BEFORE THE ILLINOIS POLLUTION CONTROL BOARD

IN THE MATTER OF:	)	
	)	
PROPOSED AMENDMENTS TO	)	R 22-18
GROUNDWATER QUALITY	)	(Rulemaking – Public Water Supplies)
35 ILL ADM. CODE 620	)	

NOTICE OF FILING

TO: Mr. Don Brown,
Clerk of the Board
Illinois Pollution Control Board
100 West Randolph Street
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(**VIA ELECTRONIC MAIL)**

Vanessa Horton,
Hearing Officer
Illinois Pollution Control Board
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(**VIA ELECTRONIC MAIL)**

(See Persons on Attached Service List)

PLEASE TAKE NOTICE that I have today filed with the Office of the Clerk of the Illinois Pollution Control Board, **THE ILLINOIS ENVIRONMENTAL PROTECTION AGENCY'S PRE-FILED ANSWERS TO THE AMERICAN CHEMISTRY COUNCIL**, copies of which are hereby served upon you.

Respectfully Submitted,

ILLINOIS ENVIRONMENTAL
PROTECTION AGENCY

Dated: March 7, 2022

By: /s/ Sara Terranova
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THE ILLINOIS ENVIRONMENTAL PROTECTION AGENCY'S PRE-FILED ANSWERS TO THE AMERICAN CHEMISTRY COUNCIL

The Illinois Environmental Protection Agency ("Illinois EPA" or "Agency"), by and through its attorneys, and pursuant to the Illinois Pollution Control Board's ("Board") Notice of Hearing dated January 13, 2022, submits the following Pre-filed Answers to the American Chemistry Council ("ACC") for hearings scheduled on March 9-10, 2022.

ACC Question 1
The definitions for LOAEL and NOAEL in Section 620.110 specify a statistically significant increase in frequency or severity of adverse effects. However, many of the values proposed by IEPA are based on benchmark dose modeling.

- *Does IEPA also require statistical significance when considering data derived from benchmark dose modeling?*

- *Does IEPA require evidence of a dose response to identify a hazard, or is a statistically significant response at any dose sufficient?*

Agency Answer 1
Illinois EPA is not proposing any numeric standards based on toxicity values derived using the NOAEL, LOAEL, or benchmark dose modeling procedures outlined in Part 620 Appendix A(b)(3) of (4). Proposed updated numeric standards use toxicity values from USEPA's hierarchy of toxicity values, as discussed in Carol Hawbaker's testimony, beginning on page 6.

ACC Question 2
Section 620.125 lists several standard test methods for analyzing PFAS, including ASTM D7979-20. However, USEPA has not yet developed a validated laboratory method for analyzing PFAS in water other than drinking water. In September 2021, the Office of Waterreleased draft method 1633 for the measurement of certain PFAS in aqueous samples but hasnot yet finalized the method.

- *Has IEPA validated ASTM D7979-20 for analyzing for PFAS in aqueous sources that arenot drinking water?*

- *How will IEPA assure that the data collected are accurate?*

Agency Answer 2
USEPA validated SW-846 Method 8327 and is available for use to analyze PFAS in water other than drinking water. Quality assurance procedures (including quality control samples during sample collection and analysis) specified in the method, the laboratory Standard Operating Procedure, and the laboratory Quality Assurance/Quality Control Manual must be followed to ensure accuracy.

ACC Question 3
Section 620.310(3) of the proposal requires that the regulatory agency determine whether preventive response shall be undertaken if a statistically significant increase occurs above background for the identified substances.

- *How does IEPA define background?*

Agency Answer 3 – part 1
Part 620 establishes groundwater quality standards, but does not contain a requirement to perform groundwater monitoring. The requirement to monitor groundwater originates from other programs. The appropriate means to establish background and therefore the definition of background derive from the specific program requirements.

- *How does IEPA determine statistical significance?*

Agency Answer 3 – part 2
Statistical significance varies depending on the statistical method being used. Allowable statistical methods are program specific. Therefore, statistical significance is method and program specific.

ACC Question 4
The proposed regulation would establish ground water standards for 22 substances (3 inorganic chemicals and 19 organic chemicals) and revise existing standards for 30 chemicals.

- *How were these substances selected?*

- *Was there a public review process for their selection?*

Agency Answer 4
The proposed amendments to 35 Ill. Adm. Code 620 would establish groundwater quality standards for 10 new constituents: 3 inorganic chemicals and 7 organic chemicals. A table listing the proposed constituents to be added to Part 620 is located on page 19 of Carol Hawbaker's pre-filed testimony. In addition, the proposed amendments would update groundwater quality standards for 39 chemicals listed in Part 620. A table identifying constituents with proposed updated groundwater quality standard is located on page 23 of Carol Hawbaker's pre-filed testimony.

Consistent with Section 8 of the Ground Water Protection Act, the Agency proposed new constituents as these chemicals have been found in groundwaters in Illinois and are known, or

suspected, of causing cancer, birth defects, or other adverse effects on human health. *See* 415 ILCS 55/8.

The Illinois EPA did not conduct a public review process solely for the selection of the chemicals to be added to Part 620. All proposed chemicals meet the requirements for inclusion in the Part 620 groundwater quality standards.

ACC Question 5
IEPA's selection of RfD sources for the PFAS substances appears arbitrary and inconsistentwith its stated hierarchy.

- *Why did IEPA select toxicity values from ATSDR, a Tier 3 source, for PFOS when a toxicity value was developed by USEPA's Office of Water in setting its 2016 LifetimeHealth Advisory (LHA) for the substance?*

- *Similarly, why does IEPA use the Notification Level recommended by California's EPA,a Tier 3 source, for PFOA when the EPA Water Office conducted a toxicity assessment in setting the LHA?*

Agency Answer 5
Please refer to Carol Hawbaker's pre-filed testimony, beginning on page 6, for the basis of selecting toxicity values from within USEPA's toxicity hierarchy. USEPA Office of Water is an unranked Tier 3 source on the hierarchy, while ATSDR is the top ranked Tier 3 source. Further, ATSDR's PFAS toxicity values rely on more recent toxicological studies with a broader scope of adverse effects than the studies relied upon for developing the toxicity values for USEPA's 2016 health advisory levels. The California EPA toxicity value selected by the Agency for PFOA is based on carcinogenic effects and is ranked second on the Tier 2 toxicity hierarchy. The 2016 health advisory level is based on noncancer toxicity.

ACC Question 6
The revised standard for 1,4-dioxane is based on an analysis conducted by USEPA for its Integrated Risk Information System (IRIS) in 2013. Considerable information has been generated on this chemical since then supporting a threshold mode of action (MOA) for carcinogenicity in laboratory animals, included an analysis by Health Canada completed in2021. As a result, government bodies around the world have concluded that 1,4-dioxane does not present a cancer risk below a threshold exposure, including the World Health Organization, the European Union, and Health Canada.

