2, and 3.0 expected deaths. This then yields 3.3 expected deaths occurring in the 3rd quartile (compared to the 0 observed deaths). Therefore, combining the upper two quartiles in Steenland and Woskie, there were then 8 observed kidney cancer deaths and approximately 6.3 expected deaths (SMR = 1.27; 95% CI 0.39 – 1.76) for estimated cumulative exposure of PFOA ≥ 1500 ng/mL-years. Thus, there appears to be no substantial differences between estimates of the magnitude of risk between the upper two exposure categories (albeit different measurements of exposure) in Raleigh et al. study for kidney cancer incidence and Steenland and Woskie study for kidney cancer mortality. As a result, chance is an unlikely explanation for why no association was found.

A reasonable question for OEHHA to have asked is why were there no observed kidney cancer deaths in the second highest exposure category in Steenland and Woskie? Was it chance or could there have been some degree of exposure misclassification? Given the fact there were 8 kidney cancer deaths in this 4th quartile, three of these deaths would

¹² Steenland and Woskie 2012 Am J Epidemiol 176 909-917

¹³ Leonard et al. 2008 Ann Epidemiol 18 15-22

have had to been misclassified from the 3rd quartile to make the SMR estimate for the 4th quartile not statistically significant.

Page 214, 4th paragraph:

The next possible explanation OEHHHA puts forward on why the Raleigh et al. study did not find an association between PFOA and kidney cancer was that it did not present any data on confounding variables such as smoking, BMI, or any other known risk factors for kidney cancer except age and sex. The Raleigh et al. study was both an occupational cohort mortality and a cancer incidence study, and as such, detailed information about these variables is not routinely available, especially for the former study design. OEHHHA fails to mention that Steenland and Woskie also did not have smoking or BMI, data or any other known risk factors for kidney cancer except age and sex data in their cohort mortality study. Likewise, Vieira et al. (2013)¹⁴ or Barry et al. (2013),¹⁵ did not adjust for BMI in their studies. As for smoking data, Shearer et al. (2021), Vieira et al. (2013), and Barry et al. (2013) adjusted for the categories of smoking (current, past, unknown, or never) with only Barry et al. (2013) adjusting for the much more quantifiable, time-varying measurement of smoking data. And OEHHHA chose not to consider the Barry et al. results.

Page 214, 4th paragraph:

The Support Document also states that “the higher SMRs seen in the St. Paul workers for outcomes not known to be associated with PFOA show that these workers were generally less healthy than the Cottage Grove workers and provide evidence that the St. Paul Plant workers were not an appropriate comparison group.” SMR analyses were provided for both the 3M Cottage Grove plant and the 3M St. Paul plant. Both plants had SMRs calculated with the Minnesota mortality rates for comparison purposes. Importantly, the SMRs from each of these two cohorts used different standards meaning these SMRs are not directly comparable to one another as readily seen in Table 1 of Raleigh et al. There was a 9-year mean year of birth difference between the two cohorts. The SMRs are not directly comparable without further adjustment. When researchers cannot be confident that the bias due to comparing SMRs directly is small, estimates should be based on a single common standard applied such as those used in a regression model that accounts for the differences among the compared populations and the effects of exposure on person-time (Rothman et al. 2008)¹⁶.

Therefore, to compare the PFOA-exposed population with the non-exposed population, Raleigh et al. estimated hazard ratios (HR) with 95% CIs for mortality and cancer incidence as a function of PFOA time-dependent exposure using extended Cox regression models. Raleigh et al. stated,

¹⁴ Vieira et al. 2013 Environ Health Perspect 121 318-323

¹⁵ Barry et al. 2013 Environ Health Perspect 121 1313-1318

¹⁶ Rothman et al. 2008 Modern Epidemiology, chapter 4

To compare the APFO-exposed population with the nonexposed population, HR with 95% CIs for mortality and cancer incidence risk were estimated as a function of APFO time dependent exposure using extended Cox regression models. In these models, the Saint Paul workers were the referent population and APFO exposure in the Cottage Grove population was classified into quartiles. The time scale was age, beginning at the date of first employment for the mortality analysis and the later of date of first employment or 1 January 1988 (when registry data were available) for cancer incidence. Follow-up continued until death, diagnosis of the cancer of interest or end of follow-up. Models were adjusted for year of birth and sex.

OEHHA's statement that "the higher SMRs seen in the St. Paul workers for outcomes not known to be associated with PFOA showed that these workers were generally less healthy than the Cottage Grove workers provides evidence that the St. Paul workers were not an appropriate comparison groups" suggests that OEHHA is inappropriately comparing the SMRs directly when age and/or sex distributions differ without a common standardization and/or regression analyses. The St. Paul plant was an appropriate referent when analyzed by Cox proportionate hazard models. Raleigh et al. (2014) also stated the results did not change appreciably when the PFOA exposures were lagged by 10 years.

Page 214, 5th paragraph, continuing onto page 215:

OEHHA was also critical of the Raleigh et al. study because ground water contamination had been "well-documented" near the Cottage Grove facility but no information was available on non-work related residential exposures. Exposures from drinking water were considered small relative to the occupational exposures for the Raleigh cohort. Indeed, in Woskie et al. (2012)¹⁷, the authors likewise stated the following in their development of their exposure matrix for the Steenland and Woskie cohort mortality study:

Another influence on worker serum levels may have come from personal exposures via water in communities surrounding the plant (Emmett et al., 2006; Steenland et al., 2009a). The exposure estimates reported here do not explicitly account for residential exposures over time, although it is believed that relative to workplace exposures these are relatively small. For example, current workers were reported to have a median serum PFOA level of 0.147 versus 0.074 ppm for former workers and 0.027 ppm for current/former residents in the study of the nearby community member PFOA levels (Steenland et al. 2009b).

Potential residential exposure therefore does not provide grounds for dismissing the study.

¹⁷ Woskie et al. 2012 Ann Occup Hyg 56 1025-1037

Page 215, 1st paragraph:

OEHHA provided only a very brief description taken from the Raleigh et al. (2014) published paper as to the process used for the construction of the exposure matrix. We refer OEHHA to Chapter 4 of the study's publicly available dissertation.¹⁸ See Exhibit A.

Page 215. 2nd Paragraph:

OEHHA suggests that little to no information is available on the degree to which inhaled PFOA is absorbed in humans or the inter-individual factors that might affect his absorption. While there have not been inhalation studies of PFOA in humans, in their review paper, Griffith and Long (1980)¹⁹ and Kennedy et al. (1986)²⁰ unquestionably concluded that PFOA is efficiently absorbed in laboratory animals following inhalation exposure and that it is not metabolized and is eliminated intact (as reviewed by Kennedy et al, 2004²¹). The findings from Griffith and Long (1980) and Kennedy et al. (1986) demonstrate that effective serum uptake of PFOA has been shown under both acute and repeated inhalation exposures in rats.

Evidence of PFOA absorption after inhalation exposure in rats (Table 1): In the study by Griffith and Long (1980), 14 days post an acute (one hour) inhalation exposure of 18600 mg/m³ APFO, there were 42 ppm and 2 ppm of organic fluorine detected in male and female rats, respectively (approximately equivalent to 60 and 3 ppm of PFOA, respectively). After a ten-day inhalation exposure with APFO at either 0, 1, 8, or 80 mg/m³ (6 hours/day, 5 days/week for 2 weeks), the respective serum PFOA levels were 1.4, 12, 47, and 108 ppm in male rats immediately after last exposure (Kennedy et al. 1986).

¹⁸ Raleigh 2013 PhD thesis

¹⁹ Griffith and Long 1980 Ame Ind Hyg Ass J 576-583

²⁰ Kennedy et al. 1986 Fd Chem Tox 24 1325-1329

²¹ Kennedy et al. 2004 Crit Rev Toxicol 34 351-384

Table 1

	Griffith and Long (1980)	Kennedy et al. 1986
Animal	CD rats, M and F	CD rats, M only
Study type	Inhalation	Inhalation
Exposure duration	1 hour	10 days
APFO atmospheric concentration	18.6 mg/L (18600 mg/m ³)	0, 1, 8, and 80 mg/m ³
Time of serum samples collected	Day 14 post-exposure	Immediately post-last exposure and on Days 14, 28, 42, and 84 post-last exposure
Serum measurement	<p>Day 14 post-exposure:</p> <p>M: 42 ppm (organic fluorine measured) F: 2 ppm (organic fluorine measured)*</p> <p>*Different serum concentration when compared to male rats due to rapid serum elimination half-life for PFOA</p> <p>A factor of 1.44 is applied to organic fluorine → PFOA conversion:</p> <p>M: 60 ppm (estimated as PFOA) F: 3 ppm (estimated as PFOA)</p>	<p>Immediately post-last exposure:</p> <p>Serum [PFOA] = 1.4, 12, 47, and 108 ppm for 0, 1, 8, and 80 mg/m³ dose groups</p>

Page 215, 2nd paragraph 2:

OEHHA also criticized the method of exposure assessment in Raleigh because “the PFOA exposure estimates ... were not based on actual PFOA measurements.” While no specific biomonitoring validation data were presented, there is strong collaborative evidence that the jobs and tasks with the highest air exposure monitoring data in Raleigh et al. study were, indeed, consistent with the higher PFOA serum concentrations measured. This can be inferred from reading Raleigh et al. (2013²², 2014²³), Olsen et al. (2000)²⁴, and Olsen et al. (2003)²⁵.

A review of the 3M Cottage Grove plant operations provides this perspective. APFO production began at the 3M Cottage Grove plant in 1947. APFO was produced via a five-stage process: electrochemical fluorination; isolating and converting the chemical to

²² Raleigh et al. 2013 PhD thesis

²³ Raleigh et al. 2014 Occup Environ Med 71 500-506

²⁴ Olsen et al. 2000 Drug Chem Tox 23 603-620

²⁵ US EPA docket AR-226-1351

a salt slurry; converting the slurry to a salt cake; drying the cake; and packaging. The greatest likelihood for exposure occurred in the drying area (Olsen et al. 2000; Raleigh et al. 2014). This is substantiated by Raleigh et al. (2013) who provided the range of TWA (mg/m³) for APFO exposure by specific job titles and years. While Raleigh et al. (2012) reported job titles affiliated with electrochemical fluorination (head cell operator, APFO kettle room operator) that had ranges of APFO TWAs (mg/m³) up to 0.04 mg/m³ APFO, those involved with the operation of the spray dryer had measurements that ranged up to 100 fold higher (0.124 mg/m³). Less exposed job titles including clerk, custodian, and finished good checkers had TWAs much lower (\leq 0.002 mg/m³).

While Olsen et al. 2000 did not report biomonitoring data by job titles, much effort for exposure reduction was made in the drying area where the highest PFOA blood levels were known to exist. Thus, while the median PFOA serum levels reported in 1993, 1995, and 1997 were 1100 – 1300 ng/ml (Olsen et al. 2000), the mean values were 5000 – 6800 ng/ml owing to the subset of workers with much higher concentrations that ranged as high as 11400 ng/mL. These employees were generally recognized as having had exposures in the drying area.

