October 28, 2021

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Re: Draft Technical Support Document for Proposed Public Health Goals for Perfluorooctanoic Acid and Perfluorooctane Sulfonic Acid in Drinking Water

Dr. Ting:

On behalf of the American Chemistry Council, Metal Finishing Association of Southern California, Metal Finishing Association of Northern California, and the California Food Producers enclosed are comments on the proposed Public Health Goals (PHGs) for perfluorooctanoic acid (PFOA) and perfluorooctane sulfonic acid (PFOS). As discussed, the PHG of 0.007 parts per trillion (ppt) proposed for PFOA is based on epidemiology studies with limited information on exposure and questionable findings; the draft PHG of 1.0 ppt for PFOS relies on the results of an animal cancer bioassay that were not statistically significant or that are consistent with rodent-specific effect. In developing these draft goals, OEHHA offers no plausible biological basis for concluding PFOA or PFOS cause cancer and makes unnecessary or overly conservative assumptions that are inconsistent with the approach outlined in its 2009 guidance. In addition, the proposed value of 0.007 ppt for PFOA suggests a level of precision that is simply not possible given the measurement error and use of multiple biological models to extrapolate backwards from serum concentrations to exposure estimates.

Considering the conflicting evidence for cancer of PFOA, and very limited information for PFOS, we urge OEHHA to base the PHGs for these two substances on non-cancer health end points. We further encourage OEHHA to provide an additional opportunity for public comment once substantial changes are made to a more realistic PHG proposal.

If you have any questions or comments, please contact me at 916-448-2581 or tim_shestek@americanchemistry.com. Thank you for your consideration of these comments.

Sincerely,

Tim Shestek
Senior Director, State Affairs

Enclosure

Comment on the
First Public Review Draft
Perfluorooctanoic Acid and Perfluorooctane Sulfonic Acid
in Drinking Water (July 2021)

October 28, 2021

Introduction

The Office of Environmental Health Hazard Assessment (OEHHA) has proposed public health goals (PHGs) for perfluorooctanoic acid and perfluorooctane sulfonic acid (PFOS) of 0.007 parts per trillion (ppt) and 1.0 ppt, respectively, based on evidence of carcinogenic potential. The PHG proposed for PFOA is based on epidemiology studies with limited information on exposure and questionable findings while the draft PHG for PFOS relies on the results of animal cancer bioassays that were not statistically significant or that are consistent with rodent-specific effects of questionable relevance to human risk assessment. In addition, OEHHA has not established a plausible biological basis for concluding that PFOA or PFAS cause cancer. In calculating the draft PHGs, moreover, OEHHA has strayed from the approach outlined in its 2009 guidance by including unnecessary or overly conservative assumptions in the application of benchmark dose (BMD) methodology. Considering the conflicting evidence for PFOA and very limited information for PFOS, the PHGs for these two substances should be reassessed based on non-cancer health end points.

Cancer Evidence for PFOA

Several epidemiology studies have investigated the association between PFOA and cancer, including studies of PFOA workers and residents exposed to contaminated drinking water. Some of these studies have reported an increase in kidney and testicular cancer. In addition, five cancer bioassays have reported an association between PFOA exposure and liver, pancreatic, and Leydig cell tumors. The draft PHG developed by OEHHA is based on the evidence for kidney cancer in humans from studies conducted by Shearer *et al*. (2021) and Vieira *et al.* (2013).[1]

Although human data are preferable to animal results in assessing potential health effects, a number of practical and resource constraints generally limit the ability for risk

[1] As OEHHA notes, kidney cancer is among the top ten cancers diagnosed in the US each year, and RCC represents about 90 percent of all kidney cancers. The most widely accepted causes of RCC are cigarette smoking, obesity, and hypertension, along with advanced age (https://www.cancer.org/cancer/kidney-cancer/causes-risks-prevention/risk-factors.html).

assessors to use epidemiological evidence for developing quantitative risk values.[2] These factors are described in more detail for the individual studies selected by OEHHA, but include uncertainty about exposure,[3] consideration of confounding factors, and adequate sample size. As a result, epidemiology is generally used to complement the animal data in corroborating or clarifying the carcinogenic potential of a substance. In the case of PFOA, however, the human cancer profiles are not consistent with observations of cancer in animal studies and in fact, contradict the animal results, without any biological plausibility or underlying mode of action differences attributable to the species under study. When this kind of disconnect occurs, further study is necessary to explain why the information generated in rodent studies is not consistent with the disease progression in humans. This lack of consistency across species undermines confidence in the use of cancer as suitable endpoint for human risk assessment.

Shearer *et al.* (2021) – Multi-Site Case-Control Study

Shearer *et al.* (2021) identified 324 cases of renal cell carcinoma (RCC) among 75,000 participants of a multi-site study from medical centers in 10 US cities.[4] The subjects had baseline serum collected during 1993-2002, although the samples were not analyzed for PFOA and other PFAS until 2018. These measures were used to back-calculate exposure estimates by OEHHA - not by Shearer *et al.* (2021). The cases were diagnosed with RCC subsequent to serum collection. A control group of 324 individuals who had never had RCC was selected from among the same study participants – matched to the RCC cases by age (>50 years of age), sex, ethnicity, study center, and year of blood draw.

The researchers calculated odds ratios (ORs) for exposure quartiles and for continuous exposure, controlling for multiple potential confounding factors[5] in addition to the case-control matching factors. The quartiles were assigned based on serum concentrations of PFOA among controls, resulting in an uneven distribution in the ranges of the quartiles which can skew the analyses for exposure-response trends. Unfortunately, it is unclear whether the covariates were addressed one at a time (varying each potential confounder, to see how the fit of the model changed) or all at once. No equation was presented in Shearer *et al.* (2021) to help

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[2] US Environmental Protection Agency. Guidelines for Carcinogen Risk Assessment. Risk Assessment Forum. EPA/630/P-03/001F (2005).

[3] Ibid, at 2-7.

[4] The total population of 150,00 individuals was divided into two groups – screening and control. RCC cases and controls were identified from the screening group.

[5] These included body mass index, smoking status, hypertension, prior freeze-thaw cycle, year of blood draw, estimated glomerular filtration rate (eGFR), and exposure to other PFAS. Several of these confounders are on their own dose-response continuum, rather than a simple yes/no comparison, which further complicates the ability to pinpoint the effects of PFOA exposure.

understand their view of the interactions of all the confounders present when assessing the correlations with RCC.