- *Did IEPA consider the evidence for a threshold cancer MOA in considering revision ofthe groundwater standard for 1,4-dioxane?*

- *What steps does IEPA take to ensure that its standards are based on the most current science?*

Agency Answer 6
Part 620.110 defines a "carcinogen" as meaning:

> *"a contaminant that is classified as a Category A1 or A2 Carcinogen by the American Conference of Governmental Industrial Hygienists; or a Category 1 or 2A/2B carcinogen by the World Health Organization's International Agency for Research on Cancer; or a "Human carcinogen" or "Anticipated Human Carcinogen" by the United States Department of Health and Human Service National Toxicological Program; or a Category A or B1/B2 Carcinogen by the United States Environmental Protection Agency in Integrated Risk Information System or a Final Rule issued in a Federal Register notice by the USEPA.* [415 ILCS 5/58/.2]

In 1999, the World Health Organization's International Agency for Research on Cancer ("IARC") classified 1,4-dioxane a "2B carcinogen". IARC has not rescinded its classification. United States Department of Health and Human Service National Toxicological Program ("NTP") classified 1,4-dioxane as "reasonably anticipated to be a human carcinogen". NTP's classification for 1,4-dioxane remains. In 2005, the USEPA Integrated Risk Information System ("IRIS") classified 1,4-dioxane as a Category B2 or "likely to be carcinogenic to humans." In 2013, following a review, IRIS's classification did not change. Pursuant to Illinois EPA definition of a "carcinogen," 1,4-dioxane is a carcinogen and Part 620 requires it to be evaluated as such. The source of the carcinogenic toxicity value for 1,4-dioxane is IRIS, the top tiered source in the toxicity hierarchy.

ACC Question 7

In the key study used in its analysis of PFOS, the Agency for Toxic Substances and DiseaseRegistry (ATSDR) ignores the conclusions of the study authors regarding the relevant dose resulting in adverse effects in the laboratory animals. The study authors identify 0.4 milligrams per kilogram (mg/kg) as a no-observed-adverse-effect level (NOAEL) and 1.6 mg/kg as a lowest-observable-adverse-effect level (LOAEL). ATSDR, in contrast, inappropriately considers the LOAEL to be 0.4 mg/kg without explanation which has a significant impact on its calculation.

- *Has IEPA reviewed the conclusions of the study authors and evaluated theappropriateness of using 0.4 mg/kg as a LOAEL.*

Agency Answer 7

The Illinois EPA selected ATSDR dose Minimum Risk Level ("MRL") as its toxicity source, for PFOS because ATSDR is a Tier 3 toxicity source permitted for use within USEPA's toxicity hierarchy; and because this is a final value. Concerns regarding the basis for ATSDR's development of its toxicity values are more appropriately directed to ATSDR.

ACC Question 8

CalEPA bases its analysis of PFOA on reports of liver and pancreatic tumors in a laboratory animal study. Available studies suggest that these tumors are associated with a mode of action that is of less relevance to humans.

- *Has IEPA assessed the relevance of the tumors reported in the animal study to human exposure?*

Agency Answer 8
The Illinois EPA selected California EPA's PFOA carcinogen toxicity value as its carcinogen toxicity source for PFOA because CalEPA California Office of Environmental Health Hazard Assessment ("OEHHA") is a Tier 3 toxicity source permitted for use within USEPA's toxicity hierarchy and because this is a final value. Concerns regarding the basis for OEHHA's development of its toxicity value are more appropriately directed to OEHHA.

Further, OEHHA's February 2022, "Response to Comments Pertaining to the Notice of Intent to List Perfluorooctanoic Acid as Causing Cancer Under Proposition 65," discusses the relevance of tumors in humans. The Response document includes the following comment and reply regarding relevance to humans:

> "Comment 6: ACC states that the findings of the NTP report "are consistent with peroxisome proliferator-activated receptor α (PPARα) activation which is of uncertain relevance to humans. Consequently, there is not sufficient evidence to conclude that PFOA exposure presents a cancer risk to humans to justify its listing under Proposition 65."
>
> "In addition to the NTP study, two chronic bioassays have been conducted in rats exposed to PFOA through diet. Although the results are not consistent, one or both studies have reported liver, LC [Leydig cell], and PAC [pancreatic acinar cell] tumors.[19]" (ACC, p. 5)
>
> "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 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 species (e.g., hamsters, guinea pigs and Cynomolgous monkeys) that are more appropriate animal model surrogates than mice and rats." (ACC, p. 6)
>
> "Several key studies provide support for the key events in the proposed PPARα-activated mode of action (MOA) for rat liver tumors (Table 1). These data are summarized by Klaunig et al. (2012)" (ACC, p. 6)
>
> "Although there are indications that PFOA may also act through PPARα-independent mechanisms[24] 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.[25] 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 [of] key liver endpoint studies in animals." (ACC, p. 7)

Response 6: OEHHA disagrees with the commenter's claim that based on data related to PPARα activation, there is not sufficient evidence to justify the listing of PFOA under Proposition 65.

The commenter is suggesting that rat liver tumors induced by PFOA are not relevant to humans because PFOA induces these tumors predominantly through a mechanism that is dependent on activation of PPARα. However, hepatotoxicity can be induced through other mechanisms. As discussed in OEHHA (2021):

> "In summary, these lines of evidence suggest that PFOA-induced hepatotoxicity, including carcinogenesis, in rodents is not solely the result of PPARα activation. Liver toxicity was observed in PPARα KO [knock out] mice, and in studies where PPARα was not activated (Filgo et al., 2015; Rebholz et al., 2016; Das et al., 2017; Li et al., 2017b; Wen et al., 2019c). Furthermore, rodent carcinogenicity studies with other PPARα activators have demonstrated that PPARα activation is not required for liver tumor induction, and that constitutive activation of PPARα does not lead to tumorigenesis. Therefore, OEHHA considers rodent liver toxicity studies, including carcinogenicity studies, to be relevant to human health."[22]

> "PFOA is a known activator of PPARα and there has been considerable discussion in the scientific literature that carcinogenesis in rodents mediated by activation of PPARα is not relevant to humans, as PPARα activation in humans is not known to induce tumors. However, there is evidence in PPARα knockout animals that PFOA induces PPARα-independent toxicity, including carcinogenesis. Additionally, toxicity is observed at doses that do not activate PPARα. This indicates that PFOA acts via multiple mechanisms." [23]

This issue is also discussed in IARC (2017):

> "The liver is the most prominent target tissue of PFOA, with rats and mice being the most responsive species to liver-specific effects. Limited data are available indicating liver toxicity in non-human primates (Butenhoff et al., 2002). Additionally, serum levels of PFOA have been positively associated with serum markers of liver injury in humans (Sakr et al., 2007; Lin et al., 2010; Gallo et al., 2012). Liver toxicity observed in rodents has been associated with both PPARα-dependent and -independent mechanisms. The analysis by the Working Group of data from humans in vitro is consistent with multiple molecular pathways being in operation.