The PFOA concentrations that have been reported in the employees at the 3M Cottage Grove plant are in the similar range of concentrations for those reported in the construction of an exposure matrix for the DuPont Washington Works plant by Woskie et al. (2012) who found that, among those working with fine powder production had the highest PFOA serum concentrations (see Table 2).

Table 2

		Worked only in PFOA production area (n=21)			Worked only in PFOS production area (n=29)			Worked only in QC lab (n=9)			Worked in both PFOA and PFOS areas (n=54)			Worked in other fluorochemical areas but not PFOS, PFOS QC lab areas (n=18)		
Olsen et al. 2003 ²⁶	Serum [PFOA], ppm = μ /mL	Mean	Median	range	Mean	Median	range	Mean	Median	range	Mean	Median	range	Mean	Median	range
		18.41	5.20	0.10-92.03	0.46	0.31	0.02-1.73	3.09	2.62	0.25-7.93	2.81	1.45	0.13-17.93	0.67	0.37	0.01-2.49
Woskie et al. 2012 ²⁷		Fine powder and granular PTFE (n=170)			FEP/PFA (n=96)			Non-PFOA (C8) use in Teflon and co-polymer production (n=480)			Maintenance (n=200)			Non-Teflon/co-polymer production division jobs with no PFOA use (n=463)		
	Serum [PFOA], ppm = μ /mL	Mean	Median	range	Mean	Median	range	Mean	Median	range	Mean	Median	range	Mean	Median	range
		5.47	2.88	0.007-59.40	2.53	1.69	0.132-14.04	2.53	0.44	0.008-14.58	0.89	0.50	0.06-6.81	0.24	0.16	0.007-4.14

Taken all together, all these data showed compelling evidence that inhalation exposure was highly likely and the job and the task-based exposure matrix used by Raleigh (2012, 2014) was consistent with biomonitoring data historically reported at the 3M Cottage Grove Plant.

²⁶ US EPA docket AR-226-1351

²⁷ Woskie et al. 2012 Ann Occup Hyg 56 1025-1037

Page 217, 1st paragraph:

In selecting only two studies for their PFOA PHG analysis, OEHHA dismissed other relevant studies that did not demonstrate an association between PFOA and excess kidney cancer cases. Not only was there no excess of kidney cancer cases reported in Raleigh et al. (2014)²⁸, neither did the community worker cohort study - by Barry et al. (2013)²⁹ report an association of kidney cancer cases among the 3,713 DuPont Washington Works employees who participated in that study. Based on their analyses, Barry et al. (2013) reported 18 verified kidney cancer cases in these occupational (DuPont) workers. For the occupationally-related kidney cancer cases, there were no significant trends for the no lag and 10 year lagged analyses. Based on these analyses, the hazard ratios were: no lag HR 0.95 (95% CI 0.5, 1.52; p-value trend = 0.82) and 10-year lag HR 0.99 (95% CI 0.67-1.46, p-value trend 0.97). Of the 28,541 community members in this cohort, Barry et al. reported 87 verified kidney cancer cases. Based on the community lagged analyses, the hazard ratios were HR = 1.14 (95% CI 0.99, 1.32; p = 0.07) and 10-year lagged analyses (HR 1.11; 95% CI 0.96, 1.29; p = 0.17). When analyzed by a linear trend test in log rate ratios across quartiles, the 87 community kidney cancer cases resulted in a p value trends for no lag and 10 year lags of 0.20 and 0.02, respectively. Thus, among three occupational analyses (Raleigh et al. 2014; Barry et al. 2013; and Steenland and Woskie et al. 2012), which likely represent the highest exposed individuals based on overall reported biomonitoring data, only one analysis showed a statistically significant association with kidney cancer. However, that association was not seen when the two highest exposure categories were used. None of these data were considered by OEHHA in their construction of a PHG for kidney cancer. And there remains the confusing possibility of overlapping of kidney cancer cases between Steenland and Woskie (2012)³⁰, Vieira et al. (2013)³¹, and Barry et al. (2013). This was acknowledged by Steenland and Winkquist (2021)³² but they did not provide any insights as to the percentage. And the Shearer et al. (2021) single serum PFOA concentrations measured at general population levels are inconsistent with the other 4 studies. An excess of renal tumors have not been reported in three stocks of Sprague Dawley rats by NTP (2020)³³, Butenhoff et al. (2012)³⁴, and Biegel et al. (2001)³⁵.

2. OEHHA should not use serum ALT and PFOA as a POD due to minimum variance explained in epidemiological studies and the fact that there is no increased risk for liver disease.

In developing the proposed HPC for PFOA, OEHHA misrepresents the relationship between alanine aminotransferase (ALT) and PFOA and how it relates to “liver damage” or

²⁸ Raleigh et al. 2014 *Occup Environ Med* 71 500-506

²⁹ Barry et al. 2013 *Environ Health Perspect* 121 1313-1318

³⁰ Steenland and Woskie 2012 *Am J Epidemiol* 176 909-917

³¹ Vieira et al. 2013 *Environ Health Perspect* 121 318-323

³² Steenland and Winkquist 2021 *Environ Res* 194 110690

³³ https://ntp.niehs.nih.gov/ntp/htdocs/lt_rpts/tr598_508.pdf

³⁴ Butenhoff et al. 2012 *Toxicology* 298 1-13

³⁵ Biegel et al. 2001 *Toxicol Sci* 60 44-55

“liver function.” ALT is a “leakage” enzyme and may be increased due to necrosis, injury or repair. Increases of two- to four-fold in rodents, canines, non-human primates, and humans indicate hepatic injury. As defined by Hall et al. (2012)³⁶:

“Based on the recommendations of regulatory authorities, (EMEA 2010; FDA 2009; HED 2002) increases in ALT activity of two-to threefold should be considered as indicated of ‘hepatocellular damage.’”

As will be discussed below, several studies in the scientific literature that have suggested an elevation of ALT remain well-within the expected physiologic range of measured ALT and therefore, using the term “damage” is misleading. It is also possible to have quite modest but statistically significant increases in ALT that are not toxicologically relevant (Cattley and Cullen, 2013³⁷). The human half-life of ALT is approximately 47 hours with significant variation of 10 – 30% on a day-to-day basis with circadian variation (Cordoba et al. 1999³⁸; Kim et al. 2008³⁹). Most cohort studies examining estimated serum PFOA concentrations when there is only a single ALT measurement period fail to note this variation in half-life.

From a disease standpoint, nonalcoholic fatty liver disease is the most common cause of mild elevations of liver enzymes (Giannini et al. 2005⁴⁰). Liver function should be considered in the context of many different biological processes that occur within the liver including: 1) production of proteins for plasma; 2) regulating blood clotting; 3) production of cholesterol and lipoproteins; 4) conversion of excess glucose to glycogen for storage; 4) regulation of blood amino acids; 5) metabolism of toxins; 6) production of bile; and 7) clearance of bilirubin.

Collectively, the studies assessed by OEHHA do not suggest “liver damage” (see above definition of a 2 to 4- fold increase) as measured by ALT associated with increasing serum concentrations of PFOA. As discussed in detail below, none of these studies, except Convertino et al. (2018), measured aspects of liver function that involved measures of blood clotting. Although some studies’ regression coefficients for PFOA may be statistically significant, the percent variation of ALT explained by PFOA is often minimal, at best, and the increase of ALT is very modest (generally an increase of 1 to 5 IU ALT). Nor was there evidence of increased mortality from increased liver disease in epidemiologic analyses of a community-based exposure to PFOA from drinking water, (Darrow et al. 2016) or in occupational cohort mortality studies (Steenland and Woskie 2012⁴¹ and Raleigh et al. 2014⁴²). These later two studies are limited by the number of deaths reported.

In conclusion, there is no apparent association between PFOA and liver disease including enlarged liver, fatty liver, or cirrhosis based on epidemiological studies. Small percentage

³⁶ Hall et al. 2012 Toxicologic Pathol 40 971-994

³⁷ Cattley, R.C., Cullen, J.M., 2013. Liver and gall bladder. In: W.M. Haschek, C.G. Rousseaux and M.A. Wallig (Eds), Toxicologic Pathology, Elsevier, New York, pp. 1509-1566.

³⁸ Cordoba et al. 1999 Hepatology 28, 1724-1725

³⁹ Kim et al. 2008 Hepatology 47, 1363-1370

⁴⁰ Giannini et al. 2005 CMAJ 172, 367-379

⁴¹ Steenland and Woskie 2012 Am J Epidemiol 176 909-917

⁴² Raleigh et al. 2014 Occup Environ Med 71 500-506

changes in ALT have been reported in some epidemiology studies across quite different perfluoroalkyl concentrations but are within normal physiological ranges. This small magnitude of change of a liver biomarker, if it presents, does not indicate liver damage by any standard clinical practice of medicine. Confounding cannot be ruled out as a possible explanation for this observation due to the many factors that can influence ALT. Thus, there is insufficient evidence of an association between PFOA and ALT in humans, and the calculation of an HPC for PFOA at general population levels by OEHHHA on these grounds is unwarranted.

Specific Responses to Liver Toxicity Studies

Gallo et al. (2012)

The study by Gallo et al. (2012), which was used by the OEHHHA to derive the HPC for PFOA, relied on the C8 Health Project cross-sectional data collected in 2005-2006. They found a positive association between PFOA and serum ALT. Based on 3 different regression models, Gallo et al. reported statistically significant ln-PFOA (ng/mL) beta coefficients in models where ln-ALT was the independent variable.

It is important to note, however, that these three models had an increasing number of covariates (2, 7, and 11) besides PFOA in each model. The R^2 s of these three models were 0.170, 0.174, and 0.265, respectively. However, the partial R^2 for PFOA (difference between R^2 including and excluding PFOA) remained 0.002, 0.001, and 0.002 for these three models, respectively. This clearly does not suggest that PFOA was a substantive contributor to the increase of ln-ALT because it only explains between 0.1 and 0.2 percent of the variance in ln ALT. The coefficient was only statistically significant because of the study sample size ($N = 47,092$). OEHHHA did mention this very low partial R^2 in the regression modeling that was done by Gallo et al., but relied on the study nonetheless. Based on their fitting values of ALT by deciles of PFOA (given the mean values of the covariates), Gallo et al. showed a mean (untransformed) ALT of approximately 20.9 IU/L at 6 ng/mL PFOA that increased to approximately an ALT of 22.2 IU/L at 30 ng/mL PFOA (+1.3 IU/L increase in ALT) but plateaued thereafter. The highest decile was 23 IU/L ALT associated with approximately 320 ng/ml PFOA. It should be noted that the upper normal reference range (depending on laboratory) for ALT is approximately 45 IU/L.