Table 1. Odds ratios and 95% confidence intervals (CIs) evaluating PFOA serum concentration and risk of renal cell carcinoma (Shearer *et al.* 2021)[6]

Serum Concentration Quartile (micrograms/Liter)	Controls	Cases	OR	95% CI
<4.0	81	47	1.00	Reference
>4.0-5.5	79	83	1.41	0.69, 2.90
>5.5-7.3	83	69	1.12	0.52, 2.42
>7.3-27.2	81	125	2.19	0.86, 5.61
Continuous[7]			1.68	1.07, 2.63

* Shading is applied to demonstrate that the 95%CI range includes the odds of 1.00, meaning the finding is *not statistically significant* and is not found to be a significantly elevated odds ratio.

As shown in **Table 1** and as emphasized with shading, the data do not support a positive dose-response relationship (CI includes 1.0) and would be considered not significantly elevated for the three higher exposure quartiles after adjusting for other PFAS exposure. The results also do not suggest a dose-response pattern, and the p value for a positive trend was not statistically significant (p=0.13) according to the researchers. Given the lack of a significance after adjusting for exposure to other PFAS, it is not clear why OEHHA would use the ORs for the exposure quartiles (prior to adjusting for other PFAS) in calculating the cancer slope factor for the study.

Although the OR for the continuous exposure analysis was statistically significant, questions remain about the meaning of this finding. Of primary concern is whether the single serum measurement taken prior to RCC diagnosis (1993-2002) is an appropriate measure of PFOA exposure. OEHHA reasons that the serum samples taken between 1993 and 2002 from the cases and controls in the Shearer *et al.* study represent a peak exposure to PFOA.[8] However, OEHHA's rationale is not consistent with the available information on serum concentrations or PFOA production. As noted in Figure 6.2.2 of the public review draft for the proposal (page 216), and as reported in Olsen *et al.* (2005), PFOA serum levels were higher in 1989. The results presented in Figure 6.2.2 indicate, moreover, that serum levels may have

[6] Source: Table 2 of Shearer *et al.* 2021.

[7] Continuous OR is in relation to a 1-unit increase in serum PFOA concentration on the log base 2 scale.

[8] OEHHA's assumption that peak exposure is a more appropriate exposure metric for assessing PFOA-related cancer risk than cumulative exposure is discussed elsewhere in this comment.

peaked prior to the initiation of serum collection for Shearer *et al.* (2021). Data from the US Environmental Protection Agency (USEPA) indicate, moreover, that while production of PFOA may have peaked around 2000, production of ammonium perfluorooctanoate (AFPO) increased significantly between 1998 and 2002.[9]

> Conducting an analysis for continuous exposure, in addition to the quartile analysis, helps to address the disparity in the range of the exposures in the quartiles. However, questions remain about the distribution of exposures between the two groups. The supplemental information[10] provided by the authors suggest that the range of serum levels was only slightly higher among the cases compared to the controls, with the exception of a serum level nearly 10 times the high end of the range in the case group. While this value may explain the use of a log base 2 scale for the continuous analysis, Shearer *et al.* do not explain the potential effect of this outlier on their results. However, the broad confidence interval in the highest exposure quartile suggests that such an explanation is necessary to adequately interpret the findings. Typical publications of this type will generally develop an equation that explains the relationship between the continuous variables, as well as provide a robust uncertainty or sensitivity analysis. These elements are missing from the Shearer *et al.* (2021) publication and would be considered "best practices" for epidemiology that is expected to become the basis for a public health regulation.

Although the researchers were able to use several factors to match controls to the RCC cases, the decision to select an equal number of controls may also limit the significance of the continuous exposure finding. While the number of controls selected per case may vary, it is common in the nested case-control literature to find four or five controls per case.[11] The researchers do not provide an explanation for the decision to identify only 324 controls, particularly given the fact that they appear to have had such a large pool of individuals from whom a serum sample had been collected.

Finally, a key topic related to the variety of RCC subtypes that can be diagnosed is the differentiation in tumor type, by genetic basis. An analysis of the subtype of RCC has been a

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[9] USEPA. Non-confidential IUR production volume information. Inventory updating reporting (July 09, 2008). Cited in Agency for Toxic Substances and Disease Registry (ATSDR). Toxicological profile for perfluoroalkyls. US Department of Health and Human Services (May 2021), at 659.

[10] https://academic.oup.com/jnci/article/113/5/580/5906528#supplementary-data

[11] Ernster VL. Nest case-control studies. *Prevent Med* 23(5):587-590 (1994). https://doi.org/10.1006/pmed.1994.1093

topic of recent interest[12] due to the variable survival rates and seemingly different course of both development and treatment. Not all RCC are the same which raises concern that any study linking PFOA to generic "RCC" could be conflating correlation with causation artificially, by not evaluating by RCC subtype. Analysis of the raw data by subtype may yield a different conclusion, and also provide clues to where to look in the animal data for subtle mode-of-action (MOA) data that could clear up the discordance between human and laboratory animal kidney disease attributed to PFOA.

Vieira *et al. 2013* – Mid-Ohio River Valley

Vieira *et al.* (2013) is one of two publications to explore cancer outcomes among residents living near a fluoropolymer manufacturing plant in Parkersburg, WV. A second publication by Barry *et al.*, also published in 2013, extended the analysis of outcomes for an additional number of years and is discussed later in this comment. In their study Vieira *et al.* identified cases of kidney and 17 other cancers among residents of the 13 counties surrounding the manufacturing facility. ORs were calculated based on estimated PFOA serum levels for the contaminated water districts in OH and WV and for individual residences in OH using a PFAS exposure model and serum data collected from the C8 Health Project in 1995. The control groups were composed of individuals with cancers other than those that have been linked to PFOA exposure.[13]

A total of 751 cases of kidney cancers were diagnosed between 1996 and 2005 in the 13 counties – 505 in WV and 246 in OH. Of these, 94 cases resided in one of the six water districts. The control groups totaled more than 23,000 for the water district analysis and over 7,000 for the analysis of serum concentration among OH residents. In the water district analysis, residents within a district were assumed to have a serum concentration equal to the median concentration for that district; individuals outside these districts were considered to have no PFOA exposure. The OR for the two water districts with the highest estimated serum concentrations was not significantly elevated (the CI included 1), nor was the OR for the total exposed group, after adjusting for several confounding factors.[14]

For the analysis of estimated serum concentration of OH residents, serum levels were estimated based on the street address from which the researchers estimated the serum level at the time of diagnosis and 10 years prior to diagnosis, as well as cumulative exposure during that period, based on estimated drinking water levels Individuals were categorized into quartiles of

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[12] Wang Z *et al.* Cause-specific mortality among survivors from T1N0M0 renal cell carcinoma: a registry-based cohort study. *Frontiers in Oncology* (2021). https://doi.org/10.3389/fonc.2021.604724

[13] Individuals with kidney, liver, pancreatic, and testicular were excluded from the control group.