> Cytotoxicity, cell proliferation, and liver hypertrophy have also been observed in studies with PFOA in rodents, indicating that other mechanisms may also contribute."[24]
>
> "Several studies in humans have examined the relationship between exposure to PFOA and toxicity, and suggest that PFOA may cause liver injury. In experimental animals, the liver is a well-established target for toxicity. Potential mechanisms for PFOA-induced toxicity and carcinogenicity in the liver include PPARα activation, involvement of other molecular pathways (i.e. constitutive androstane receptor, pregnane X receptor, estrogen receptor), and cytotoxicity. There is moderate evidence for these mechanisms, largely from studies in rats and mice. Based on the available evidence, human relevance of the liver findings in rodents cannot be excluded."[25]
>
> Based on a careful consideration of the data as well as the findings summarized in OEHHA (2021) and IARC (2017), the relevance of the liver effects in rodents to humans should not be dismissed. Regarding the comment that "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", the commenter has not provided any evidence to support this statement. In contrast, studies indicate that PFOA can, in fact, induce tumors in humans; for example, there is compelling evidence from epidemiology studies that PFOA increases the risk of kidney tumors in humans, as discussed in OEHHA (2021)[26]."

See Attachment 1.

ACC Question 9

USEPA's Drinking Water Treatability Database indicates that available treatment technologies can remove up to 99 percent of concentrations of HFPO-DA, PFBS, PFHxS,PFNA, PFOA, and PFOS in water.

- *Why are the standards for Class II (Ground Resource) Groundwater for these substances in Section 620.420 not adjusted by a treatment factor of 10 as is done for other substancesfor which >90 percent removal efficiency can be achieved?*

Agency Answer 9

The Agency used the method discussed in Carol Hawbaker's prefiled testimony beginning on page 28. The proposed PFAS constituents do not meet the criteria for applying treatment factors, as presented in the prefiled testimony. Chemical-specific parameters utilized to determine treatability are available at Attachment 1J 1, beginning on page 4,854 of the Agency's December 7, 2021 filing. The Agency also presented the procedures regarding the applications of treatability factors for Class II groundwater at the December 2019 and May 2021 Outreach sessions. This same

information is also included in the Agency's December 7, 2021, filing as Attachment 3, beginning on page 4,905 and Attachment 4, beginning on page 4,937.

ACC Question 10
Section 620.605 indicates that a health advisory for a substance for which a threshold doseexists should be based on the lower of the HTTAC or HNTAC if an MCL Goal does not exist.

- *What is the basis for calculating a HNTAC for a substance for which a threshold exists?*

Agency Answer 10
Since its promulgation in 2012, Section 620.605 requires that an HNTAC must be the guidance level if the chemical substance is a carcinogen. The proposed updates to Section 620.605 require that the more stringent of the HTTAC and HNTAC be the guidance level. This ensures that a person ingesting groundwater is protected from both cancer effects and noncancer adverse health effects. The method of choosing the lower of the concentrations is consistent with the methods prescribed in 35 Ill. Adm. Code 742: Tiered Approach to Corrective Action Objectives regulations ("TACO"). TACO requires users to select the more stringent remediation objective calculated by carcinogen and noncarcinogen methods.

ACC Question 11
Under USEPA's voluntary stewardship program, manufacture of PFOA, PFOS, and other long-chain PFAS was phased out in the early 2000s in the United States, Europe, and Japan, As a result, data from the Center for Disease Control and Prevention indicates that blood serum levels of PFOA and PFOS have declined by 60 and 85 percent, respectively. Based onthis decline, several states have assumed a relative source contribution (RSC) of 50 percent or more for these two substances.

- *What is the basis for IEPA's decision to use the default RSC of 20 percent in deriving the groundwater quality standards for these two substances?*

- *What chemical-specific data are considered for determining the appropriate RSC for a substance?*

Agency Answer 11
USEPA determined, and Illinois EPA agrees, that RSCs cannot be set at levels other than the default for PFAS due to insufficient data. PFAS constituents are ubiquitous in the environment outside of groundwater. Its many uses in manufacturing goods, such as clothing, furniture, carpeting, food packaging, personal care products, and a myriad of other items provides ample opportunity for exposure to PFAS from sources other than drinking water. In addition, bioaccumulation of PFAS in plants and animals used for food sources indicates significant opportunity for exposures to PFAS other than through ingestion of water. The presence of PFAS in the blood of virtually every person in the world, particularly in people living in areas where contaminated drinking water is not a source of exposure, indicates evidence of multiple exposure routes.

ACC Question 12
There is compelling and robust scientific evidence that mechanisms of carcinogenicity which operate in adults also operate in children, and that to the extent children may be more, less, or equally sensitive to some substances, current cancer assessment methodology is sufficiently conservative to protect children. In its guidance for assessing early life exposures, moreover,EPA indicates that even if the data indicate a mutagenic mode of action, available chemical specific data should be considered before applying the age-dependent adjustment factors

- *How will IEPA consider chemical-specific data when assessing whether to add an adjustment factor for early life exposures for substances determined by USEPA to be mutagenic carcinogens?*

Agency Answer 12
The Illinois EPA will evaluate mutagenic carcinogens, as determined by USEPA, using early life exposure adjustments for the same instances as utilized by the USEPA Regional Screening Levels.

ACC Question 13
Under the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA, or Superfund), USEPA conducts a screening assessment for all substances affecting the same organ system. However, the Agency only assumes dose additivity for substances acting by a common mode of action when conducting a more refined assessment.Appendix C of the proposal appears to suggest that dose addition will be applied to substances affecting the same organ system, regardless of mode of action.

- *Under what circumstances does IEPA assume dose additivity when assessing exposuresto multiple substances?*

- *Does IEPA require that both criteria listed in paragraph (a) of Appendix C be met to consider substances to be similar-acting?*

Agency Answer 13
IEPA assumes dose additivity when a mixture contains two or more constituents that are similar-acting as defined by Part 620 Appendix C. Substances are considered similar-acting if they affect the same target organ or have the same mode of action. IEPA requires at least one criterion to be met to consider substances similar acting.

ACC Question 14
Appendix C indicates that nervous system depression and liver toxicity are "modes of action"when they are actually health endpoints that can result from a variety of modes of action?

- *How does IEPA define a "mode of toxic action"?*

- *Why is IEPA using a different definition for "mode of action" than that used by USEPAand the scientific community?*

Agency Answer 14
Illinois EPA defines a mode of toxic action as when substances have the same pharmacological mechanism of toxicity. Substances are also considered similar-acting when they have the same physiological target in an organism.

ACC Question 15
Appendix C lists decreased body weight and developmental effects as separate health endpoints, when body weight decrease in offspring is very often the basis for identifying adevelopmental effect

- *What is the basis for considering the two separately?*

- *What body weight effects is IEPA considering, if not those observed in offspring ofexposed mothers?*

Agency Answer 15
Decreased body weight may be a health effect that occurs at any stage in life as the result of adverse effects from exposure to a substance. Developmental delays or effects are more specific to types of delays or effects, and not decreased birth weight in offspring.