OEHHHA should not rely on the enzyme findings from Gallo et al. (or Darrow et al. discussed below), which suggest “liver damage” is associated with PFOA. In fact, the C8 Science Panel (2012) admitted the lack of evidence for the association between PFOA and liver disease, stating:

From our studies of patterns of diagnosed liver disease there is no evidence of any increased risk of liver disease in relation to PFOA exposure. Based on our studies of liver enzymes and inconsistent findings in reported literature there is some evidence of small shifts in liver function, mainly within the normal physiologic range, being associated with increasing PFOA exposure. It is uncertain if PFOA is the cause of the association, but if so there is no evidence

that this is reflected in any increase in overall incidence of diagnosed liver disease. Therefore, the Science Panel does not find a probable link between exposure to PFOA and liver disease.

Other studies show there is no apparent association between PFOA and liver disease, including enlarged liver, fatty liver, or cirrhosis based on epidemiological studies.

Darrow et al. (2016)⁴³

In their cross-sectional analysis, Darrow et al. (2016) suggested the results of the C8 Science Panel's community worker cohort study were consistent with the Gallo et al. (2012) (above) showing an increasing trend in the β coefficients across quintiles. The estimated serum PFOA in 2005-2006 was Quintile 1 2.6-<5.8 ng/mL PFOA; Quintile 2 5.8-<11.4 ng/mL; Quintile 3 11.4-<26.7 ng/mL PFOA; Q4 26.7-<81.5 ng/mL PFOA; and Q5 81.5-3558.8 ng/ml PFOA. There were up to 11 covariates in these models, which were the same as model 3 in Gallo et al. Darrow et al. (2016) did not provide R^2 or partial R^2 values in these cross-sectional analyses. Neither study adjusted for serum lipids (see below discussion by Deb et al. 2018⁴⁴).

In their analysis of estimated cumulative exposure of PFOA in the C8 Science Panel's community and worker study on liver function and disease, Darrow et al. (2016) provided the linear regression coefficients for ln-transformed ALT per ln-PFOA (see Table S1 of Darrow et al. 2016). These coefficients for PFOA for the 3 models were Model 1 ($\beta = 0.003$); Model 2 ($\beta = 0.012$); and Model 3 ($\beta = 0.011$) adjusted for the same number of covariates in addition to PFOA (2, 7, and 11). The R^2 for these 3 models were 0.15, 0.232, and 0.235 respectively, similar in magnitude to Gallo et al. for the same models, adjusted for the covariates in their cross-sectional analysis. However, PFOA in Darrow et al. (2016) was an estimated cumulative ng/mL-year metric versus measured (ng/mL), and unlike Gallo et al. (2012), Darrow et al. (2016) did not show the partial R^2 for PFOA.

Because the coefficients of determination for the Darrow et al. models 1, 2, and 3 are very similar to Gallo et al. (despite a different metric for PFOA), it is highly likely the partial R^2 for PFOA in the Darrow et al. study also remained in the extremely low range. Thus ln-PFOA (ng/ml-years) explained very little of the variance of ln-ALT in the Darrow et al. study, as shown in Table S1 of its publication.

Additional Studies Showing Lack of Relationship between PFOA and Liver Enzymes

Sakr et al. (2007a)⁴⁵

The authors conducted a cross-sectional analysis of 1,025 active workers at the DuPont Washington Works plant. Median serum PFOA concentrations among 259 of the workers assigned in PFOA (ammonium salt) production areas was 494 ng/mL (range 17

⁴³ Darrow et al. 2016 Environ Health Perspect 124 1227-1233

⁴⁴ Deb et al. 2018 Int J Hepatol 2018 1286170

⁴⁵ Sakr et al. 2007 J Occup Environ Med 49 1086-1096

– 9,550). Lesser exposed groups with more intermittent or past exposures had median PFOA concentrations ranging from 114 to 195 ng/mL. Based on a linear regression analysis with 6 other covariates (model $R^2 = 0.276$), the regression coefficient for ALT was not statistically significant ($\beta = 0.023$, $p = 0.124$). Examining only those workers not taking cholesterol lowering medications ($n = 840$), the regression coefficient became $\beta = 0.031$, $p = 0.071$.

Sakr et al. (2007b)⁴⁶

A longitudinal analysis of ALT and PFOA that involved 231 workers and their measured ALT. The regression coefficient for PFOA was not statistically significant ($\beta = 0.54$, 95% CI -0.46, 1.54).

Costa et al. (2007)⁴⁷

A very small study of 53 male PFOA workers (37 currently exposed and the other 16 previously exposed) and a control group of 107 male workers. Among currently exposed workers, their median serum PFOA concentration was 5,710 ng/mL while the formerly exposed workers had a median serum PFOA concentration ($n = 11$) of 4,430 ng/mL. The mean ALT in the exposed workers was 47.8 IU/L with 17.9% outside reference range. For the control group, the mean ALT was 40.6 IU/L with 26.2% outside of reference range. A comparison of 34 exposed and non-exposed workers matched by age, work seniority, day/shiftwork, and living conditions did not find a statistically significant difference between mean ALT values between exposed and non-exposed workers.

Olsen and Zobel (2007)⁴⁸

A cross-sectional study of 506 male 3M workers, not taking cholesterol lowering medications, working at 3 different production sites. Analyzed by deciles, they reported the adjusted mean of the 1st decile was 29 IU/L (95% CI 25 – 33) compared to the mean of the 10th decile was 34 IU/L (95% CI 30 – 38). These means were not statistically significantly different. The median PFOA concentrations were 60 ng/mL (range 7 – 130) in the first decile compared to 4,940 (range 3,710 – 92,030) in the 10th decile. An adjusted (age, BMI, alcohol) regression analysis that examined \ln ALT and \ln PFOA resulted in a coefficient for \ln PFOA of 0.0249 (p-value 0.06). A different analysis that substituted triglycerides for BMI resulted in an adjusted coefficient of 0.0115 (p-value 0.40). The latter was examined because ALT can also be elevated due to dyslipidemia (see further discussion below).

⁴⁶ Sakr et al. 2007 J Occup Environ Med 49 872-879

⁴⁷ Costa et al. 2009 J Occup Env Med 51 364-372

⁴⁸ Olsen and Zobel 2007 Int Arch Occup Env Hea 81 231-246

Olsen et al. (2012)⁴⁹

A longitudinal analysis of workers who were engaged in the decommissioning, demolition and removal of production buildings that were involved with the production of perfluorooctanesulfonyl fluoride (POSF) and PFOA. This remediation work occurred over a 2-year time period although not all workers were engaged for that period of time. Baseline clinical chemistries and perfluoroalkyl measurements were taken before a worker became involved with the project, which was followed by similar end-of-project measurements. Of 120 workers with baseline concentrations < 15 ng/mL PFOA and < 50 ng/mL PFOS, their median increase at end-of-project was 5.3 ng/mL PFOA (mean 44.2 ng/mL) ($p < 0.0001$) and 0.7 ng/mL PFOS (median 4.2 ng/mL) ($p < 0.0001$). Given these modest increases in serum PFOA or PFOS concentrations, there was no change in median ALT and the mean ALT change was -0.7 IU/L ($p = 0.53$).

Convertino et al (2018)⁵⁰

A human experimental study as it related to PFOA and liver enzymes. The study was a 6-week phase one clinical trial conducted in Scotland to determine the maximum tolerated dose that could be provided with the weekly oral administration of PFOA (ammonium salt). The ultimate goal was to evaluate the chemotherapeutic potential of PFOA in patients with solid tumors (Convertino et al. 2018). The study was a standard 3+3 dose escalation phase 1 study with forty-nine subjects participated. Subjects received PFOA (ammonium salt) on a single weekly dose as high as 1200 mg week. Monitoring of clinical chemistries, including ALT, AST, GGT, alkaline phosphatase and total bilirubin were done as well as fibrinogen, prothrombin time, and activated partial thromboplastin time. Based on analysis of the probability distribution functions, ALT was unchanged for different categorizations with the highest PFOA category at 870 – 1530 μ M (~360,000 – ~632,000 ng/mL) where a modest reduction of serum cholesterol was evident.

Additionally, there are several general population studies exploring PFOA and liver enzymes.

Several of the studies reported by OEHHA analyzed NHANES data. The challenges of using NHANES biomonitoring data to incorporate into any form of risk assessments has been well-described by Sobus et al. (2015)⁵¹. In this regard, both Lin et al. (2010)⁵² and Gleason et al. (2015)⁵³ have analyzed multiple 2-year cycle NHANES cross-sectional data with liver enzymes and PFOA or PFOS. As part of their analysis of NHANES data, Lin et al. or Gleason et al have not been able to address an important methodological limitation regarding the relationship between liver enzyme and serum lipids.

⁴⁹ Olsen 2018 JOEM 60 e563-e566

⁵⁰ Convertino et al. 2018 Toxicol Sci 163 293-306

⁵¹ Sobus et al. 2015 Environ Health Perspect 123 919-927

⁵² Lin et al. 2010 Am J Gastroenterol 105 1354-1363

⁵³ Gleason et al. 2015 Environ Res 136 8-14

As shown by Deb et al. (2018)⁵⁴ in their analysis of NHANES data from 1999-2012, there is an association between measured liver enzymes and lipid levels. Deb et al. reported that LDL was associated with a 2-fold increase in odds of an elevated ALT and AST measurements. Any association between perfluoroalkyls measurements and liver enzymes should consider adjusting for age, sex, race/ethnicity, and lipids. If lipids are associated with liver enzymes, then lipids might be a confounder in studying the association between perfluoroalkyls and liver enzymes.

However, some suggest PFOA may be associated with lipids (at lower PFOA concentrations). Therefore, lipids, at low concentrations, might be on the causal path between the exposure (perfluoroalkyls) and increased liver enzymes. OEHHHA offered no insights into the relationship between perfluoroalkyls, lipids, and liver enzymes.

In addition, in their analyses of 2011 – 2014 NHANES data, Jain and Ducatman (2019)⁵⁵ reported there was no association with serum ALT and PFOA in non-obese people. The Canadian Health Measures Survey (Fisher et al. 2013)⁵⁶ contains no self-reported cases of liver disease arising from the NHANES data (Melzer et al. 2010).⁵⁷ There are also no self-reported cases of medically validated liver disease with exposure to PFOA in the C8 Health Panel study (Darrow et al. 2016), including fatty liver disease.

It is incorrect to infer that the weak associations between ALT and measured perfluoroalkyls, in populations whose serum PFAS concentrations can be orders of magnitude different, cause any increased risk of liver disease. Numerous confounding factors must be considered in analyses of ALT. These include the usual confounders of age, sex, body mass index, alcohol, glucose in women, physical activity, smoking, triglyceride level, total cholesterol, and exposures to toxins in an environmental and/or occupational setting.

3. Additional Comments on OEHHHA's Conclusions about the Health Effects of PFOA

3M's response to additional conclusions made by OEHHHA about the health effects of PFOA in the Support Document are provided below.

Page 140,4th paragraph.