[14] As OEHHA notes, Vieira *et al.* did not adjust for body mass index which is an identified risk factor for kidney cancer.

estimated serum concentration among the exposed group and adjusted ORs were calculated for each quartile compared to the unexposed group. As shown in **Table 2**, adjusted ORs for the low and medium do not support a positive dose-response relationship for kidney cancer, while there is a positive association at the two higher exposure categories. As with Shearer *et al.*, the serum concentration groupings are unevenly distributed which may impact the reported results.

Table 2. Estimated annual and cumulative PFOA serum exposure categories and risk of kidney cancer for Ohio residents assuming 10-year residency and latency (Vieira *et al.* 2013)[15]

Serum Concentration	Concentration Range (µg/L)	No. of Cases	Annual		Cumulative	
			Adjusted OR	95% CI	Adjusted OR	95% CI
No	0	187	Reference			
Low	3.7-12.9	11	0.8	0.4, 1.5	0.8	0.4, 1.5
Medium	12.9-30.7	17	1.2	0.7, 2.0	1.2	0.7, 2.0
High	30.8-109	22	2.0	1.3, 3.2	2.0	1.3, 3.2
Very High	≥110	9	2.0	1.0, 3.9	2.1	1.1, 4.2

Although Vieira *et al.* estimated PFOA exposure for the OH residents, they did not consider individual residential history and drinking water consumption. These important factors were considered in a follow-up study by Barry *et al.* (2013) that followed the Mid-Ohio Valley residents through 2011.

The results from Viera *et al.* (2013) summarized in Table 2 did not show statistical significance (e.g., OR with a 95%CI that did not overlap unity, or 1.0) except in the serum range considered "high" or "very high" (> 30.8 ug/L, which is several orders of magnitude higher than the proposed PHG). In addition, no evaluation of the various subtypes of RCC was conducted to try to better inform the likelihood of confounders. A detailed uncertainty analysis for assessment of the sensitivity of the decisions in study design (*e.g.*, where to set the cutoffs for the exposure ranges) was not presented. An alternative analysis at more regular concentration/exposure ranges or with nonparametric analytical techniques may provide a different conclusion, if the raw data were to be reassessed.

Barry *et al*. 2013 – Mid Ohio Valley Residents

The study by Barry *et al.* (2013) was conducted in the same study area as Vieira *et al*. and likely included many of the same participants. However, Barry *et al.* included information

[15] Source: Table 2 of Vieira *et al.* 2013 and supplemental material available at https://ehp.niehs.nih.gov/doi/suppl/10.1289/ehp.1205829.

from additional years of follow-up and provides a more recent analysis of cancer incidence in the Mid-Ohio River Valley. Also, as indicated above and as described in more detail below, Barry *et al.* includes a more comprehensive assessment of exposure. Moreover, Barry *et al.* included an analysis of cancer incidence among the workers of the manufacturing facility whereas the previous study of these workers by Steenland and Woskie (2012) was limited to cancer mortality.

The cohort assembled by Barry *et al.* included 28,541 residents and 3,713 workers who participated in at least one of the follow-up surveys conducted between 2008 and 2011 and for whom an exposure estimate was available. A total of 105 cases of kidney cancer were identified with a complete data set within the cohort – 87 among the residents and 18 among the workers. Barry *et al.* developed estimates of the cumulative PFOA serum concentration using the same model as Vieira *et al.*, but accounted for each participant's reported residential history, drinking water source, tap water consumption, and workplace water consumption.[16] The researchers calculated hazard ratios (HRs) for an increase in kidney cancer among residents, workers, and the combined group cohort for both continuous and quartiles of PFOA serum concentration.[17]

Table 3. Exposure quartiles and continuous log estimated cumulative PFOA serum concentration and risk of kidney cancer risk with a 10-year lag (Barry *et al.* 2013)[18]

Serum Concentration Quartile	Residents		Workers		Total	
	HR (95% CI)	p-Value	HR (95% CI)	p-Value	HR (95% CI)	p-Value
Quartile 1	1.0		1.0		1.0	
Quartile 2	0.94 (0.45, 1.99)	0.02	1.22 (0.28, 5.3)	0.42	0.99 (0.53, 1.85)	0.34
Quartile 3	1.08 (0.52, 2.25)		3.27 (0.76, 14.10)		1.69 (0.93, 3.07)	
Quartile 4	1.50 (0.72, 3.13)		0.99 (0.21, 4.68)		1.43 (0.76, 2.69)	
Continuous	1.11 (0.96, 1.29)	0.17	0.99 (0.67, 1.46)	0.97	1.09 (0.97, 1,21)	0.15

[16] Based on measurements taken in 2005-2006, mean serum concentrations were 0.024 mg/L for community residents and 0.113 mg/L for workers.

[17] The cutoffs for the exposure quartiles are not provided in the publication of supplemental material. The model was adjusted for the same potential confounders as in the analysis by Vieira *et al.*

[18] Source: Barry *et al.* 2013 and supplemental material available at https://ehp.niehs.nih.gov/doi/suppl/10.1289/ehp.1306615.

As a result of the additional follow up, refined exposure assessment, and larger cohort size in the analysis by Barry *et al.*, the association between PFOA exposure and risk of kidney cancer is substantially reduced. Significantly, the hazard ratio is weakest for workers with a significantly higher median estimated exposure.

Animal Carcinogenicity Data

Considering the uncertainty in the epidemiological database, it is important to look at the results of cancer studies in laboratory animals. While several bioassays have been conducted, none have reported an increase in kidney cancer among the exposed animals. Reported cancers have included liver, pancreas, and Leydig cell cancers. The most recent of these studies from the National Toxicology Program (NTP) is reviewed in the PHG draft[19] and is discussed below.

The NTP bioassay reported liver adenomas and pancreatic acinar cell (PAC) adenomas in male Sprague-Dawley (SD) rats exposed to PFOA in the diet.[20] In the study, male rats were exposed postweaning to 0, 1.0, 2.2, and 4.6 milligrams per kilogram (mg/kg per day), while females were exposed to 0, 18.2, and 63.4 mg/kg per day.[21] The male rat portion of the study was repeated using significantly lower exposures after "unanticipated toxicity" was observed in male rats exposed to 150 and 300 ppm after 16 weeks. In light of the fact that male SD rats tolerated doses as high as 300 ppm in previous chronic studies (described below), the reports of unanticipated toxicity at comparable levels in the male rats in the NTP study raise concerns about the overall confidence in the study.[22]

NTP reported statistically significant increases in hepatocellular adenomas among the male rats exposed to the two highest doses (2.2 and 4.6 mg/kg per day). Hepatocellular carcinomas were increased at the highest dose (4.6 mg/kg per day), but the increase was not statistically significant. The study also reported significant increases in hepatocyte cytoplasmic alteration and hypertrophy in the males in all exposure groups. Significant increases also were observed in hepatocyte single cell death, necrosis, mixed cell foci, inflammation, cystic degeneration, and bile duct hyperplasia.