ACC Question 16
The following organ systems have not been identified as targets for the specified chemical inthe source cited by IEPA's for its toxicity assessment of the chemical: HFPO-DA – kidney (USEPA), PFBS – reproductive (USEPA), PFOS – reproductive (ATSDR)

- *What is the basis for listing these targets in Appendix E?*

Agency Answer 16
For HFPO-DA, the kidney is a target organ for adverse effects. Refer to the USEPA Office of Water's HFPO-DA toxicity values document, beginning on page 2,334 of the Agency's December 7, 2021, filing.

PFBS was inadvertently added to reproductive effects and will be removed. The reproductive effects noted in the studies are more appropriately placed as developmental effects.

PFOS may cause adverse health effects during gestation. Therefore, it is properly included under Reproductive System. Refer to the USEPA PFOS Health Effects document available as Attachment 1D 4, beginning on page 1,021, and ATSDR's toxicological profile for perfluoroalkyls as Attachment 1D 5, beginning on page 1,268 of the Agency's December 7, 2021, filing.

ACC Question 17
Although several of the substances are listed to affect multiple target organs, the referencedose (RfD) for each substance is based on effects in a single organ.

- *How will IEPA assess dose additivity for a health endpoint if that endpoint is not thebasis of the toxicity value calculation for the identified substances?*

- *Has IEPA conducted additional analysis to derive toxicity values for each of the endpoints for which a substance is identified? If not, how can IEPA consider addingdoses from multiple health endpoints?*

Agency Answer 17
In regard to dose additivity, the Agency assumes the question references the procedures listed at Part 620 Appendix B for determining hazard indices for mixtures of similar-acting substances. Appendix B(d) identifies how the additivity of toxicities must be considered. This procedure has been in place since Part 620's original promulgation in 1991. The procedure is also listed in 35 Ill. Adm. Code 742.805(c) for addressing similar-acting chemicals under TACO.

Respectfully Submitted,

ILLINOIS ENVIRONMENTAL
PROTECTION AGENCY

Dated: March 7, 2022

By: /s/ Sara Terranova
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CERTIFICATE OF SERVICE

I, the undersigned, hereby certify that I have electronically served **THE ILLINOIS ENVIRONMENTAL PROTECTION AGENCY'S PRE-FILED ANSWERS TO THE AMERICAN CHEMISTRY COUNCIL** on March 7, 2022, to the attached service list. I further certify that my email address is sara.terranova@illinois.gov and that the email transmission took place before 5:00pm.

ILLINOIS ENVIRONMENTAL
PROTECTION AGENCY

Dated: March 7, 2022

By: /s/ Sara Terranova
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ATTACHMENT 1

Response to Comments Pertaining to the Notice of Intent to List Perfluorooctanoic Acid as Causing Cancer Under Proposition 65

Office of Environmental Health Hazard Assessment
California Environmental Protection Agency

February 2022

The Office of Environmental Health Hazard Assessment (OEHHA) has determined that perfluorooctanoic acid (PFOA) meets the criteria for listing under Proposition 65[1] via the authoritative bodies mechanism. This determination is based on conclusions by the National Toxicology Program (NTP) that PFOA causes cancer, and on the scientific evidence relied on by NTP[2]. NTP is designated as an authoritative body for purposes of listing chemicals as causing cancer pursuant to Title 27, Cal. Code of Regulations, section 25306[3]. PFOA will therefore be added to the Proposition 65 list as a chemical known to cause cancer on February 25.

OEHHA made this determination after reviewing public comments on the proposed listing of PFOA. On March 19, 2021, OEHHA issued a Notice of Intent to List (NOIL)[4] PFOA under Proposition 65 as a chemical known to the state to cause cancer. The action was based on Proposition 65 statutory requirements[5] and the criteria in Section 25306 for listing chemicals based on the findings of authoritative bodies. This document responds to public comments received on the NOIL under Proposition 65.

Background

Under Section 25306, a chemical has been "formally identified" as causing cancer by an authoritative body if: (1) the chemical has been included on a list of chemicals causing cancer published by the authoritative body; or is the subject of a report which is published by the authoritative body and which concludes that the chemical causes cancer; or has been "otherwise identified" as causing cancer by the authoritative body in

[1] The Safe Drinking Water and Toxic Enforcement Act of 1986 (codified at Health and Safety Code section 25249.5 *et seq*.) hereinafter referred to as Proposition 65 or the Act.
[2] National Toxicology Program (NTP 2020). NTP Technical Report on the *Toxicology and Carcinogenesis Studies of Perfluorooctanoic Acid (CASRN 335-67-1 Administered in Feed to Sprague Dawley (Hsd:Sprague Dawley® SD®) Rats*. Technical Report Series No. 598. US Department of Health and Human Services, NTP, Research Triangle Park, NC. https://ntp.niehs.nih.gov/ntp/htdocs/lt_rpts/tr598_508.pdf
[3] All further references are to sections of Title 27 of the California Code of Regulations, unless otherwise indicated.
[4] Notice of Intent to List: *Perfluorooctanoic Acid* (PFOA). Available at: https://oehha.ca.gov/proposition-65/crnr/notice-intent-list-chemical-authoritative-bodies-mechanism-perfluorooctanoic
[5] Health and Safety Code section 25249.8(b).

a document that indicates that the identification is a final action; and (2) if the list, report, or document meets specified criteria in Section 25306(d)(2).

Basis for Listing

OEHHA has reviewed the conclusions and statements in the 2020 NTP Technical Report on the *Toxicology and Carcinogenesis Studies of Perfluorooctanoic Acid (CASRN 335-67-1) Administered in Feed to Sprague Dawley (Hsd:Sprague Dawley® SD®) Rats*[6]. OEHHA has determined that these conclusions and statements satisfy the Section 25306(d)(1) requirements. Specifically, PFOA is the subject of a report published by the authoritative body that concludes that PFOA causes cancer, and the NTP Technical Report indicates this identification is a final action. Further, OEHHA has determined that the report meets the Section 25306(d)(2) requirements. Thus, the NTP Technical Report satisfies the formal identification criteria in the Proposition 65 regulations for PFOA. NTP's conclusions in the report on which OEHHA relies include the following:

NTP (2020) states in the Conclusion section of the report's Abstract (page xviii):

> "Under the conditions of these 2-year feed studies, there was *clear evidence of carcinogenic activity*…of PFOA in male Hsd:Sprague Dawley® SD® rats based on the increased incidence of hepatocellular neoplasms (predominately hepatocellular adenomas) and increased incidence of acinar cell neoplasms (predominately acinar cell adenomas) of the pancreas. The additional effect of perinatal exposure in combination with postnatal exposure was uncertain and limited to the observation of hepatocellular carcinomas."[7] (Emphasis in original)

The NTP (2020) report states in the main body of the report (pages 88 and 89, respectively):

> "In males, the incidences of hepatocellular adenomas were increased in the 40 and 80 ppm groups with and without perinatal exposure and exceeded the historical control range. In addition, hepatocellular carcinomas, a rare neoplasm (0/340 historical control), occurred in the 300/80 group."
>
> "Increased incidences of pancreatic acinar cell adenomas and adenocarcinomas were observed in exposed males, as was the combined incidence of these neoplasms. Significantly increased incidences of adenomas in all postweaning exposed groups (36–64%) were higher than the historical control range for adenomas in males (45/340 historical control; range 0–28%) and the occurrence of rare adenocarcinomas (2/340 historical control; range 0–2%) were observed in all postweaning exposure groups (20, 40, and 80 ppm)."

