3M Company

3M Center
St. Paul, MN 55144-1000
651 733 1110

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Pesticide and Environmental Toxicology Branch
Office of Environmental Health Hazard Assessment
California Environmental Protection Agency
P.O. Box 4010, MS-12B
Sacramento, California 95812-4010
Attention: Hermelinda Jimenez

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 ("OEHHA") on July 30, 2021 to support OEHHA'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 OEHHA 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 OEHHA explicitly notes that the Proposed PHG values are "not regulatory and represent only non-mandatory goals," and that HPCs are "advisory," OEHHA 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, OEHHA 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 though 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 PFOA[10] 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 OEHHA 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. OEHHA 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 OEHHA 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, 2004[21]). 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/m^3 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/m^3 (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	**Day 14 post-exposure:** M: 42 ppm (organic fluorine measured) F: 2 ppm (organic fluorine measured)* *Different serum concentration when compared to male rats due to rapid serum elimination half-life for PFOA A factor of 1.44 is applied to organic fluorine → PFOA conversion: M: 60 ppm (estimated as PFOA) F: 3 ppm (estimated as PFOA)	**Immediately post-last exposure:** Serum [PFOA] = 1.4, 12, 47, and 108 ppm for 0, 1, 8, and 80 mg/m3 dose groups

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. (2013[22], 2014[23]), 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/m^3) 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/m^3) up to 0.04 mg/m^3 APFO, those involved with the operation of the spray dryer had measurements that ranged up to 100 fold higher (0.124 mg/m^3). Less exposed job titles including clerk, custodian, and finished good checkers had TWAs much lower (<= 0.002 mg/m^3).

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]		Mean	Median	range	Mean	Median	range	Mean	Median	range	Mean	Median	range	Mean	Median	range
	Serum [PFOA], ppm = µ/mL	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)		
		Mean	Median	range	Mean	Median	range	Mean	Median	range	Mean	Median	range	Mean	Median	range
	Serum [PFOA], ppm = µ/mL	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 anlyses. 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 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 signfiicant associaton 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 Winquist (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 populaton 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 Winquist 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, 2013[37]). 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. 1999[38]; Kim et al. 2008[39]). 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. 2005[40]). 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 a. 2016) or in occupational cohort mortality studies (Steenland and Woskie 2012[41] and Raleigh et al. 2014[42]). 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

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[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 OEHHA 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 OEHHA 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^2s 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). OEHHA 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.

OEHHA 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. 2018[44]).

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 (β = 0.003); Model 2 (β =0.012); and Model 3 (β = 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 been 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 μM (~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. OEHHA 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 OEHHA's Conclusions about the Health Effects of PFOA

3M's response to additional conclusions made by OEHHA 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. OEHHA 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 110[59]. 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/m^3-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_{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_{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 >= 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: PPARa-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 (PPARα), 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 PPARα-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 PPARα 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]

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[74] https://ntp.niehs.nih.gov/whatwestudy/assessments/cancer/criteria/index.html, accessed 22August 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-PPARα 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 PPARα 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 OEHHA) also did not find a statistically significant increasing trend in pancreatic islet adenoma, carcinoma, or combined adenoma and carcinoma. The reason OEHHA 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. OEHHA 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. 2012[93] 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 cholecystokinin ("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, 2016[97]

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, 2018[98]

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

EFSA, 2020[99]

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 include two workshop panel reports, published in 2021 (Fragki et al. 2021;[104] Andersen et al. 2021[105]), 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 Ocrtober 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, EFSA[106], 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 uncertainies 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. 2020[114]) 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. 2021[115] and Andersen et al. 2021[116]

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 (2018[122], 2020[123])

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. 2017[124] 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 PFOS." 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 OEHHA 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 OEHHA 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 $C_8HF_{15}O_2NH_3$; and PFOA $C_8HF_{15}O_2$) 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/m^3 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:
$C_j = \Sigma_{ni=1}\, c_i t_i / \Sigma_{ni=1}\, t_i$ Equation (1)

Cj are the mean concentrations in mg/m3 of PFO- for a given job title for the *ith* worker, *ti* are the amounts of time in minutes and *ci* 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 x 10-7 to 1.1 x 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 x 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.