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[19] The NTP study was the key study selected by OEHHA for its 2019 notification level for PFOA.

[20] NTP. Technical report on the toxicology and carcinogenesis studies of perfluorooctanoic acid administered in feed to Sprague-Dawley rats. Technical Report 598. Department of Health and Human Services. Research Triangle Park, North Carolina (2019).

[21] The study included groups of animals exposed to PFOA perinatally and postweaning to assess the potential impact of gestational and lactational exposure. The study reported very few significant differences between the response in animals exposed postweaning only to those with both perinatal and postweaning exposure.

[22] In addition, survival rates among the female animals were quite low – ranging from 46 percent in the control group to between 46 and 64 percent in the exposure groups.

An increase in PAC adenomas was statistically significant in male rats in all exposure groups, but not in the female groups.[23] PAC adenocarcinomas were also increased in the males, but the increase was not statistically significant. The study also noted a significant increase in PAC hyperplasia – a potentially preneoplastic lesion - in all the male groups, including the control group in which hyperplasia was reported in 36 percent of the animals. The high background rate for preneoplastic lesions observed in this study is consistent with the historical sensitivity of the SD rats compared to other rat stains – and more significantly when compared to humans.

An earlier study by Butenhoff *et al.* (2012) in SD rats exposed to dietary levels of 30 and 300 parts per million (ppm) of PFOA (approximately 1.5 and 15 mg/kg per day), observed a dose-dependent increase in Leydig cell (LC) adenomas that was statistically significant at the highest dose.[24] Elevated incidence of hepatic and PAC lesions were reported in males at 300 ppm, but the authors did not report increases in hepatic or PAC tumors.

A single-dose, dietary study with male CD rats reported LC adenomas, as well as liver and PAC adenomas and combined pancreatic adenomas and carcinomas at 300 ppm (13.6 mg/kg per day).[25] Increased incidences of LC and PAC hyperplasia were also observed. Hepatic ß-oxidation activity was significantly elevated, but cell proliferation in the liver was not.

Relevance of the Animal Data

A significant amount of genotoxicity and mechanistic data are available to assist in evaluating the results of the epidemiology and animal bioassay results described above. Multiple *in vivo* and *in vitro* assays provide clear evidence that PFOA is not mutagenic and may only cause genotoxicity at toxic concentrations. Consequently, it is generally agreed that PFOA causes tumors in laboratory animals via a non-genotoxic or epigenetic mechanism.[26]

The tumor types that have been reported consistently in rats exposed to PFOA – liver, LC, and PAC – have been observed with other substances that are PPARα agonists. Because of

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[23] A non-significant increase of combined PAC adenomas and carcinomas was observed in females at the highest dose. Unlike in the males, acinus hyperplasia was not reported in the females.

[24] Butenhoff JL *et al.* Chronic dietary toxicity and carcinogenicity study with ammonium perfluorooctanoate in Sprague-Dawley rats. *Toxicol* 298(1–3): 1–13 (2012). Target doses for the study were 0, 1.3, and 14.2 mg/kg body weight per day in males and 0, 1.6, and 16.1 mg/kg per day in females. https://doi.org/10.1016/j.tox.2012.04.001

[25] Biegel LB *et al.* Mechanisms of extrahepatic tumor induction by peroxisome proliferators in male CD rats. *Toxicol Sci* 60(1): 44–45 (2001). https://doi.org/10.1093/toxsci/60.1.44

[26] USEPA. Health Effects Support Document for Perfluorooctanoic Acid (PFOA). EPA 822-R-16-003. Office of Water. Washington, DC. (May 2016).

key toxicodynamic and biological differences in responses between rodents and humans, PPARα activators are considered unlikely to induce tumors in humans. For liver tumors, this conclusion is based on minimal or no effects observed on growth pathways, hepatocellular proliferation and liver tumors in humans and/or other species (*e.g.*, hamsters, guinea pigs and *Cynomolgous* monkeys) that are more appropriate animal model surrogates than mice and rats.

The relevance of the liver tumor data from the animal studies is further called into question based on recent clinical data reported by Convertino *et al.* (2018).[27] In a study of a sensitive subpopulation of cancer patients with normal liver function exposed to weekly PFOA doses as high as 1,200 milligrams (about 16 mg/kg per day), Convertino *et al.* reported no differences in clinical hepatic measures.[28] Similarly a study of PFOA production workers reported no abnormal liver function, hypolipidemia, or cholestasis.[29]

Several key studies provide support for the key events in the proposed PPARα-activated MOA for rat liver tumors (Table 1). These data are summarized by Klaunig *et al.* (2012) –

> Analysis of gene expression changes elicited following short-term administration of PFOA demonstrated the up regulation of genes characteristic of PPARα activation, including genes involved in fatty acid homeostasis/peroxisomal proliferation as well as those related to cell cycle. In addition, PFOA has been shown to induce peroxisome proliferation in mouse and rat liver and causes hepatomegaly in mice and rats. While the liver growth caused by PFOA was predominantly attributed to a hypertrophic response, an increase in DNA synthesis following PFOA exposure was observed and predominated in the periportal regions of the liver lobule. Thus, the effect of PFOA on induction of cell cycle gene expression and the increase in DNA synthesis provide evidence in support of both key events 2 and 3 in the proposed MOA for liver tumor induction by PFOA. Empirical evidence also exists in support of the clonal expansion of preneoplastic hepatic lesions by PPARα activators (Step 4). Using an initiation protocol for induction of liver tumors in Wistar rats, PFOA was shown to increase the incidence of

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[27] Convertino M *et al.* Stochastic pharmacokinetic-pharmacodynamic modeling for assessing the systematic health risk of perfluorooctanoate (PFOA). *Toxicol Sci* 163(1) 293-306 (2018).

[28] Clinical measurements included triglycerides, urea, glucose, AST, GGT, alkaline phosphatase, total bilirubin, fibrinogen, PTT and aPTT.