[6] NTP (2020), full citation provided in footnote 2.
[7] *Ibid.*

Thus, NTP (2020) found that PFOA causes increased incidences of combined malignant and benign tumors at two sites (liver and pancreas) and increased the incidences of rare malignant tumors (hepatocellular carcinoma and pancreatic acinar cell adenocarcinoma) in male rats.

The evidence cited by NTP[8] in support of these conclusions was reviewed by OEHHA with regard to the sufficiency of evidence criteria in Section 25306(e)(2). Based on NTP's conclusions and the data relied on by NTP in reaching those conclusions, OEHHA has determined that PFOA meets the sufficiency of evidence criteria in Section 25306.

Public Process – Comments and Responses

The March 19, 2021 notice initiated a 45-day public comment period (extended from 30 days by an additional 15 days due to the COVID-19 emergency) that closed on May 3, 2021. Five sets of comments were submitted by the following organizations:

- 3M Company (3M)
- American Chemistry Council (ACC)
- Breast Cancer Prevention Partners (BCPP)
- Environmental Working Group, Center for Environmental Health, Natural Resources Defense Council, Clean Water Action, CALPIRG, and Environment California (EWG et al.)
- Queensland Department of Environment and Science (Queensland)
    - These comments also contained three publications/reports as attachments (Butt et al. 2014[9]; ECHA 2015[10]; UNEP/POPS/COP 2018[11])

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

Comments relevant to the NOIL are summarized, grouped, and numbered by topic. Responses follow below.

[8] NTP (2020), full citation provided in footnote 2.
[9] Butt CM, Muir DC, Mabury SA (2014). Biotransformation pathways of fluorotelomer-based polyfluoroalkyl substances: a review. Environ Toxicol Chem 33(2):243-67.
[10] European Chemicals Agency (ECHA 2015). Committee for Risk Assessment (RAC) Committee for Socio-economic analysis (SEAC) background document to the Opinion on the Annex XV dossier proposing restrictions on Perfluorooctanoic acid (PFOS), PFOA salts and PFOA-related substances. ECHA/RAC/RES-O-0000006229-70-02/F.
[11] UNEP/POPS/COP.9/14 (2018). Recommendation by the Persistent Organic Pollutants Review Committee to list perfluorooctanoic acid (PFOA), its salts and PFOA-related compounds in Annex A to the Convention and draft text of the proposed amendment. Stockholm Convention on Persistent Organic Pollutants.

Comments that criteria for listing PFOA have been met

Comment 1: EWG et al. and BCPP support the listing of PFOA under Proposition 65. They note that the proposed listing meets the requirements of the Proposition 65 regulations. An authoritative body, NTP, has formally identified PFOA as a carcinogen in the NTP technical report. NTP found that there was sufficient evidence in animals to make this determination, thus satisfying the regulation's scientific sufficiency criteria. The scientific basis of the determination by NTP has been confirmed by BCPP.

"Our organizations strongly support OEHHA's determination to list PFOA as known to the state to cause cancer. There is an expansive body of scientific literature reaching back more than three decades[1] that links increased PFOA exposure to increased rates of cancer. These findings are drawn from studies in animals and workers, and of exposed communities." (EWG et al., p. 1)

"We write in support of OEHHA's Intent to list PFOA as a carcinogen under the Safe Drinking Water and Toxic Enforcement Act of 1986 (Proposition 65)." (BCPP, p. 1)

"NTP's formal identification of PFOA as a carcinogen is consistent with multiple previous research studies which have linked PFOA to carcinogenicity in human breast cancer cells." (BCPP, p. 2)

Response 1: OEHHA agrees with EWG et al.'s and BCPP's comments that an authoritative body, NTP, has formally identified PFOA as a carcinogen in the NTP Technical Report on PFOA[12] and that the basis for NTP's findings of sufficient evidence of carcinogenicity from studies in experimental animals meets the sufficiency of evidence criteria in Section 25306.

Comments that formal identification criteria are not met

Comment 2: "[T]he record does not establish that an authoritative body has formally identified PFOA as a known carcinogen". (3M, p. 1)

"[T]hough the NTP Report does note evidence of PFOA carcinogenic activity of PFOA in certain rats, the NTP Report *does not* specifically *conclude* that PFOA causes cancer, as suggested in the Notice. Instead, the NTP Report's "Conclusions" section finds that "there was clear evidence of carcinogenic activity of PFOA in male Hsd:Sprague Dawley® SD® rats" and "some evidence of carcinogenic activity of PFOA in female Hsd:Sprague Dawley® SD® rats."" (3M, p. 5) (emphasis in original)

Response 2: Chemicals are required to be listed via the authoritative bodies listing mechanism as known to cause cancer if they meet certain criteria specified in Section 25306. Under Section 25306, a chemical is known to the state to cause cancer if a body considered authoritative has "formally identified" the chemical as causing cancer and if

[12] NTP (2020), full citation provided in footnote 2.

certain scientific criteria are met. OEHHA has determined that an authoritative body, NTP, has formally identified PFOA as causing cancer in its Technical Report, *Toxicology and Carcinogenesis Studies of Perfluorooctanoic Acid (CASRN 335-67-1) Administered in Feed to Sprague Dawley (Hsd:Sprague Dawley® SD®) Rats* (NTP 2020).

NTP (2020) found that PFOA causes increased incidences of combined malignant and benign tumors at two sites (liver and pancreas) and increased the incidences of rare malignant tumors (hepatocellular carcinoma and pancreatic acinar cell adenocarcinoma) in male rats. These conclusions by NTP about the carcinogenic activity of PFOA in male rats, and the data in the report supporting the conclusions, are the basis for OEHHA's determination that PFOA meets the criteria for listing pursuant to the authoritative bodies mechanism set out in Section 25306. The regulatory criteria do not require NTP to use the words "causes cancer" in its conclusions. The phrase "*clear evidence of carcinogenic activity*" is widely accepted scientific parlance meaning, in this case, that NTP has concluded that there is a clear association between exposure to PFOA and the development of cancerous tumors in the laboratory rats.

With regard to the formal identification criteria, this report meets both the "identification" and "formality" requirements of Section 25306. The identification requirements are met because PFOA is the subject of a report[13] that is published by the authoritative body (i.e., NTP) and that concludes the chemical causes cancer. The formality requirements are met because NTP specifically identifies PFOA as causing cancer in a report (1) that is peer reviewed in a public meeting, (2) is subject to public review and comment, and (3) is formally published by NTP.