See above comments regarding the Raleigh et al. (2014) study. OEHHHA did not provide a detailed analysis of the "potential reasons" the results from this study differ from others regarding the association between kidney cancer and PFOA.

⁵⁴ Deb et al. 2018 Int J Hepatol 2018 1286170

⁵⁵ Jain and Ducatman 2019 J Occup Environ Med 61 293-302

⁵⁶ Fisher et al. 2013 Environ Res 121 95-103

⁵⁷ Melzer et al. 2010 Environ Health Perspect 118 686-692

Page 141, 2nd paragraph.

We do not disagree with the analysis in of liver cancer and PFOA in Eriksen et al. (2009)⁵⁸ (e.g., range 5th percentile men for liver cancer was 2.5 ng/mL and 13.7 ng/mL for the 95th percentile). However, the exposure range reported in Shearer et al. (2021) should be discussed as limited in the preceding paragraph on kidney cancer, just as the exposure ranges were limited in the Eriksen et al. (2009) study.

Page 141, 2nd paragraph.

Unlike liver cancer and TFE reported in rodent studies discussed in this paragraph, OEHHA did not mention in the previous paragraph on kidney cancer that TFE caused an increased incidence of renal cell adenoma or carcinoma (combined) at the highest dose of TFE in both male and female rats compared to controls. See pages 121-124 of IARC Monograph 110⁵⁹. OEHHA should correct this oversight.

Page 142, 2nd paragraph.

OEHHA should have mentioned that Raleigh et al. (2014)⁶⁰ conducted a cancer incidence study (1988 – 2008) of the 3M Cottage Grove workforce and calculated hazard ratios (95% CI). For the 188 prostate cancer cases reported by Raleigh et al. (2014) when compared to the referent St. Paul plant (n = 253 cases) in a Cox proportional regression model, the hazard ratios for the four quartiles of increased exposure to cumulative PFOA (ug/m³-yrs) were: 1.0 (reference); 0.80 (95% CI 0.57, 1.11); 0.85 (0.61, 1.19); 0.89 (0.66, 1.21); and 1.11 (0.82, 1.49). OEHHA also should provide the hazard ratio results for the community worker study by Barry et al. (2013)⁶¹ which consisted of a total of 446 prostate cancer cases that resulted in a 10-year lag exposure analysis for PFOA of HR = 0.99 (95% CI 0.94, 1.05).

Page 202, 1st Paragraph with Figure 6.2.1.

OEHHA's statement that "although it is unknown how much of this leveling off may be due to decreases in PFOA exposure in the US, similar latency patterns following exposure cessation have been seen for other carcinogens, including smoking (Tindle 2018)" is not supported by the reference cited. The Tindle reference is only about smoking – a well known association where the risk for lung cancer among ex-smokers does decline years after cessation but does not reach the level of nonsmokers. The Tindle 2018 reference, however, is not about "other carcinogens." OEHHA should identify these 'other carcinogens' with references. Furthermore, an equally logical explanation, if not more so, is the early detection of latent renal cell cancers detected inadvertently by imaging that was conducted for other reasons. Early detection of prostate cancer by PSA

⁵⁸ Eriksen et al. 2009 JNCI 101 605-609

⁵⁹ IARC Monograph 110, pgs. 121-124, <https://publications.iarc.fr/Book-And-Report-Series/Iarc-Monographs-On-The-Identification-Of-Carcinogenic-Hazards-To-Humans/Some-Chemicals-Used-As-Solvents-And-In-Polymer-Manufacture-2016>, accessed 23 October 2021

⁶⁰ Raleigh et al. 2014 Occup Environ Med 71 500-506

⁶¹ Barry et al. 2013 Environ Health Perspect 121 1313-1318

also initially increased the diagnoses of prostate cancer in the early 1990s, but subsequently declined.⁶²

Page 203, Table 6.2.2.

OEHHA provides the exposure category midpoint value (ng/mL) for the four exposure categories listed (2.0, 4.7, 6.4, 17.3). This is misleading because this is not the average value found for the distribution in each of these exposure category ranges. This value is not provided in Shearer.

Page 204, 2nd Paragraph

OEHHA states the long half-life of elimination of PFOA indicates a single serum measurement would be sufficient to provide an accurate and precise measurement of a person's long-term PFOA exposure. There continues to be considerable controversy regarding the distribution, calculation, and measurement biases associated with the serum elimination half-lives of PFOA in the human population (Dourson et al. 2020)⁶³. The OEHHA position of a single PFOA measurement is sufficient is not defensible when measured between 2 and 18 years prior to the diagnosis of the disease. Clearly, if the serum elimination half-life ranges between 0.5 and 2.0 years, a PFOA measurement taken 8.8 years prior to the diagnosis could be 5+ half-lives casting questions on the relationship between a single PFOA measurement and its relation to the diagnosis of kidney cancer.

Page 207, Table 6.2.3

OEHHA must explain why they chose not to include the P_{trend} statistics that were in Shearer et al.⁶⁴ (labeled therein as Table 2). Alternatively it must put the P_{trend} statistics back into the OEHHA abstracted Table 6.2.3. As Shearer explained on page 582 of their JNCI paper, “we observed statistically significant positive trends in RCC risk with increasing pre-diagnostic conditions of several PFAS, including PFOA (highest quartile vs lowest, OR = 2.63, 95% CI = 1.33 to 5.20) $P_{\text{trend}} = 0.007$ ” based on intraquartile median value without adjusting for other PFAS. Adjusting for other PFAS, they did not observe a statistically significant P_{trend} with PFOA (highest quartile vs lowest OR = 2.19, 0.86 to 5.61), $P_{\text{trend}} = 0.13$.

Page 207, Table 6.2.3.

In this matched case-control study, according to Shearer et al, the category cut points were assigned based on quartiles of serum concentrations of each PFAS among controls (except for PFUnDA and PFDA). By standard definition the odds ratio of the least exposed category (referent) is set at 1.0. However, there were only 47 cases in this reference group with the least exposure to PFOA (< 4.0 ng/mL). This distribution seems

⁶² <https://seer.cancer.gov/archive/studies/surveillance/study6.html>, accessed 23 October 2021

⁶³ Dourson et al. 2020 Regul Toxicol Pharmacol 110 104502

⁶⁴ Shearer et al. 2021 J Natl Cancer Inst 113 580-587

rather odd where there are 81 controls and only 47 cases in the referent group. One would expect more similar distribution among the least exposed. Neither Shearer et al nor OEHHA commented on this referent group which becomes the main driver in the subsequent OR calculations for the other 3 exposure categories.

Steenland et al. (2020)⁶⁵ cautioned readers about interpreting data from low exposure contrast studies. This included the Shearer et al. study. OEHHA was no less cautious with low exposure range studies when they discussed with their critique of the Eriksen et al. (2009)⁶⁶ study.

Reverse causation is referred to as a type of pharmacokinetic bias (Andersen et al. 2021)⁶⁷ and occurs when measurement of the physiological outcome (e.g., eGFR) has been moderated by the health outcome itself. It is difficult to understand how Shearer et al. (2021) can infer a disease state that will not be diagnosed until, on average, 8+ more years after a single serum measurement of PFOA, could have influenced that single measurement. OEHHA offers no biological explanation. The pharmacokinetic bias occurs when there is a sufficient window of time for the disease state to influence the measured physiological outcome. In this situation, the lack of an association between eGFR, PFOA, and kidney cancer, is little proof that reverse causation does, or does not, exist. Certainly, it is possible there could be some pre-diagnostic conditions that result in declining renal function but it remains highly speculative for OEHHA (and Shearer et al.) to surmise that the lack of an association between a single eGFR measurement and the diagnosis of kidney cancer eliminates the concern about this pharmacokinetic bias in the association between the exposure (single measurement of PFOA) and kidney cancer.

Page 211, 7th Paragraph

OEHHA states that although no dose-response was presented in Vieira et al. (2013)⁶⁸, the ORs for the two highest exposure categories were increased and statistically significant for the relationship between PFOA and kidney cancer. OEHHA did not decide to similarly combine the top two exposure categories in the Steenland and Woskie (2012)⁶⁹ cohort mortality study. If they had, the results would not have been statistically significant. Combining the upper two quartiles in Steenland and Woskie (2012), there were 8 observed kidney cancer deaths and approximately 6.3 expected deaths (SMR = 1.27; 95% CI 0.39 – 1.76) for estimated cumulative exposure of PFOA \geq 1500 ng/mL-years. *See infra*, extended comments for Page 214, 3rd paragraph.

⁶⁵ Steenland et al. 2020 Environ Int 145 106125

⁶⁶ Eriksen et al. 2009 JNCI 101 605-609

⁶⁷ Andersen et al. 2021 Environ Res 197 111183

⁶⁸ Vieira et al. 2013 Environ Health Perspect 121 318-323

⁶⁹ Steenland and Woskie 2012 Am J Epidemiol 176 909-917

The Vieira et al. (2013) study is an epidemiology, not toxicology, study where OEHHA decided to exclude the top dose category of around 500 ng/mL to enhance model fit and this value was “well above those seen in the large majority of the US population.” If the latter is the case, then OEHHA also needs to remove the next highest dose 64.70 ng/mL as well as this is also well above the PFOA values seen in the large majority of the US population today. As shown for NHANES, data in 1999-2000 the 95th percentile for PFOA serum concentration was 8.70 ng/mL (95% CI 7.00 – 10.0) and by 2007-2008 the 95th percentile declined to 6.90 ng/mL (95% CI 5.90-7.60)⁷⁰. In the NHANES early release of the 2017-2018 data, the 95th percentile for PFOA had declined to 3.77 ng/mL (95% CI 3.17 – 5.07)⁷¹. Therefore, OEHHA should not retain the 64.70 ng/mL data point in the regression analysis of the Vieira et al study. It is well above the 95th percentile of 3.77 ng/mL in the US general population. Both the 500 ng/mL data point and the 64.70 ng/mL data point well exceed the large majority of the US population today. If the two highest Vieira et al. data points are excluded (500 ng/mL and 64.70 ng/mL) then the next highest data point becomes 16.60 ng/mL, which is still nearly 5 times higher than the 95th percentile for PFOA in 2017-2018. Both data points should be removed in data analyses; otherwise OEHHA can be accused of data manipulation. Alternatively, OEHHA should leave all 5 data points to be analyzed from the Vieira et al. study.

B. PFOS

1. PFOS should not be considered a carcinogenic agent based on liver tumors observed in rats.

The data OEHHA cites as demonstrating an association between PFOS and liver cancer in rats does not support such a conclusion. Based on the differences in species-specific mechanisms between humans and rodents, however, 3M finds that the Butenhoff study and the other publications, do *not* support the conclusion that PFOS is carcinogenic to humans.