[29] Olsen GW *et al.* Plasma cholecystokinin and hepatic enzymes, cholesterol and lipoproteins in ammonium perfluorooctanoate production workers. *Drug Chem Toxicol*23(4):603–20 (2000). https://doi.org/10.1081/DCT-100101973

hepatocellular carcinomas in rat liver (33% in PFOA exposed rats vs. 0% in controls).[30]

Klaunig *et al.* also note that the key events in **Table 4** appear in a temporal sequence and demonstrate dose-related effects further strengthening the evidence for the PPARα-agonist MOA. Although there are indications that PFOA may also act through PPARα-independent mechanisms[31] in rodents, differences in binding affinity between the rodent and human receptors suggest that it is also unlikely that PFOA induces cancers in humans through the other mechanisms that have been suggested.[32] In evaluating their results, Convertino *et al.* concluded that the disparity between animal and human liver endpoint studies, emphasizing a lack of risk of hepatomegaly, fatty liver, or cirrhosis, are likely due to MOA differences. Increased liver weight due to hepatocellular hypertrophy can often be an adaptive (protective)response in animals due to up-regulation of detoxification enzymes, leading toxicologists to revisit the relevance key liver endpoint studies in animals.[33]

Table 4. PPARα Mode of Action for PFOA-Induced Liver Tumors in Rats (Klaunig *et al.* 2012)[34]

	Key Event	Support	Key Reference
1	Activation of the PPARα receptor	✓	Maloney & Waxman 1999; Vanden Heuvel *et al.* 2006
2	Induction of cell growth gene expression in the liver	✓	Martin *et al.* 2007; Kennedy *et al.* 2004
3	Cell proliferation	✓	Biegel *et al.* 2001; Martin *et al.* 2007; Thottassery *et al.* 1992
4	Selective clonal expansion of preneoplastic hepatic foci	✓	Abdellatif *et al.* 1990
5	Liver neoplasms	✓	Biegel *et al.* 2001

[30] Klaunig JE *et al.* Mode of action analysis of perfluorooctanoic acid (PFOA) tumorigenicity and human relevance. *Reprod Toxicol* 33:410-418 (2012). https://doi.org/10.1016/j.reprotox.2011.10.014

[31] Activation of the constitutive activated receptor (CAR) and pregnane X receptor (PXR) by PFOA have been suggested in animal studies.

[32] Hall AP *et al.* Liver Hypertrophy: A Review of Adaptive (Adverse and Non-Adverse) Changes-Conclusions from the 3rd International ESTP Expert Workshop. *Toxicol Pathol* 40:971-994 (2012). https://doi.org/10.1177%2F0192623312448935

[33] See for example: Bjork JA *et al.* Multiplicity of nuclear receptor activation by PFOA and PFOS in primary human and rodent hepatocytes. *Toxicol* 288: 8-17 (2011). https://doi.org/10.1016/j.tox.2011.06.012

[34] Source: Table 2A in Klaunig *et al.* 2012.

For the induction of rat PAC tumors by PFOA, the available mechanistic data are less robust, but also point to the importance of PPARα activation in the liver. Several factors may contribute to the development of PAC hypertrophy, hyperplasia, and adenomas in the rat, such as testosterone and estradiol levels, growth factor expression (cholecystokinin, or CCK), growth factor receptor overexpression (CCKA receptor), and high fat diet (Klaunig *et al.*).[35] Studies with the compound Wyeth 14,643, a well-studied and potent peroxisome proliferator in rodents, suggest that peroxisome proliferation induces PAC tumors by an indirect mechanism. In this study PPARα activation in the liver caused by exposure to Wyeth triggered reduced bile flow and/or changes in bile composition that produced an increase in CCK levels secondary to hepatic cholestasis.[36] As CCK has been shown to act as a growth factor for PACs in rats, a sustained increase in CCK levels would explain the increase in PAC proliferation observed following PFOA exposure and is likely therefore a preneoplastic lesion.

Expression of CCK receptors in humans is much lower compared to rodents, and the available non-human primate and human data suggest that the CCK pathway is not relevant to human cancer risk. A study with Cynomolgus monkeys exposed to PFOA did not demonstrate an effect on CCK levels or evidence of hepatic cholestasis.[37] Olsen *et al.* reported a statistically significant negative (inverse) association between mean CCK levels and serum PFOA levels among PFOA production workers, even after adjusting for potential confounders.[38]

Mechanistic Data

OEHHA's discussion of MOA and mechanistic considerations for the carcinogenicity of PFOA is devoted almost exclusively to a discussion of effects in the liver. The discussion offers no suggestion of an MOA for kidney cancer, nor does the document demonstrate biological plausibility for renal tumors as part of the application of the Bradford Hill criteria for causality. The failure to offer evidence for an MOA is particularly concerning given OEHHA's use of peak exposure as a more relevant exposure metric than cumulative exposure approach used by both Vieira *et al.* and Barry *et al.* The decision appears based more on justifying the use of the Shearer *et al.* data, and rejecting the data from Barry *et al.*, than on any biological or mechanistic rationale.

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[35] Differences in the diets used in the Butenhoff *et al.* and Biegel *et al.* studies have been suggested as the likely reason for the quantitative difference in the PAC lesions observed in the two studies (USEPA 2016).

[36] Obourn JD *et al.* Mechanisms for the pancreatic oncogenic effects of the peroxisome proliferator Wyeth-14,643. *Toxicol Appl Pharmacol* 145:425–36 (1997). https://doi.org/10.1006/taap.1997.8210

[37] Butenhoff J *et al.* Toxicity of ammonium perfluorooctanoate in male cynomolgus monkeys after oral dosing for 6 months. *Toxicol Sci* 69(1):244–57 (2002).

[38] Olsen *et al.* 2000.

As noted above the time period in which the serum samples were collected in the population studied by Shearer *et al.* and Vieira *et al.* does not represent peak exposure as USEPA data indicate that production and import of PFOA and its ammonium salt continued to increase during this period. Moreover, OEHHA has not offered any possible explanation for why peak exposure is more relevant and, in fact, reasons elsewhere in the draft PHG document that "a single measurement of PFOA or PFOS can be a good long-term marker of exposure in many people."[39] The analysis conducted by Vieira *et al.*, summarized in Table 2, shows little difference between the odds ratios calculated using "peak" and cumulative exposure.

Cancer Evidence for PFOS

Contrary to OEHHA's analysis, both the European Food Safety Authority (EFSA)[40] and Health Canada[41] have concluded that the available evidence does not support the carcinogenicity of PFOS. The EFSA and Health Canada conclusions are based on a thorough review of the human and animal data for the substance.