The conclusions of the NTP Technical Report on PFOA also satisfy the "sufficiency of evidence criteria set out in Section 25306 (see Topic 3 below for discussion of the sufficiency of evidence criteria).

Comment 3: "PFOA has not been added to the NTP Report on Carcinogens, and NTP has not proposed to do so." (3M, p. 5)

"OEHHA's Notice does not identify any other document in which the NTP has taken final action to formally identify PFOA as causing cancer. As such, the NTP has not "formally identified" PFOA as a carcinogen within the meaning of the governing regulation." (3M, p. 5)

Response 3: The NTP Technical Report Series development process is a separate and distinct activity from the NTP Report on Carcinogens. Both the NTP Technical Reports and the NTP Reports on Carcinogens are reports by an authoritative body, and either would satisfy the "formal identification" criteria of Section 25306(d). There is no

[13]NTP (2020), full citation provided in footnote 2.

requirement that chemicals identified as causing cancer in NTP Technical Reports be listed in the Report on Carcinogens. Issuance of the NTP Technical Report on PFOA is also a final action by the authoritative body. Thus, the NTP Technical Report on PFOA satisfies the "formal identification" criteria (see response to Comment 2.1 above) and the "sufficiency of evidence" criteria set out in Section 25306[14] (see Topic 3 below for discussion of the sufficiency of evidence criteria).

Comments on sufficiency of evidence criteria

Toxicity in the NTP study

Comment 4: "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 a 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." (ACC, p. 1-2)

Response 4: The fact that NTP selected lower doses of PFOA to administer to male rats in the carcinogenesis study, after observing toxicity in 16-week old males exposed post-weaning to 150 and 300 ppm in the diet does not raise concerns about the quality of the NTP male rat study. On the contrary, it increases confidence in the selection of the doses employed in the study. Exposure concentrations were initially selected by the NTP based on previous chronic and reproductive studies reported in the literature, as well as known sex differences in elimination rates of PFOA[15]. When toxicity was observed in 16-week old males in the 150 and 300 ppm dose groups, NTP decided to stop the initial male rat study and conduct a new study, using lower doses (i.e., 20, 40 and 80 ppm). NTP studies are conducted according to strict protocol specifications[16], and the evaluation of toxicity at 16 weeks of age and subsequent decision to make an adjustment to the selected doses does not invalidate study results. It is appropriate, and necessary, to adjust dosing in studies following observations of overt toxicity.

The toxicity observed in male rats exposed post-weaning to 150 and 300 ppm PFOA in the diet presented as statistically significantly decreased body weights in all treated groups and liver necrosis in the 0/150 (perinatal/postweaning exposures) and 300/300 ppm groups compared to controls. Two incidences of liver necrosis were also observed

[14] *Exxon Mobil Corp v OEHHA* (2009) 169 Cal.App.4th 1264; *Western Crop Protection Assn. v. Davis* (2000) 80 Cal.App.4th 741.
[15] NTP (2020), full citation provided in footnote 2.
[16] National Toxicology Program (NTP 2011). Specifications for the conduct of studies to evaluate the toxic and carcinogenic potential of chemical, biological and physical agents in laboratory animals for the National Toxicology Program (NTP). January 2011. https://ntp.niehs.nih.gov/ntp/test_info/finalntp_toxcarspecsjan2011.pdf

in the 0/300 and 150/150 ppm groups[17]. Necrosis is not an outcome specific to the NTP study of PFOA; it was also observed in one of the studies of PFOA (or salts of PFOA) referenced by the commenter. In that study, Butenhoff et al. (2012)[18] reported hepatocellular necrosis in the male rats necropsied at 1 year (6/15 in the 300 ppm group vs. 0/15 in the control group). This demonstrates that necrosis was not a rare event that occurred only in the NTP study.

Thus, NTP's decision to administer lower doses of PFOA to male rats in the carcinogenesis study, after observing toxicity at higher doses, was appropriate and does not reduce confidence in the study's results.

Mutagenicity of PFOA

Comment 5: "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." (ACC, p. 6)

Response 5: This comment focuses on mechanisms of action and is outside of the scope of the NOIL. However, OEHHA would like to clarify that mutagenicity is only one endpoint of genotoxicity.

Regarding genotoxicity, NTP states:

> "The genetic toxicity of PFOA has been evaluated in bacterial mutagenicity assays, in vitro tests using human and rodent cells, and one animal study. Whereas bacterial mutagenicity assays using several *Salmonella typhimurium* test strains were uniformly negative, conflicting results were obtained for PFOA using in vitro tests with mammalian cells. In the single in vivo study, PFOA was reported to induce oxidative damage to DNA obtained from rat liver cells."[19]

[17] NTP (2020), full citation provided in footnote 2.
[18] Butenhoff JL, Kennedy GL Jr, Chang SC, Olsen GW (2012). Chronic dietary toxicity and carcinogenicity study with ammonium perfluorooctanoate in Sprague-Dawley rats. Toxicology 298(1-3):1-13.
[19] NTP (2020), full citation provided in footnote 2.

OEHHA (2021)[20] reviewed genotoxicity studies of PFOA, and summarized the findings as follows:

> "There is some positive evidence of genotoxicity for PFOA…For PFOA, the evidence of mutagenicity is limited, but chromosomal effects and DNA damage have been observed both *in vivo* and *in vitro*."

Thus, "genotoxicity cannot be dismissed as a possible mode of action for PFOA"[21]. Evidence of genotoxicity, however, is not required in order for a chemical to be identified as causing cancer, either by the scientific community at large, or under Section 25306 for purposes of listing carcinogens under Proposition 65. Indeed, a number of carcinogens are known to act via non-genotoxic mechanisms in addition to or instead of genotoxicity.

Relevance to humans

Comment 6: ACC states that the findings of the NTP report "are consistent with peroxisome proliferator-activated receptor α (PPARα) activation which is of uncertain relevance to humans. Consequently, there is not sufficient evidence to conclude that PFOA exposure presents a cancer risk to humans to justify its listing under Proposition 65".

"In addition to the NTP study, two chronic bioassays have been conducted in rats exposed to PFOA through diet. Although the results are not consistent, one or both studies have reported liver, LC *[Leydig cell]*, and PAC *[pancreatic acinar cell]* tumors.[19]" (ACC, p. 5)

"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 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 species (e.g., hamsters, guinea pigs and Cynomolgous monkeys) that are more appropriate animal model surrogates than mice and rats." (ACC, p. 6)

"Several key studies provide support for the key events in the proposed PPARα-activated mode of action (MOA) for rat liver tumors (Table 1). These data are summarized by Klaunig et al. (2012)" (ACC, p. 6)

[20] Office of Environmental Health Hazard Assessment (OEHHA 2021). Proposed Public Health Goals for Perfluorooctanoic Acid and Perfluorooctane Sulfonic Acid in Drinking Water. See p.228. https://oehha.ca.gov/media/downloads/crnr/pfoapfosphgdraft061021.pdf

[21] OEHHA (2021), full citation provided in footnote 21. See p. 228.