In the only 2-year cancer bioassay for PFOS, Butenhoff et al.⁷² reported that PFOS treatment was related to an increase in benign hepatocellular adenomas in Sprague Dawley rats. The US EPA and NTP have issued cautionary guidance for making conclusions about carcinogenicity in humans based on evidence in laboratory animals. There are differences in the mechanism of action (MOA) between animals and humans.⁷³ For example, NTP states:

[c]onclusions regarding carcinogenicity in humans or experimental animals are based on scientific judgment, with consideration given to all relevant information. Relevant

⁷⁰ https://www.cdc.gov/exposurereport/pdf/FourthReport_UpdatedTables_Volume1_Mar2021-508.pdf, accessed 23 October 2021

⁷¹ https://www.cdc.gov/exposurereport/pfas_early_release.html, accessed 23 October 2021

⁷² Butenhoff et al. 2012 Toxicology 293 1-15

⁷³ Proposed OPPTS science policy: PPARα-mediated hepatocarcinogenesis in rodents and relevance to human health risk assessments, USEPA, 2003.

*information includes, but is not limited to, dose response, route of exposure, chemical structure, metabolism, pharmacokinetics, sensitive sub-populations, genetic effects, or other data relating to mechanism of action or factors that may be unique to a given substance. For example, there may be substances for which there is evidence of carcinogenicity in laboratory animals, but there are compelling data indicating that the agent acts through mechanisms which do not operate in humans and would therefore not reasonably be anticipated to cause cancer in humans.*⁷⁴

3M's review of the established mechanistic data does not lead to the conclusion that PFOS is likely to cause liver cancer in humans. The mechanistic research shows that liver tumors in rats with exposures to PFOS are explained by the activation of several hepatic xenosensor nuclear receptors, such as peroxisome proliferator-activated receptor α (PPAR α), constitutive androstane receptor (CAR), and pregnane X receptor (PXR).^{75,76,77,78,79}

The qualitative differences between humans and rodents in the susceptibility of the xenosensor nuclear receptor activation brings into question the relevance of rodent liver tumor response and biological significance, if any, to humans, as it relates to PFOS exposure.

OEHHA acknowledged "there is substantial debate about whether hepatic effects of PPAR α -activating compounds in rodents are relevant to humans due to interspecies differences in activation characteristics."⁸⁰ However, OHHEA ignored these interspecies differences in activation characteristics for CAR and PXR, noting that the uncertainty about whether hepatic tumors are caused "solely" by activation of PPAR α means that evidence of liver tumors in rodents should not be dismissed "due to the assumption that it lacks human relevance."⁸¹

OEHHA's conclusion is *not* supported by the available scientific data because similar to PPAR α , detailed mechanistic studies in regards to the hyperplastic responses have also shown a species-specific difference in the functions of CAR and PXR between rodents (more susceptible) and humans (less sensitive).^{82,83,84,85,86,87}

⁷⁴ <https://ntp.niehs.nih.gov/whatwestudy/assessments/cancer/criteria/index.html>, accessed 22 August 2021

⁷⁵ Bjork et al. 2011 Toxicology 288 8-17

⁷⁶ Bjork and Wallace 2009 Toxicol Sci 111 89-99

⁷⁷ Elcombe et al. 2012 Toxicology 293 16-29

⁷⁸ Elcombe et al. 2012 Toxicology 293 30-40

⁷⁹ Vanden Heuvel et al. 2006 Toxicol Sci 92 476-489

⁸⁰ Proposed Public Health Goals for Perfluorooctanoic Acid and Perfluorooctane Sulfonic Acid in Drinking Water, Office of Environmental Health Hazard Assessment at 153 (July 2021).

⁸¹ Proposed Public Health Goals for Perfluorooctanoic Acid and Perfluorooctane Sulfonic Acid in Drinking Water, Office of Environmental Health Hazard Assessment at 159 (July 2021).

⁸² Corton et al. 2014 Crit Rev Toxicol 44 1-49

⁸³ Elcombe et al. 2014 Crit Rev Toxicol 44 64-82

⁸⁴ Gonzales and Shah 2008 Toxicology 246 2-8

⁸⁵ Klaunig et al. 2012 Reprod Toxicol 33 410-418

⁸⁶ Lake 2009 Xenobiotica 39 582-596

⁸⁷ Ross et al. 2010 Toxicol Sci 116 452-466

The significance of the above-mentioned mechanistic data which demonstrated the additional non-PPAR α nuclear receptor activation by CAR and PXR in rodents are two-fold:

- 1) It provides the direct evidence of a plausible biological mechanism in rodents, and
- 2) It also illustrates a species-specific difference in the functions of these xenosensor nuclear receptors that likely explain why humans are considerably less sensitive to the pleiotrophic effects of CAR and PXR activation than rodents, similar to what PPAR α MOA data have shown.

Overall, because PFOS is neither genotoxic nor mutagenic and it does not metabolize,⁸⁸ the known species differences between rodent and human strongly support that PFOS-induced hepatic tumors in rodents are unlikely to occur in humans. This is further substantiated by the lack of epidemiological evidence for liver tumors in highly-exposed populations.⁸⁹ Therefore, the qualitative differences in the susceptibility of the xenosensor nuclear receptor activation undermine OHHEA's conclusion that PFOS presents a carcinogenic hazard to humans.

2. PFOS should not be considered a carcinogenic agent based on pancreatic islet cell tumor observed in male rats

PFOS should also not be considered as a carcinogenic agent to humans based on pancreatic islet cell tumor observed in rats. In the same 2-year cancer bioassay for PFOS, Butenhoff et al.,⁹⁰ the authors did NOT find a statistically significant PFOS treatment-related relationship between PFOS ingestion and pancreatic islet cell carcinoma in male Sprague Dawley rats. The original study (referenced as Thomford 2002 by the OEHHHA) also did not find a statistically significant increasing trend in pancreatic islet adenoma, carcinoma, or combined adenoma and carcinoma. The reason OEHHHA concluded "[a]n increase in pancreatic islet cell carcinoma (by trend) was also observed in male rats[,]” was solely due to a different method of calculating the tumor incidence rate.

The table below summarizes the difference of the two analyses. As shown, Thomford 2002 calculated the total tumor incidence rate based on the total number of the tissues examined per specific dose group. OEHHHA calculated the tumor incidence rate based on the number of animals alive at the time of first occurrence of the tumor.

⁸⁸ https://www.epa.gov/sites/production/files/2016-05/documents/pfos_hesd_final_508.pdf, accessed 22 August 2021

⁸⁹ Alexander et al. 2003 Occ Env Med 60 722-729

⁹⁰ Butenhoff et al. 2012 Toxicology 293 1-15

Table 3

From Thomford 2002 (Text Table 5)			From OEHHA (Table 5.7.7)		
K ⁺ PFOS concentration in feed (ppm)	Total # of tissues examined	Pancreas Islet cell carcinoma, Total incidence (Rate)	K ⁺ PFOS concentration in feed (ppm)	Total # of tissue examined (per number of animals alive at the time of first occurrence of the tumor)	Pancreas Islet cell carcinoma, Total incidence (Rate)
0	60	1 (1/60=0.017)	0	38	1 (1/38=0.026)
0.5	49	2 (2/49=0.041)	0.5	41	2 (2/41=0.049)
2	50	2 (2/50=0.040)	2	44	2 (2/44=0.045)
5	50	5 (5/50=0.100)	5	44	5 (5/44=0.113)
20	60	5 (5/60=0.083)	20	40	5 (5/40=0.125)
Trend test		p = 0.0681	Trend test		p < 0.05

The relationship between pancreatic islet cell tumors and PFOS is further called into question because these tumors are one of the common spontaneous tumor types documented in aged Sprague Dawley rats.^{91,92} While the specific mechanisms are not fully understood, scientists believe that genetic and environmental factors could be involved in tumor growth. For instance, increased dietary calories (i.e., via *ad libitum* food consumption) could contribute to the development of spontaneous age-related tumors in Sprague Dawley rats such as chronic nephropathy, exocrine pancreatic atrophy and fibrosis, pancreatic islet hyperplasia and fibrosis, and the early development of potentially lethal tumors in the pituitary and mammary glands.

In the 2-year cancer bioassay study for PFOS where food was given *ad libitum*, Butenhoff et al. 2012⁹³ reported that the control and K⁺PFOS-treated male rats had generally similar food consumption rates. However, there were intermittent lower body weights observed in the 20 ppm-treated group animals. While the actual metabolic caloric balance was not evaluated in that study, it is possible that the subtle difference in food consumption per body weight may have, in part, contributed to the observation of intermittent lower body weights.

In addition, the pancreatic islet cell tumor type (endocrine-based) should not be confused with the pancreatic acinar cell tumor (exocrine-based) that has been reported in rats with exposure to PFOA.^{18,94,95} The MOA of the pancreatic acinar cell tumors in the rats exposed to PFOA is likely through increased cholecystikinin (“CCK”) as a consequence of cholestasis. While CCK promotes acinar cell hyperplasia in the rats, this MOA is not considered to be relevant to human risk. In humans, the causal mechanism in the development of the human

⁹¹ Suzuki et al. 1979 J Cancer Res Clin Oncol 95 187-196

⁹² Dillberger 1994 Toxicol Path 22 48-55

⁹³ Butenhoff et al. 2012 Toxicology 293 1-15

⁹⁴ Butenhoff et al. 2012 Toxicology 298 1-13

⁹⁵ Biegel et al. 2001 Toxicol Sci 60 44-55

pancreatic (ductule) adenocarcinomas is neurogenically dependent, rather than the CCK pathway, as observed in rodents.⁹⁶

Collectively, these data clearly illustrate why PFOS should not be considered as a carcinogenic agent based on either liver tumor or pancreatic islet cell tumor observed in rats. Several regulatory bodies have also reached similar conclusions, including:

USEPA, 2016⁹⁷

In the case of PFOS, the existing evidence does not support a strong correlation between the tumor incidence and dose to justify a quantitative assessment.

Health Canada, 2018⁹⁸

Some associations between PFOS and risk of cancer... were observed; however, the evidence does not support the carcinogenicity of PFOS.

EFSA, 2020⁹⁹

In the Opinion on PFOS and PFOA (EFSA CONTAM Panel, 2018), a number of studies on cancer incidence or cancer mortality at occupational or environmental exposure were reviewed. In summary, those studies provided insufficient support for carcinogenicity of PFOS and PFOA in humans.

A quantitative assessment for PFOS carcinogenicity based on the available data is not supported. 3M recommends that OEHHA reconsider its approach on cancer assessments for PFOS.

3. There is insufficient evidence to explain the underlying reasons for an epidemiological association with increased total cholesterol and PFOS.

OEHHA considered four cross-sectional studies (Dong et al. 2019);¹⁰⁰ Steenland et al. (2009);¹⁰¹ Frisbee et al. (2009);¹⁰² and Starling (2014)¹⁰³ in their determination of a PHG and PHC for PFOS based on increased serum total cholesterol in the human. 3M believes the use of these studies, and particularly Steenland et al. (2009) study to evaluate an HPC is highly premature given recent scientific literature, which OEHHA did not consider. Recent studies include two workshop panel reports, published in 2021 (Fragki et al. 2021;¹⁰⁴ Andersen et al. 2021¹⁰⁵), that related to the question what might be the underlying reasons why many

⁹⁶ Myer et al. 2014 Toxicol Pathol 42 260-274.