Several epidemiology studies have attempted to assess cancer incidence in populations exposed to PFOS, including both occupational and community studies. The worker studies have focused on a fluorochemicals production facility in Alabama. Significant community studies include populations in France, Denmark, Sweden, Holland, Taiwan, and Greenland. These studies show no association of PFOS with liver, pancreatic, or prostate cancer or of cancers of the digestive, respiratory, lymphatic, or hematopoietic systems. While Alexander *et al*. (2003) reported an increase in in bladder cancer in the worker population in Alabama,[42] a more detailed follow-up study found no association with bladder cancer and PFOS exposure.[43] No increase in breast cancer incidence was observed among 263 female employees at the production facility in Alabama,[44] although the number of cases was too small for further analysis.

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39 Draft PHG, at 75.

40 EFSA. Risk to human health related to the presence of perfluoroalkyl substances in food. Panel on Contaminants in the Food Chain. *EFSA Journal* 18(9):6223 (2020). https://doi.org/10.2903/j.efsa.2020.6223

41 Health Canada. Guidelines for Canadian Drinking Water Quality. Guideline Technical Document – Perfluorooctane Sulfonate (PFOS). Ottawa, Ontario (December 2018). https://www.canada.ca/en/health-canada/services/publications/healthy-living/guidelines-canadian-drinking-water-quality-guideline-technical-document-perfluorooctane-sulfonate.html

42 Alexander *et al.* Mortality of employees of a perfluorooctanesulphonyl fluoride manufacturing facility. *Occup Env Med* 60:722-729 (2003).

43 Alexander BH and Olsen GW. Bladder cancer in perfluorooctanesulphonyl fluoride manufacturing workers. *Ann Epidem* 17:471-478 (2007).

44 Grice M *et al.* Self-reported medical conditions in perfluorooctanesulfonyl fluoride manufacturing workers. *J Occup Environ Med* 49(7):722–729 (2007).

Several community studies have investigated the association with breast cancer and have reported mixed results. In general, the number of cases investigated in these studies has been relatively small - significantly limiting their interpretation. Two recent case-control studies have investigated the hormone receptor status among women with breast cancer in France and Taiwan. Both have suggested an association between PFOS exposure and estrogen receptor positive (ER+) tumors, the most diagnosed tumor type. In both studies, the analysis was based on a single blood sample which, in the case of the study of French women was collected several years before cancer diagnosis. PFOS levels vary widely between the two studies, with the blood collected in the Taiwan study between 2013 and 2015 – well after the voluntary phase out of PFOS in Japan, Europe, and the US. As a result, the relevance of the PFOS blood levels is uncertain.

Mancini *et al.* (2020) investigated breast cancer incidence in 194 post-menopausal women (mean age of diagnosis – 68.8, range 58.3 to 84.9) diagnosed prior to 2013 for which a single blood sample had been collected between 1994 and 1999.[45] No summary data on PFOS levels is provided, but levels ranged from 5.8 to 13.6 nanograms per milliliter (ng/mL) in the lowest quartile of serum level to 22.5 to 85.3 ng/mL in the highest quartile. Mancini *et al.* report no association with breast cancer incidence in their adjusted model including eight covariables (Model 1), and an association for quartiles 2 and/or 3 but not quartile 4 in the unadjusted and two other adjusted models (Models 2 and 3). In all, 15 covariables were included in Model 3. The association with ER+ tumors was only observed in adjusted Model 3 where the inclusion of so many covariables results in wide confidence intervals, limiting the study's power.[46]

In a study of Taiwanese women, Tsai *et al.* (2020) observed an association between PFOS levels and the incidence of breast cancer overall and for ER+ tumors in 120 woman less than 50 years old (mean age of 48.9 at diagnosis).[47] The mean serum level in the women was 5.64 ng/mL, which represents the lowest serum level quartile in the study by Mancini *et al.* Contrary to the results of the Mancini study, there was no association with breast cancer or ER+ tumors in woman over the age of 50 – despite the fact these women were likely to have experienced higher overall exposure to PFOS. Interpretation of these results is complicated by an overall increase in breast cancer incidence among younger women in Taiwan and other East Asian countries which has been associated with a reduction in the number of births and an

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[45] Mancini FR *et al.* Perfluorinated alkylated substances serum concentration and breast cancer risk: Evidence from a nested case-control study in the French E3N cohort. *Intl J Cancer* 146:917-928 (2020).

[46] Tumor hormone receptor expression was available for 158 of the 194 cases (81%). Of these, 132 tumors (83%) were ER+.

[47] Tsai M-s *et al.* A case-control study of perfluoroalkyl substances and the risk of breast cancer in Taiwanese women. *Environ Intl* 142:105850 (2020). https://doi.org/10.1016/j.envint.2020.105850

increase in the child bearing age of the women.[48] The study also may be complicated by exposure to other pollutants.

Animal Carcinogenicity Data

Only one chronic animal bioassay has been performed for PFOS. The study exposed SD rats to up to 20 parts per million (ppm) K+PFOS in their diet (daily dose of 0 to 0.984 milligrams/kg in males and 0 to 1.251 mg/kg for females) for 2 years.[49] Carcinogenic effects in the study included tumors in the liver, thyroid, and mammary gland. An increased incidence of total hepatocellular adenoma, statistically significant at the highest dose, was observed in both sexes in rats exposed for 2 years. The increased incidence of hepatocellular adenomas in the male and female rats and of combined adenomas/ carcinomas in the females, however, did not display a clear dose-related response.

A statistically significant increase in the incidence of hepatocytic necrosis and hypertrophy in both males and females observed in this study and in other short-term studies, combined with evidence of PPARα and CAR/PXR activation,[50] suggests that the liver tumors observed in the rats may be of limited relevance to humans. The authors concluded that the liver effects were consistent with PPARα and CAR/PXR activation and that the available human and animal data "do not provide support for cancer risk from exposure to PFOS."

Thyroid and mammary tumors also were observed in the study by Butenhoff *et al.* Thyroid follicular cell tumors (adenomas in males, and adenomas/carcinomas combined in females) were significantly increased in recovery group males and in the second highest exposure group in females (0.299 mg/kg per day), but not in the other exposure groups. In females, mammary fibroadenomas and combined fibroadenomas/adenomas were increased over controls only in the lowest dose group and showed a significant negative trend.

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[48] Chen SL *et al.* Childbearing and quality of life decisions for women in Taiwan. *Intl J Healthcare* 4:16-24 (2018). Cited in Tsai *et al.*

[49] Butenhoff *et al.* Chronic dietary toxicity and carcinogenicity study with potassium perfluorooctanesulfonate in Sprague Dawley rats. *Toxicol* 293(1-3):1-15 (2012).

[50] Elcombe CR *et al.* Hepatocellular hypertrophy and cell proliferation in Sprague–Dawley rats from dietary exposure to potassium perfluorooctanesulfonate results from increased expression of xenosensor nuclear receptors PPARα and CAR/PXR. *Toxicol* 293(1-3):16-29 (2012).