"Although there are indications that PFOA may also act through PPARα-independent mechanisms[24] 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.[25] 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 [of] key liver endpoint studies in animals." (ACC, p. 7)

Response 6:

OEHHA disagrees with the commenter's claim that based on data related to PPARα activation, there is not sufficient evidence to justify the listing of PFOA under Proposition 65.

The commenter is suggesting that rat liver tumors induced by PFOA are not relevant to humans because PFOA induces these tumors predominantly through a mechanism that is dependent on activation of PPARα. However, hepatotoxicity can be induced through other mechanisms. As discussed in OEHHA (2021):

> "In summary, these lines of evidence suggest that PFOA-induced hepatotoxicity, including carcinogenesis, in rodents is not solely the result of PPARα activation. Liver toxicity was observed in PPARα KO *[knock out]* mice, and in studies where PPARα was not activated (Filgo et al., 2015; Rebholz et al., 2016; Das et al., 2017; Li et al., 2017b; Wen et al., 2019c). Furthermore, rodent carcinogenicity studies with other PPARα activators have demonstrated that PPARα activation is not required for liver tumor induction, and that constitutive activation of PPARα does not lead to tumorigenesis. Therefore, OEHHA considers rodent liver toxicity studies, including carcinogenicity studies, to be relevant to human health." [22]
>
> "PFOA is a known activator of PPARα and there has been considerable discussion in the scientific literature that carcinogenesis in rodents mediated by activation of PPARα is not relevant to humans, as PPARα activation in humans is not known to induce tumors. However, there is evidence in PPARα knockout animals that PFOA induces PPARα-independent toxicity, including carcinogenesis. Additionally, toxicity is observed at doses that do not activate PPARα. This indicates that PFOA acts via multiple mechanisms." [23]

[22] OEHHA (2021), full citation provided in footnote 21. See p.155.
[23] *Ibid.* See p.228.

This issue is also discussed in IARC (2017):

> "The liver is the most prominent target tissue of PFOA, with rats and mice being the most responsive species to liver-specific effects. Limited data are available indicating liver toxicity in non-human primates (Butenhoff et al., 2002). Additionally, serum levels of PFOA have been positively associated with serum markers of liver injury in humans (Sakr et al., 2007; Lin et al., 2010; Gallo et al., 2012). Liver toxicity observed in rodents has been associated with both PPARα-dependent and -independent mechanisms. The analysis by the Working Group of data from humans in vitro is consistent with multiple molecular pathways being in operation. Cytotoxicity, cell proliferation, and liver hypertrophy have also been observed in studies with PFOA in rodents, indicating that other mechanisms may also contribute."[24]

> "Several studies in humans have examined the relationship between exposure to PFOA and toxicity, and suggest that PFOA may cause liver injury. In experimental animals, the liver is a well-established target for toxicity. Potential mechanisms for PFOA-induced toxicity and carcinogenicity in the liver include PPARα activation, involvement of other molecular pathways (i.e. constitutive androstane receptor, pregnane X receptor, estrogen receptor), and cytotoxicity. There is moderate evidence for these mechanisms, largely from studies in rats and mice. Based on the available evidence, human relevance of the liver findings in rodents cannot be excluded."[25]

Based on a careful consideration of the data as well as the findings summarized in OEHHA (2021) and IARC (2017), the relevance of the liver effects in rodents to humans should not be dismissed.

Regarding the comment that "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", the commenter has not provided any evidence to support this statement. In contrast, studies indicate that PFOA can, in fact, induce tumors in humans; for example, there is compelling evidence from epidemiology studies that PFOA increases the risk of kidney tumors in humans, as discussed in OEHHA (2021)[26].

Comment 7: "The relevance of the liver tumor data from the NTP study is further called into question based on recent clinical data reported by Convertino et al. (2018).[16] In a study of a sensitive subpopulation of cancer patients with normal liver function exposed

[24] International Agency for Research on Cancer (IARC 2017). Some Chemicals Used as Solvents and in Polymer Manufacture. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans Volume 110. Available at: https://publications.iarc.fr/547. See p.95.
[25] *Ibid.* See p.97.
[26] OEHHA (2021). Full citation provided in footnote 21.

to weekly PFOA doses as high as 1,200 mgs (about 16 mg/kg per day), Convertino et al. reported no differences in clinical hepatic measures.[17] Similarly a study of PFOA production workers reported no abnormal liver function, hypolipidemia, or cholestasis.[18]"[Olsen et al. 2000] (ACC, p. 5)

Response 7: The study conducted by Convertino et al. (2018)[27] is not an epidemiological study designed to assess the long-term effects of PFOA. This phase I clinical trial treated 49 cancer patients with weekly oral doses of 50-1200 mg PFOA for 6 weeks and measured cholesterol, thyroid hormones, liver enzymes, and other clinical chemistry parameters. The recruited subjects had advanced solid tumors that were refractory to standard anticancer therapy or for which no standard therapy existed. Late-stage cancer or prior cancer treatment can affect liver function, which could diminish the ability of the study to detect the effects of PFOA. Further, the study design was limited by the small sample size and length of the study.

The second study mentioned by the commenter, Olsen et al. (2000)[28], was a cross-sectional study that reported medical surveillance data from male workers involved in ammonium perfluorooctanoate production in 1993, 1995, and 1997. The authors reported no associations between serum PFOA concentrations and several measures of liver function.

However, there are multiple other human epidemiological studies in the literature that show contrasting results. US EPA evaluated the findings across many studies and concluded,

> "Overall, an association of serum PFOA concentration with elevations in serum levels of ALT [alanine transaminase] and GGT [gamma glutamyltransferase] has been consistently observed in occupational, highly exposed residential communities, and the U.S. general population. The associations are not large in magnitude, but indicate the potential to affect liver function".[29]

OEHHA (2021) evaluated the literature published after the US EPA review and came to similar conclusions:

> "Overall, the recent epidemiologic evidence OEHHA identified supports the conclusions reached by US EPA: the majority of studies available to date support an association between PFOA and increases in liver enzymes in adults…

[27] Convertino M, Church TR, Olsen GW, Liu Y, Doyle E, Elcombe CR, Barnett AL, Samuel LM, MacPherson IR, Evans TRJ (2018). Stochastic Pharmacokinetic-Pharmacodynamic Modeling for Assessing the Systemic Health Risk of Perfluorooctanoate (PFOA). Toxicol Sci 163(1):293-306.
[28] Olsen GW, Burris JM, Burlew MM, Mandel JH (2000). Plasma cholecystokinin and hepatic enzymes, cholesterol and lipoproteins in ammonium perfluorooctanoate production workers. Drug Chem Toxicol 23(4):603-20.
[29] US EPA (2016). Health Effects Support Document for Perfluorooctanoic Acid (PFOA). *EPA Document Number: 822-R-16-003*.