⁹⁷ https://www.epa.gov/sites/production/files/2016-05/documents/pfos_hesd_final_508.pdf, accessed 22 October 2021

⁹⁸ <https://www.canada.ca/en/health-canada/services/publications/healthy-living/guidelines-canadian-drinking-water-quality-guideline-technical-document-perfluorooctane-sulfonate/document.html>, accessed 23 October 2021

⁹⁹ Schrenk et al. 2020 EFSA J 18 e06223

¹⁰⁰ Dong et al. 2019 Ecotoxicol Environ Saf 173 461-468

¹⁰¹ Steenland et al. 2009 Am J Epidemiol 170 1268-1278

¹⁰² Frisbee et al. 2009 EHP 117 1873-1882

¹⁰³ Starling et al. 2014 Environ Int 62 104-112

¹⁰⁴ Fragki et al. 2021 Crit Rev Toxicol 51 141-164

¹⁰⁵ Andersen et al. 2021 Toxicol 459 152845

epidemiological studies, primarily cross-sectional, have reported positive association between serum concentrations of perfluoroalkyl substances (in particular PFOS, PFOA, PFHxS) and modestly elevated serum cholesterol. In addition, the recent scientific opinion by a regulatory body, EFSA¹⁰⁶, also did not consider this association (observation of increased cholesterol with PFAS in humans) to be a driver in its calculation of a TWI because of the uncertainties that have recently arisen in the literature. More recently, Dzierlenga et al. (2021)¹⁰⁷ reported an association with increased dietary fiber and decreased PFAS levels using NHANES data. Dietary fiber is known to reduce serum cholesterol levels. This raises the question, which was not examined in the four studies evaluated by the OEHHA (Dong, Steenland, Frisbee, or Starling) as to the confounding presence of dietary fiber in studying the association between PFOS/PFOA and serum total cholesterol.

Because of the timing of their publications, it is understandable the OEHHA may not have been aware of these recent publications. 3M recommends that OEHHA devote sufficient resources to more thoroughly understand the pharmacokinetics and mechanisms concerning the association between lipids and PFOA, as recommended by the two workshop panels (Fragki et al. 2021 and Andersen et al. 2021) before issuing a HPC based on such an association.

3M is not aware of other state, federal, or international regulatory agencies that have chosen to use the Steenland et al. (2009) cross-sectional study on PFOS and lipids as their Point of Departure to calculate a health-based guidance value. We are not aware of any regulatory agency that has declared a causal association between low concentrations of PFAS and modestly elevated serum total cholesterol. Many of the questions raised by others (Fragki et al. 2021;¹⁰⁸ Andersen et al. 2021;¹⁰⁹ EFSA 2020;¹¹⁰ ATSDR 2021;¹¹¹ Dzierlenga et al. 2021;¹¹² Chang et al. 2017;¹¹³ and Canova et al. 2020¹¹⁴) need to be addressed for further elucidation of this epidemiologic association. Thus, there is insufficient evidence of an association with cholesterol in humans at general population levels, to warrant it as a POD for the calculation of a PHG for PFOS by OEHHA

To assist OEHHA with its review of more recent literature, 3M provides the following summaries of published papers and reports to OEHHA's attention, including a list of excerpts from the two workshop panels (Fragki et al. 2021 and Andersen et al. 2021) for OEHHA's consideration.

¹⁰⁶ Schrenk et al. 2020 EFSA J 18 e06223

¹⁰⁷ Dzierlenga et al. 2021 Environ Int 146 106292

¹⁰⁸ Fragki et al. 2021 Crit Rev Toxicol 51 141-164

¹⁰⁹ Andersen et al. 2021 Toxicol 459 152845

¹¹⁰ Schrenk et al. 2020 EFSA J 18 e06223

¹¹¹ <https://www.atsdr.cdc.gov/toxprofiles/tp200.pdf>, accessed 10-19-2021

¹¹² Dzierlenga et al. 2021 Environ Int 146 106292

¹¹³ Chang et al. 2017 Toxicol Sci 156 387-401

¹¹⁴ Canova et al. 2020 Environ Int 145 106117

Fragki et al. 2021¹¹⁵ and Andersen et al. 2021¹¹⁶

A 16-member panel that participated in the Fragki et al. 2021 paper conducted a workshop, supported by the European Union's Horizon 2020 research and innovation program. None of the authors had been involved in legal or regulatory matter related to the content of their article. The 11 members of the Andersen et al. (2021) paper held a workshop held under the auspices of Ramboll with funds appropriated to Ramboll for this workshop by 3M. None of these authors were directly compensated by 3M. None of the authors were engaged to testify as experts on behalf of the sponsors and statements made in the paper are those of the authors and not of the author's employer or the sponsors. One workshop participant was a member of both of these panels (Tony Fletcher) who was one of the three members of the C8 Science Panel.

Participants from both panels were asked to provide their professional insights into addressing the question, that was raised as early as 2010 in the review paper by Steenland et al. (2010)¹¹⁷ about the evidence of a modest positive association with cholesterol in primarily cross-sectional epidemiological studies although the magnitude of the cholesterol effect was considered inconsistent across different exposure levels. Fragki et al. points this out by saying much of the increase observed at low PFOS/PFOA serum levels of above 50 ng/mL. In contrast, the reported magnitude of the effect on cholesterol is much lower in workers at much higher serum concentrations (e.g., a 2-3% increase in cholesterol per increase in serum PFOA levels of 1000 ng/mL was reported by Sakr et al. 2007).¹¹⁸ These observations are contrary to the toxicological evidence that has demonstrated a reduction in cholesterol due to well-known mechanisms involving nuclear receptors such as PPAR_{alpha} and likely other transcription factors.

It is also worth noting that 3M has been working with TNO Biosciences (Leiden, The Netherlands) using humanized Apo*E3.Leiden.CETP mice to study lipid metabolism and PFOS. This mouse model mimics human lipoprotein metabolism and is widely used in human atherosclerosis research. While the study data from these humanized mice has identified the key mechanism in terms of how higher levels of PFOS (i.e., toxicological doses) can decrease serum lipids (Bijland et al. 2011),¹¹⁹ they did not support a causal explanation for the positive association observed between serum lipid and low PFOS levels in humans (3M unpublished data). This observation was consistent with conclusion reached by these two independent expert workshop panels (Andersen et al. 2021 and Fragki et al. 2021). Furthermore, 3M has conducted a detailed clinical study with a cohort of 36 cynomolgus monkeys (n=18/sex). The monkeys were extensively followed for up to 105 days for their baseline (background) serum PFOS levels and detailed serum clinical chemistries, including lipid profile. There were no elevated serum lipids in the control monkeys that had ambient background PFOS exposure (in the low ng/mL level, which is

¹¹⁵ Fragki et al. 2021 Crit Rev Toxicol 51 141-164

¹¹⁶ Andersen et al. 2021 Toxicol 459 152845

¹¹⁷ Steenland et al. 2010 Environ Health Perspect 118 1100-1108

¹¹⁸ Sakr et al. 2007 J Occup Environ Med 49 1086-1096

¹¹⁹ Bijland et al. 2011 Tox Sci 123 290-303

similar to the general population level in the United States based on the most recent NHANES data) (Chang et al. 2017)¹²⁰.

The statements below are excerpted from each workshop report which offer additional insights on this topic:

Fragki et al. 2021.

- Associations between per and polyfluoroalkyl substances (PFASs) and increased blood lipids have been repeatedly observed in humans, but a causal relation has been debated (see abstract).
- Despite the fact that perturbed lipid homeostasis associated with PFAS exposure has received substantial attention, clear understanding of the mechanisms involved in both animals and humans, is still lacking.
- The goal of the present paper is to present the state of the art knowledge on the disturbance of cholesterol and triglyceride homeostasis by PFASs, and to bring forward the most important issues pertaining to this topic. Possible explanation for the findings and discrepancies observed between different lines of evidence are identified, with an emphasis on the underlying mechanisms, especially those that could be relevant for humans.
- Many epidemiological studies have shown associations between increased blood levels of PFOS/PFOA and increased blood total cholesterol, and in some cases TGs. Exposure to the substances have occurred for several decades. Nonetheless, many of these studies are cross-sectional and consequently, the extent to which the relationship between PFOS/PFOA exposure and these altered levels of blood lipids are causal remains uncertain. Also, there are no associations with related adverse outcome, like CVD. Even so, given the very small changes in the involved risk factors, such effects could be possibly detected only in very large studies. (pages 156-157)
- The recorded associations could also be the result of confounding related to excretion and re-absorption in the enterohepatic cycling process of PFOS/PFOA and bile acids, which can affect serum cholesterol levels. However, until now this remains only a postulation that requires experimental evidence. (page 157)
- In order to support (or not) a causal inference and to elucidate whether such findings are a real health concern for humans, a clear mechanistic understanding relevant for humans is essential. (page 157)
- Together with studies on chimeric mice, further in vitro investigations with human hepatocytes may help clarify the pathway underlying the potential PFOS/PFOA-induced lipid perturbations. Specifically, more information is needed on the involvement of the HNF_{alpha} signaling pathway, as well as interference of PFOS/PFOA with cholesterol transformation into bile acids. Still, given the specific limitations of such in vitro models, the extrapolation of the effects of humans shall be done carefully by taking into consideration the dosing and integrating the kinetic aspects. The latter can be achieved with the use of

¹²⁰ Chang et al. 2017 Toxicol Sci 156 387-401

physiologically based kinetic modeling, together with measurements of the actual intracellular concentration of the compounds. (page 159)

- If such studies are fine-tuned to the human situation and interpreted in the context of the intact human, they can generate valuable information that will contribute to a better understanding of PFAS-mediated lipid perturbations and the issues involved in their interpretation for human health risk assessment. (page 159)