Other Relevant Data

Supporting documentation developed by OEHHA staff[51] also reviews the findings of mechanistic studies examining the effects of PFOS on seven characteristics that have been identified as associated with carcinogenicity.[52] Although the application of these characteristics may be useful for identifying and organizing relevant data, it is critical that they be combined with an understanding of the plausibility and causal linkages of the sequence of key events and biological responses involved in carcinogenesis.[53] Without a critical evaluation and integration of the mechanistic evidence with the other realms of evidence, moreover, application of the identified characteristics is of limited value in supporting a scientifically defensible conclusion of carcinogenicity.[54]

The limitations of the key-characteristics approach have been highlighted by two recent publications. The first by Bus (2016) reviews the challenges in the use of oxidative stress as a key characteristic in the evaluation of glyphosate by the International Agency for Research on Cancer (IARC).[55] The second publication by Becker *et al.* (2017)[13] applied the key characteristics to the data from high-throughput studies[56] for about 250 chemicals evaluated for carcinogenicity by USEPA's Office of Pesticide Programs for which ToxCast/Tox21 data are available. The authors conclude that the ability to predict cancer hazard by applying the key characteristics, alone or in combination, with the high-throughput data was "no better than chance." Moreover, interpretation of in vitro assays is complicated by the surfactant properties of PFOS and other PFAS.[57]

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51 OEHHA. Prioritization: Chemicals Identified for Consultation with the Carcinogen Identification Committee (September 2020).

52 Smith MT *et al.* Key characteristics of carcinogens as a basis for organizing data on mechanisms of carcinogenesis. *Environ Health Perspect* 124(6):713-721 (2016).

53 Becker *et al.* How well can carcinogenicity be predicted by high throughput "characteristics of carcinogens" mechanistic data? *Reg Tox Pharma* 90:185-196 (2017). http://dx.doi.org/10.1016/j.yrtph.2017.08.021

54 Goodman J and Lynch H. Improving the International Agency for Research on Cancer's consideration of mechanistic evidence. *Toxicol Appl Pharma* 319:39-46 (2017). https://doi.org/10.1016/j.taap.2017.01.020

55 Bus JS. IARC use of "oxidative stress" as key mode of action characteristic for facilitating cancer classification: glyphosate case example illustrating a lack of robustness in interpretative implementation. *Regul Toxicol Pharma* 86:157-166 (2017). https://doi.org/10.1016/j.yrtph.2017.03.004

56 The USEPA's ToxCast program and the Tox21 federal agency collaboration.

57 Chiu WA *et al.* Use of high-throughput in vitro toxicity screening data in cancer hazard evaluations by IARC monograph working groups. *ALTEX* 35(1):51-64 (2018). https://www.altex.org/index.php/altex/article/view/98

Estimating Human Exposures to PFOA and PFOS

OEHHA's assessment of PFOA and PFOS depends largely on its assumptions about the clearance rate of these substances in humans. As noted, large pharmacokinetic differences exist between humans and animals for PFOA and PFOS, with lower clearance (i.e., higher half-life values) reported for humans than for rats, mice, and non-human primates. These differences result in higher target tissue doses in humans when exposed to the same external doses as laboratory animals. Consequently, default approaches for interspecies extrapolation (e.g., using an interspecies uncertainty factor of 10 or allometric scaling) are not considered to be sufficiently predictive. To better account for these interspecies toxicokinetic differences, the World Health Organization (WHO) developed an approach using chemical-specific adjustment factors (CSAF).[58] Consistent with this approach, OEHHA calculates a human equivalent dose (HED) for PFOA and PFOS by adjusting the serum concentration in rodents measured at the drinking water exposure by the rate of clearance (CL) of the substance from the human body. The CL was calculated using the estimated volume of distribution and serum elimination half-life.[59]

Internal dose ratios predicted by the available physiologically-based pharmacokinetic (PBPK) models indicate, however, that the interspecies extrapolations for PFOA and PFOS are highly dose dependent, and result from nonlinear toxicokinetics.[60] As a result, a single interspecies extrapolation factor such as that used by OEHHA is not scientifically supportable for either PFOA or PFOS. Instead, an approach that uses CSAF values derived from the PBPK models better addresses the issue of nonlinear toxicokinetics and its impact on interspecies extrapolation.

Using such an approach, Health Canada compared dose metrics predicted by the various animal PBPK models to calculate a CL ratio between species (CL_A/CL_H).[61] They reasoned that using the model data to derive the CL_A/CL_H allows for a more appropriate comparison of doses

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58 WHO. Chemical specific adjustment factors for interspecies differences and human variability: guidance document for use of data in dose/concentration–response assessment. International Programme on Chemical Safety. World Health Organization. Geneva (2005). http://apps.who.int/iris/bitstream/handle/10665/43294/9241546786_eng.pdf;jsessionid=45918ABD3B07EF944ACD546CF50B974F?sequence=1

59 The volume of distribution is defined as the volume of blood (in milliliters per kilogram) in which the amount of a chemical would need to be uniformly distributed to produce the observed blood concentration. Half-life is a measure of the time (in days) required to eliminate one half of a quantity of a chemical from the body.

60 Loccisano AE *et al.* Comparison and evaluation of pharmacokinetics of PFOA and PFOS in the adult rat using a physiologically based pharmacokinetic model. *Reprod Toxicol* 33(4):452–467 (2012).

61 For each species, the PBPK model was used to predict internal doses for a broad range of oral doses. Model simulations were continued until steady-state conditions or expected lifetimes were reached (Loccisano *et al.* 2012).

of the same magnitude.[62] Using the CL ratio to estimate exposures, Health Canada's analysis indicates that the approach taken by OEHHA significantly underestimates the human clearance rate and, as a result, OEHHA calculates HED values that are 10 to 500 times lower than actual. The decline in biomonitoring data by the Center for Disease Control and Prevention (CDC) over the last 20 years support this point. [63]

As described, the risk assessment calculations by OEHHA are highly dependent on the estimate of the elimination half-life in humans. Reported half-life estimates in humans range considerably and appear to show a gender difference for at least some PFAS. Estimates of the mean half-life for PFOA vary from 2.3 years in a study of a general population exposed via drinking water[64] to 3.8 years in an occupationally-exposed cohort.[65] For PFOS, a recent analysis of data from the CDC biomonitoring data estimated a serum elimination half-life of PFOS of 3.8 years in males and 3.4 years in females.[66] Similarly, data from a community in Sweden exposed to PFAS via a contaminated water supply following installation of a treatment system suggested a serum elimination half-life for PFOS of 3.4 years for 106 residents aged 4 to 83.[67] An earlier study of occupational exposures, on the other hand,suggested a half-life of 5.4 years for PFOS among retired workers.

Draft PHG Derivation for PFOA and PFOS

The problems with OEHHA's selection of key studies notwithstanding, we have several concerns with the derivation of the draft cancer PHGs for PFOA and PFOS. In both cases, a benchmark response (BMR) of 5 percent despite OEHHA guidance that a BMR of 10 percent be used for animal studies and for typical epidemiology studies, although lower effect levels may be appropriate for large epidemiological data sets.[68] While the OEHHA guidance suggests that

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62 Health Canada 2018.

63 https://www.cdc.gov/exposurereport/index.html.

64 Bartell SM *et al.* Rate of decline in serum PFOA concentrations after granular activated carbon filtration at two public water systems in Ohio and West Virginia. *Environ Health Perspect* 118(2):222-228 (2010).

65 Olsen GW *et al.* Half-life of serum elimination of perfluorooctanesulfonate, perfluorohexanesulfonate and perfluorooctanoate in retired fluorochemical production workers. *Environ Health Persp* 115:1298–1305 (2007).

66 Gomis MI *et al*. Historical human exposure to perfluoroalkyl acids in the United States and Australia reconstructed from biomonitoring data using population-based pharmacokinetic modelling. *Environ Int.* 108: 92-102 (2017).

67 Li Y *et al.* Half-lives of PFOS, PFHxS and PFOA after end of exposure to contaminated drinking water. *Occup Environ Med.* 75:46-51 (2018).

68 OEHHA. Technical Support Document for Cancer Potency Factors: Methodologies for Derivation, Listing of Available Values, and Adjustments to Allow for Early Life Stage Exposures. Sacramento, CA, Office of

a lower effect level may be appropriate for large epidemiological data sets, neither the Shearer *et al*. or Vieira *et al*. studies can be considered large. OEHHA provides no rationale for why a lower BMR was chosen.

OEHHA also applied a body weight scaling factor to the human equivalent dose (HED) for PFOS,[69] despite using a benchmark dose (BMD) model and applying a dose adjustment factor (DAF) to account for the difference in serum half-live between humans and the Sprague Dawley rats used in the study by Butenhoff *et al.* OEHHA guidance notes, however, that -

> The basic approach [to benchmark dose methodology] is to fit an arbitrary function to the observed incidence data, and to select a "point of departure" (POD) (benchmark dose) within the range of the observed data. From this a low dose risk estimate or assumed safe level may be obtained by extrapolation, <u>using an assumed function (usually linear) or by application of uncertainty factors.</u> The critical issue here is that no assumptions are made about the nature of the underlying process in fitting the data. The assumptions about the shape of the dose response curve (linear, threshold, etc.) are explicitly confined to the second step of the estimation process, and are chosen on the basis of policy, mechanistic evidence or other supporting considerations. The benchmark chosen is a point at the low end of the observable dose-response curve. . . Because real experimental data include variability in the response of individual subjects, and measurement errors, likelihood methodology is applied in fitting the data. A lower confidence bound (usually 95%) of the effective dose (LED10), rather than its maximum likelihood estimate (MLE), is used as the point of departure. This properly reflects the uncertainty in the estimate, taking a cautious interpretation of highly variable or error-prone data. It also reflects the instability of MLE values from complex curve-fitting routines, which has been recognized as a problem also with the linearized multistage model.[70] (emphasis added)

Since OEHHA uses a linear, low dose extrapolation to calculate the cancer slope factor, there is no need to apply an additional body-weight adjustment.

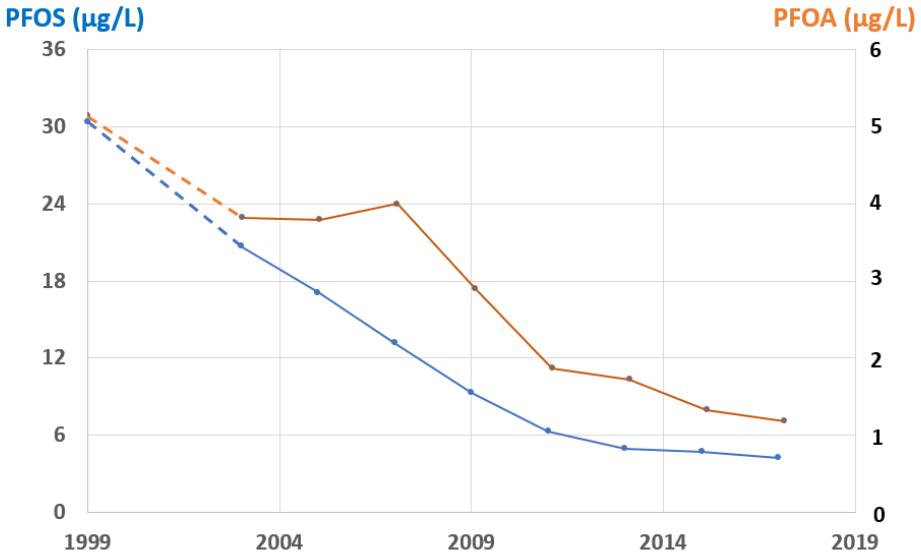
Environmental Health Hazard Assessment, California Environmental Protection Agency (2009), at 27. OEHHA 2009.

[69] According to the draft PHG, OEHHA applied an adjustment of $(BW_{animal}/BW_{human})^{1/8}$ to account for toxicodynamic differences between the species.

[70] OEHHA 2009, at 27.

We also are concerned about the use of a relative source contribution of 20 percent to develop the draft non-cancer PHGs for PFOA and PFOS. Although 20 percent is often used as a default assumption for the exposure resulting from drinking water, the available evidence suggest that other sources of potential exposure to PFOA and PFOS have declined drastically. According to data collected by the Center for Disease Control and Prevention (CDC), mean serum levels of PFOS declined by 85 percent in the US population between 1999 and 2016.[71] According to CDC, mean serum levels of PFOA declined by 60 percent over the same time frame (see Figure 1). Given those dramatic declines, it is inappropriate to assume that 80 percent of exposure to these substances comes from sources other than drinking water. While a few other states have assumed an RSC of 50 or 60 percent, it is likely that the contribution of drinking water to overall exposure is even higher – particularly in areas where drinking water contamination has been detected.

Figure 1. Mean serum levels of PFOA and PFOS, 1999-2018.[72]



[71] CDC. Fourth national report on human exposure to environmental chemicals, updated tables (January 2019). https://www.cdc.gov/exposurereport/index.html

[72] Human exposure monitoring is conducted as part of CDC's National Health and Nutrition Examination Survey (NHANES).