Andersen et al. 2021

- The associated change in cholesterol is small across a broad range of exposure to PFOA and PFOS. Animal studies generally have not indicated a mechanism that would account for the association in humans. To the extent to which the relationship is causal is an open question (Andersen et al. 2021, abstract).
- This report summarizes salient background material and documents the discussions and conclusion reached at the workshop – with an emphasis on identifying data gaps regarding the interactions of PFAS lipids – and suggests experimental, modeling, and epidemiological studies that could further elucidate the quantitative nature of any interactions. (page 2)
- The shape of the relationship is remarkably consistent across studies even though the average range of exposures in different populations – workers, residents in contaminated areas around production plants and the general population – vary considerably. (Page 3)
- The expert workshop provided an opportunity for cross-disciplinary discussion on toxicokinetics of PFAS and physiological control of plasma cholesterol, including lipid/lipoprotein processing. The primary focus was to evaluate whether PFAS might affect cholesterol synthesis and metabolism or whether cholesterol metabolic process might alter PFAS disposition. (Pages 3 and 4)
- Four hypotheses were discussed: direct causality; reverse causality; confounding by disease; confounding by common pharmacokinetic processes that alter both cholesterol and PFAS kinetics. This latter possibility received more attention than the other three hypotheses at the meeting – emphasizing characteristics of PFAS kinetics and cholesterol disposition that might share common pathways. (Page 5-6)
- Several follow-on studies of possible confounding in the relationship of cholesterol with PFAS were discussed. (page 7)
- Correlated absorption of bile salts or cholesterol and PFAS could occur in enterocytes.
- It has been demonstrated that several bile acid transporters expressed in enterocytes and hepatocytes can also transport PFAS.
- Correlated excretion of PFAS and bile salts or cholesterol is also conceivable.
- 3-broad categories of recommended studies were the result of the workshop: 1) biology associated with possibilities of direct causation; 2) pharmacokinetic factors affecting PFAS and cholesterol levels, and 3) epidemiologic evaluations. However, the information obtained from studies in any one of these categories would have broader utility. (Page 7). The workshop participants proposed a list of 19 studies and analyses, involving 9 experimental investigations, 1 PBPK

model, and 9 epidemiological studies that could provide the necessary insights. (Page 5)

- The workshop's conclusion was that mechanisms underlying the associations of serum cholesterol with exposure to PFAS have not been determined. Experimental studies, e.g., using human-relevant models and that include lower dose ranges could provide valuable mechanistic insights. PK modeling of both PFAS and cholesterol may also provide valuable clues. Epidemiologic studies that address mechanistic hypotheses, e.g., regarding an effect of PFAS on CYP71A activity, or that evaluate potential confounding by dietary factors, are among the key recommendations resulting from the workshop. (Page 8)

ATSDR (2021)¹²¹

In its finalized toxicology profile, ATSDR (2021) commented on epidemiology and human dosimetry by stating that:

Although many studies found statistically significant associations between serum perfluoroalkyl levels and the occurrence of an adverse health effect, the findings were not consistent across studies. Interpretation of the human data is limited by the reliance of cross-sectional studies, which do not establish causality, and the lack of exposure data. Studies on serum lipids suggest that the dose-response curve is steeper at lower concentrations and flattens out at higher serum perfluoroalkyl concentrations (Steenland et al. 2010a); additional studies that could be used to establish dose-response relationships would be valuable. Mechanistic studies examining the association between perfluoroalkyl exposure and serum lipid levels would also provide valuable insight. Clarification of the significance and dose-response relationships for other observed effects is also needed. Longitudinal studies examining a wide range of endpoints would be useful for identifying critical targets of toxicity in humans exposed to perfluoroalkyls. The available human studies have identified some potential targets of toxicity; however, cause-and-effect relationships have not been established for any of the effects, and the effects have not been consistently found in all studies. Mechanistic studies would be useful for establishing causality.

EFSA (2018¹²², 2020¹²³)

In its 2018 provisional scientific opinion with cross-sectional study data, EFSA proposed a TWI for PFOS and PFOA based on observations of increased serum total cholesterol in humans. After several member states such as German and Dutch agencies raised concerns about the scientific uncertainty of this assessment, EFSA decided to not to use this endpoint in its 2020 assessment. As stated in their 2020 scientific opinion:

¹²¹ <https://www.atsdr.cdc.gov/toxprofiles/tp200.pdf>, accessed 10-19-2021

¹²² Knutsen et al. 2018 EFSA J 16 5194

¹²³ Schrenk et al. 2020 EFSA J 18 e06223

Variability in intestinal reabsorption might therefore explain the observed association between serum cholesterol and serum PFAS levels. This is a reasonable potential mechanism for confounding, but it has not been convincingly demonstrated. EFSA 2020 page 137

Because of this potential source of confounding there is uncertainty regarding causality, making it less appropriate to use increased serum cholesterol as the basis for a health-based guidance value. EFSA 2020 page 137

4. Additional Comments on OEHHA's Conclusions about the Health Effects of PFOS

3M's response to additional conclusions made by OEHHA about the health effects of PFOS in the Support Document are provided below.

Pages 88 and 98.

It is unclear why the study by Chang et al. 2017¹²⁴ was included in Table 5.2.3 (a table animal studies of liver effects) but excluded from Table 5.3.2 (a table of animal studies that reported lipid effects). See detailed comments below regarding the Chang et al. 2017 study as related to the findings from Steenland et al. 2009.

In their study, Chang et al. administered a single K+PFOS dose (9 mg/kg) to a low-dose group (n = 6/sex) or 11-18.2 mg/kg K+PFOS on 3 occasions to a high-dose group (n = 4-6/sex). Scheduled blood samples were conducted on all monkeys prior to, during, and after administration for up to 1 year. They were analyzed for PFOS concentrations and clinical chemistry markers including serum lipids. When compared with time-matched controls, PFOS administration did not result in any toxicologically meaningful or clinically relevant changes in serum clinical measurement for coagulation, lipids, hepatic, renal, electrolytes and thyroid-related hormones.

Chang et al. did report a slight reduction in serum cholesterol (primarily HDL). Using a Bayesian approach, Chang et al. implemented Monte Carlo Markov Chain techniques and calculated a corresponding lower-bound 5th percentile benchmark concentrations (BMCL_{1sd}) of 74,000 and 76,000 ng/mL for male and female monkeys, respectively, based on the slight reduction in HDL. Compared to the 2013-2014 geometric mean serum PFOS level of 4.99 ng/mL from NHANES, this amounted to a 4 orders of magnitude margin of exposure. Therefore, the obvious striking contrast between Chang et al. cynomolgus monkey results, and the 16.4 ng/mL LOAEC for increased cholesterol (identified by OEHHA from the Steenland et al. 2009 study) as shown in Table 6.1.13 by OEHHA, should be addressed by OEHHA.

¹²⁴ Chang et al. 2017 Toxicol Sci 156 387-401

Pages 105, 194, and 196:

OEHHA writes about cross-sectional studies being “frequently criticized based on their potential for reverse causation.” OEHHA appears to be confusing concepts of reverse causation with temporality. One of the primary criticisms of cross-sectional studies is that they cannot assess temporality – *i.e.*, did the exposure precede the condition being studied. We refer OEHHA to a paper on pharmacokinetic bias that can occur from either confounding or reverse causation (Andersen et al. 2021a) that provides both PFAS and non-PFAS examples. In their workshop, Andersen et al. (2021b) examined reverse causality as one of their 4 hypotheses but this has to do with the possible mechanism of incorporation of PFAS into cholesterol containing particles such as LDL. PFAS would then increase proportionally with the LDL. OEHHA acknowledges that the major transport proteins for cholesterol in the blood are the lipoproteins (not albumin). OEHHA dismisses PFAS binding to lipoproteins because of the results from Butenhoff et al. 2012.¹²⁵ While this one study investigated the issue, it was based on a blood sample from only one individual and cannot reasonably be relied upon to support the conclusion OEHHA attempts to draw. Andersen et al. also briefly mentioned the co-distribution – hypothesis.

Pages 104, 105, and 193:

OEHHA discusses possible sources of dietary confounding but considers it unlikely. OEHHA then concentrates on adjustments for fat, total calorie, meat and vegetable intake but never considered dietary fiber as a potentially confounding factor. While the Support Document states that no major confounding has been identified related to the Steenland et al. 2009 study (page 193), it acknowledges that consumption of a high fat diet or high total caloric intake could potentially be related to total cholesterol and PFOS exposure, although both could be in the causal pathway. Both high fat or high total caloric intake were strongly related to factors that were controlled for in the Steenland et al. study (BMI, smoking, and exercise), and therefore according to the authors were unlikely to have been “fully” responsible for the PFOS and total cholesterol association in the study. Not discussed by OEHHA, however, is the possible confounding effect of fiber intake. Dzierlenga et al. (2021)¹²⁶ suspected consumption of dietary fiber can be a confounding factor in an association between PFAS and serum cholesterol because dietary fiber is inversely related with dietary cholesterol and may decrease PFAS levels through increased gastrointestinal secretion.

Analyzing dietary survey data from NHANES data 2005-2006 through 2015-2016 among 6,482 adult participants (20 – 79 years of age), which consisted of two 24-hour diet recalls, Dzierlenga et al. derived nutrient intakes, including an index for total dietary fiber. The calculated median fiber intake of 16g/ was consistent with other data reported in the United States. Dzierlenga et al. calculated the percent difference in PFAS concentration per interquartile range increase in fiber with the NHANES sampling parameters used to make the results generalizable to the U.S. Thus, the adjusted percent

¹²⁵ Butenhoff et al. 2012 Toxicol Letters 210 360-365

¹²⁶ Dzierlenga et al. 2021 Environ Int 146 106292

difference in PFOA, PFOS, and PFNA, per interquartile increase in fiber was -3.64%, -6.69%, and -8.36%, respectively. Dzierlenga et al. suggested their analyses indicated that dietary fiber increases the gastrointestinal excretion of PFOA, PFOS, and PFNA in humans. Although this was less than a 10% difference in PFAS with IQR difference in dietary fiber, Dzierlenga et al. suggested these findings may be important in those studies of health outcomes where the outcome-PFAS association is also modest.

Page 191, Table 6.1.16

It is a critically important often overlooked point, including in the Support Document, that Steenland et al. 2009 noted on page 1276 of their paper that, “although PFOA and PFOS were highly significant predictors of lipid levels (their study had high power to detect statistically significant differences compared with prior smaller studies), the perfluorinated compounds themselves did not explain a large portion of the variance in lipids. For total cholesterol, the most important predictors were age, gender, and body mass index, not serum levels of PFOS or PFOA.” 3M is unable to find the actual percent of variance of lipids that were actually explained by PFOA or PFOS in the Steenland et al. paper, nor could this information be found in the C8 Science Panel’s probable link statements regarding this particular research.¹²⁷ This contributes to the fact that the association between total cholesterol and PFOS was quite modest, despite its statistical significance as a result of the sample size. Given the associational relationship is modest at best, OEHHA should revisit its analysis regarding the PFOS POD.

Page 193, 1st Paragraph

The Support Document states that “while the relatively small changes in mean TC levels seen with increasing PFOS exposure levels may not affect many people, on an individual basis, the population effects of these small changes, given that TC is a major risk factor for cardiovascular disease, are likely to be widespread and large.” If that were true, then the C8 Science Panel would have observed some level of association in the community. They did not.¹²⁸ Nor did the C8 Science Panel declare a probable link with heart disease (see above).

Page 193, 3rd Paragraph

The referenced studies by Canova et al. (2020)¹²⁹ and Li et al. (2020)¹³⁰ are both cross-sectional studies of the Veneto (Northeastern Italy) and Ronneby, Sweden regions. While these studies report an association between cholesterol and PFOS (and PFOA, PFHxS) neither addressed, with data, the methodological questions raised by Fragki et al. and Andersen et al. It should be noted that Tony Fletcher was a co-author of the Canova et al. and Li et al. papers, too, as he was with Fragki et al. (2021)¹³¹ and Andersen et al.

¹²⁷ http://www.c8sciencepanel.org/pdfs/Probable_Link_C8_Heart_Disease_29Oct2012.pdf, accessed 10-19-2021

¹²⁸ Winquist and Steenland 2014 Environ Health Perspect 122 1299

¹²⁹ Canova et al. 2020 Environ Int 145 106117

¹³⁰ Li et al. 2020 Environ Health 19 33

¹³¹ Fragki et al. 2021 Crit Rev Toxicol 51 141-164

(2021).¹³² The discussion section in the Canova et al. paper mirrors much of what Fragki et al. (2021) and Andersen et al. (2021) have written. In this regard, there is a consistency of findings on what needs to be done. Canova et al. (2020) concluded, “More effort is needed to study mechanisms of action of PFAS in human cells and tissues to understand potential causality, and longitudinal studies of cardiovascular risk in relation to PFAS, particularly lipid subfractions, are warranted.” The Li et al. (2020) paper reiterated its other limitations, including information on cholesterol-lowering medications, dietary habits, and socioeconomic status, all of which affect serum lipids and are potential confounders if they happened to be associated with PFAS levels.

Page 194, 2nd Paragraph.

While it is true that approximately 80% of the community participated in the C8 Health Project, the Steenland 2009 study never addressed the question of nonresponse bias. Thus, it is somewhat misleading for OEHHHA to say there is no obvious selection bias because it was never examined.

Page 194, 3rd Paragraph.

As discussed above, reverse causality is only one type of pharmacokinetic bias and that does not mean there is the absence of confounding or shared co-distribution (e.g., enterohepatic circulation) between PFOS and some other factor that confounds the association between PFOS and cholesterol.

* * *

3M appreciates the opportunity to provide these technical comments on the Support Document and encourages OEHHHA to review its conclusions and consider revisiting its analysis of the potential health effects of exposure to PFOA and PFOS as outlined above. 3M looks forward to reviewing a revised Support Document. Thank you for your consideration.

¹³² Andersen et al. 2021 Toxicol 459 152845

Exhibit A

Excerpt from Raleigh et al. (2014), Chapter 4

The following is excerpted from Chapter 4 of Raleigh et al. (2014).

Study Population

The cohort included all workers employed at the Cottage Grove 3M plant for a minimum of one year of employment between 1947 through 2008 (N=4,668). The Cottage Grove campus was divided into Chemical and Non-Chemical Divisions, with APFO production limited to the Chemical Division. Within the Chemical Division a few departments were directly involved with the production of APFO and these changed over time. Other departments may have had some involvement with APFO, but were not the main production sites. The APFO chemical group locations were verified by reviewing company production records and with input from former employees.

Production Process

The production of APFO was a multi-step process that included many tasks with various opportunities for workers to be exposed. Inhalation exposure occurred from both the acid vapor and ammonium salt particulate phase during regular production duties and other less frequent responsibilities such as cleaning equipment, changing filters, and quality control checks. Production workers had the potential for high-level exposure during rare events such as incidental spills, filter clogs and dust releases. Low-level continuous exposure to APFO occurred from working in the general production environment without direct involvement in chemical production.

The manufacture of APFO initially began in a small chemistry pilot plant in the late 1940s and expanded to an entire building with four main areas starting in 1951. The production process evolved over time including changes in equipment and volume output. It increased steadily by decade until the 1980s when production fell from approximately 60,000 to 2,000 pounds per year. In the 1990s there was sharp increase until the end of production in 2002 (Table 1).

The production process included the following steps: electrochemical fluorination, stabilization, fractionation, distillation, purification, the addition of ammonium, drying, and packaging the final product. Electrochemical fluorination (ECF) reactions took place in the Cell Room. The ECF reactions were conducted with the use of electrical currents that replaced all of the hydrogen atoms with fluorine atoms by adding hydrogen fluoride (HF). HF was added to the eight-chain carbon compound inside 1,000 gallon stainless steel cells with encapsulated metal plates. The material was piped through a closed system from the Cell Room to the reactors in the Kettle Room where the perfluorooctanoic acid (PFOA) was fractionated by separating out the eight-chain carbon compound. PFOA was purified after high and low vapor pressure constituents were boiled off from the mixture by charging, distilling, and draining the material. After the acid was purified it was drained into large drums and stored in a hot room at 150 °F. Next, ammonium (anhydrous ammonia) was added to the acid to make a slurry mixture in 50 gallon reactors through 1978, after 1978 this was done in a larger reactor (400 gallons). The slurry was stored in 55 gallon drums or 200 gallon totes. There was potential for exposure during the purifying process of production from occasional leaks and spills. Other opportunities for exposure occurred when the workers replaced the filters, when the metal plates from the cells were cleaned or replaced, and when quality control samples were collected.

Through the end of 1977 the material was dried by a tray dry method. From 1978 until 1981, a variety of drying methods were attempted including a filter press and oven with a pulverizer method and a Bird Young™ filter/blender-dryer method. After 1981 the inert material was evaporated from the acid using a spray dryer. The ammonium salt was blended, packaged, and finally

shipped to various locations. During the drying process there was potential for very high inhalation exposure while spray-drying and packaging the powder. In the 1990s, a curtain barrier was used in the Spray Dry Room to isolate the ammonium salt and reduce contamination. In 1999 a plexi-glass barrier was installed in the Spray Dry Room, and in 2000 the use of full-face respirators was mandated for the production workers.

Work History

Work history records indicating the job department, job title, and start and end dates were used to identify the duration and calendar period of employment. Several thousand job titles were standardized to represent the workers' duties for each position. A total of forty-five unique job titles were identified and used for the Chemical Division from 1951-2002. All job titles for pre and post-production Chemical Division workers, and all workers in the Non-Chemical Division, were standardized by division and year of employment.

Exposure Data

There were a total of 205 personal and 659 area APFO/PFOA (APFO $C_8H_{15}O_2NH_3$; and PFOA $C_8H_{15}O_2$) air measurements used in the quantitative exposure assessment. Air data collection for APFO/PFOA began in 1977 and ended in 2000 (Table 2). Both PFOA and APFO were sampled depending on the process step and exposure (i.e., vapor or particulate phase). The following sampling media were used to collect PFOA vapors; Impinger (0.01N NaOH methanol), silica gel tubes, and ethylene glycol coated Tenax tubes through the 1980s. After the 1980s, PFOA was captured using Tenax tubes, silica gel acid tubes and finally OVS-XAD-4 resin tubes. From 1977-1999, APFO was collected with tared 0.8 micrometer pore size Nuclepore filters; with a switch to OVS-XAD-4 resin tubes in 2000. The PFOA anion (PFO-) was the measured analytic compound using gravimetric gas chromatography, flame ionization and electron capture analyses.

All the personal air samples were breathing zone samples taken during various exposure tasks including; charging, draining, fractionation, stabilization, changing filters, spray drying, grinding, manual crushing, dumping trays, packaging the material, and cleaning. The area samples were taken in the production room and represented the background exposure value during production and non-production activities. Both personal and area samples were short term, task-based samples—the duration varied from twenty minutes to over two hours, depending on the task. Using the data from the air measurements and professional judgment regarding the amount of time spent at the various exposure tasks performed during a typical shift, we estimated daily inhalation exposure values.

Exposure Values: Daily Time-Weighted Averages

We created an exposure data matrix with annual estimated time weighted average (TWA) exposure values for all jobs held from 1947 through 2008. For Chemical Division workers during production years (1951-2002), we estimated a daily TWA in mg/m³ for each year-job title-department combination using the task-based arithmetic mean and duration of task per shift. We calculated close to 3,000 TWAs from 1951 through 2002 to create the EDMs. Exposures for the concurrent year were used when available. Fewer than 20% of the TWAs were computed directly from concurrent year measurements. There were 2,462 imputed TWAs using air measurements from a specific job title and department combination, but different year(s). The imputed TWAs in years without sampling data were calculated by adjusting for production rates—reflected in the amount of time spent conducting an exposure task. The amount of time for an eight hour shift was divided into three parts; 1) time spent outside of the production room ("**Outside Production Room**"), 2) time spent in the production room without directly performing a APFO/PFOA-related exposure task

(“**Inside Production Room: No Exposure Task**”), and 3) time spent in the production room conducting APFO/PFOA-related exposure tasks (“**Inside Production Room: Exposure Task**”). For the time spent “Outside Production Room”, we used a constant value of 0.001 mg/m³.

The daily TWA exposure in mg/m³ of air was calculated as:

$$C_j = \sum_{i=1}^n c_i t_i / \sum_{i=1}^n t_i \text{ Equation (1)}$$

C_j are the mean concentrations in mg/m³ of PFO- for a given job title for the i th worker, t_i are the amounts of time in minutes and c_i are the air concentrations for each of n distinct work-time areas. A total of 480 minutes were used in the denominator for each calculation representing an eight-hour work shift. The method for estimating the TWA that incorporates different task-based exposures for the same job are displayed in Tables 3 and 4.

All Non-Chemical Division workers’ daily TWAs were estimated using an APFO/PFOA background exposure estimate—taken from facility area and public environmental sampling data. Likewise, Chemical Division workers’ pre and post-production (1947-1951, and 2003-2008) daily TWAs were calculated with a similar method as all Non-Chemical workers. Specifically, prior to the start of production, we used a step-wise algorithm to estimate TWAs. Area samples from non-production measurements and from local and regional environmental air data provided by the Minnesota Pollution Control Agency (MPCA) and reported by Stock et al. (2004) were reviewed. Stock et al (2004) measured atmospheric fluorinated telomer alcohols (FTOHs), which degrade in the environment to PFOA, at several locations in North America with a range of concentrations of 1.65×10^{-7} to 1.1×10^{-8} mg/m³. We calculated a daily TWA for all Chemical Division workers by increasing exposure by 50% for each year from 1947-1951 starting with a baseline TWA established with expert input and the review of the aforementioned non-production area measurements and atmospheric data. We assumed the annual increase would be based on a gradual production rate increase, which would reflect background exposure levels. Workers in the Non-Chemical Division were assigned the same initial ambient measurements that were assigned to Chemical Division workers in 1947. These increased by 50% every three years through 1951. From 1952 through 1959 the daily TWA increased by one order of magnitude to account for transient exposures. For the 1960s we increased the TWA by one order of magnitude. The following decades through 2002, we increased exposure once more to reach 1.0×10^{-5} mg/m³ to account for the change in production rates.

After production ceased in 2002, we continued to assign exposure levels (daily TWAs) for all workers based on their division from the on-site chemical residuals. We decreased the Chemical Division workers’ TWAs by 50% annually through 2008. The calculation for the Non-Chemical Division workers’ TWAs followed the same method; however the TWAs were one order of magnitude lower than the Chemical Division workers (Table 6). End of Raleigh 2013 statements.