> Associations between PFOA and increased liver enzymes were reported in a number of different study populations, across several different exposure scenarios (occupational, high environmental, and general population exposures), in studies using both cross-sectional and prospective designs, and in studies that adjusted for the common causes of liver disease such as alcohol use, BMI, and medication use… In summary, the current epidemiologic literature provides consistent evidence that PFOA can cause hepatotoxicity in humans, and in particular, increases in liver enzyme levels."[30]

Thus, findings from the two studies referred to by the commenter do not provide substantial evidence that PFOA cannot affect liver function in humans, nor do they show that animal liver tumor data are not relevant to humans.

Comment 8: "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.*).[28] 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.[29] 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." (ACC, p. 8)

"Expression of CCK receptors in humans is much lower as 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.[30] 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." (ACC, p. 8)

Response 8: As discussed in the previous response, PFOA likely induces tumors through multiple mechanisms. There are data from studies of PFOA supporting several of the key characteristics of carcinogens, including the ability to induce oxidative stress, inflammation, and modulate receptor-mediated effects. Plus, there is little support for

[30] OEHHA (2021). Full citation provided in footnote 21.

the PPARα mode of action for pancreatic acinar cell tumors. OEHHA (2021) summarizes the data regarding a PPARα mode of action for pancreatic tumors:

> "However, there is little experimental support for the PPARα MOA for these tumor types (Peraza et al., 2006). Biegel et al. (2001) reported that 300 ppm (13.6 mg/kg-day) PFOA in the diet for two years induced pancreatic acinar proliferation in male Sprague Dawley rats, but the PPARα model agonist Wy-14,643 did not, suggesting that PPARα is not involved in pancreatic tumor formation, and that a different MOA is responsible for tumor induction. Additionally, NTP (2020) reported a large increase in pancreatic acinar cell tumors in male rats, a modest increase in liver tumors, and no significant increase in Leydig cell tumors. If the proposed PPARα MOA is dominant, then one would expect liver tumors to be the most prevalent tumor type."[31]

Additionally, there are insufficient data available to support the involvement of CCK or CCK receptors in this proposed PPARα-dependent mechanism for the induction of pancreatic tumors by PFOA. One study found that PFOA was not an agonist for the CCK_A receptor that activates CCK release in mouse pancreatic cells *in vitro*[32]. No studies were identified that measured CCK levels in rodents treated with PFOA.

Other evidence

Comment 9: "California courts interpreting Proposition 65 have repeatedly stressed that '[o]nly those chemicals that are *known*, and not merely suspected, of causing cancer or reproductive toxicity must be [placed] on the [Proposition 65] list.' *W.n Crop Prot. Ass'n v. Davis*, 80 Cal. App. 4th 741, 749 (2000) quoting *AFL-CIO v. Deukmejian*, 212 Cal. App. 3d 425, 436-37 (1989) (emphasis added) (alterations in *W. Crop Prot. Ass'n*). In this regard, the record as a whole, including all scientifically valid data, must be considered in determining whether to add a chemical to the Proposition 65 list as a known carcinogen. *See, e.g.*, 27 CCR § 25306(f). Here, there is significant evidence that was not before nor considered by the NTP, thereby precluding reliance on the NTP Report in these streamlined proceedings. *Id.*" (3M, p. 6)

Response 9: California courts have found that OEHHA may consider the entire record before the authoritative body as a whole to determine whether the listing criteria in the regulation have been met. See *Exxon Mobil Corporation v OEHHA* (2009) 169 Cal. App. 4th 1264.

[31] OEHHA (2021). Full citation provided in footnote 22. See pp. 155-156.
[32] Obourn JD, Frame SR, Bell RH Jr, Longnecker DS, Elliott GS, Cook JC (1997). Mechanisms for the pancreatic oncogenic effects of the peroxisome proliferator Wyeth-14,643. Toxicol Appl Pharmacol 145(2):425-36.

OEHHA cannot substitute its scientific opinion for that of NTP. Instead, OEHHA must determine whether a chemical has been formally identified by an authoritative body as causing cancer for purposes of Proposition 65[33,34,35].

The Final Statement of Reasons (FSOR) for Section 25306 states that, because an entity has been designated as an authoritative body, "…there is a presumption that the authoritative body properly applied the criteria [in the regulation]."[36] When determining whether the criteria in Section 25306(e) have been satisfied, OEHHA may make its determination based on the document issued by the authoritative body; or as noted by the commenter, OEHHA may make its determination on the entire scientific record on which the authoritative body relied, including the scientific literature relied on by the authoritative body and OEHHA's knowledge of the authoritative body's methodology[37].

As discussed in the NOIL and in this Response to Comments, OEHHA determined that the NTP Technical Report satisfies the formal identification and sufficiency of evidence criteria in Section 25306 and therefore must be listed. Additionally, Section 25306(f) is inapplicable, as there are no scientifically valid data not considered by NTP which clearly establish that PFOA does not cause cancer[38].

Comment 10: "Steenland and Winquist (2020)[8] recently published a scoping review of the epidemiologic evidence of per- and polyfluoroalkyl substances ('PFAS') (which includes PFOA) and cancer. They identified 16 cohort or case-cohort studies, 10 case-control studies (four nested within cohorts), one cross-sectional, and one ecologic study. Each study was critiqued for its strengths and weaknesses. The authors concluded the evidence for an association between PFAS and cancer remains 'sparse.'" (3M, p. 6)

"A review of the epidemiological evidence for cancer from 18 studies of occupational and general population exposure to PFOA reported a lack of concordance between community exposures and occupational exposures one or two magnitudes higher than those for the general population.[14] The authors evaluated the studies based on the study design, subjects, exposure assessment, outcome assessment, control for confounding, and sources of bias using Bradford Hill guidelines and concluded that the discrepant findings across the study populations were likely due to chance, confounding, and/or bias. A more recent review of the evidence by epidemiologists

[33] OEHHA has been designated by Executive Order of the Governor as the Lead Agency pursuant to Health and Safety Code section 25249.12 and Title 27, Cal. Code of Regs., section 25102(o). Health and Safety Code section 25249.8(b)
[34] Section 25306(c).
[35] Final Statement of Reasons for Section 25306 (formerly 12306), page 16 and *Exxon Mobil Corporation v OEHHA* (2009) 169 Cal.App. 4th 1264, at page 1283.
[36] *Ibid*.
[37] *Exxon Mobil Corporation v OEHHA* (2009) 169 Cal.App. 4th 1264, at pages 1280-1281.
[38] Section 25306(f).

involved in the C8 study concluded that the evidence for an association between PFOA exposure and kidney and testicular cancer was suggestive overall, there was little evidence for an association with liver or pancreatic cancer." (ACC, p. 4-5)

"Occupational studies examining cancer mortality have been conducted among workers occupationally exposed to PFOA in Minnesota and West Virginia focusing on kidney, bladder, liver, pancreatic, testicular, prostate, thyroid, and breast cancers. Two studies of communities exposed to PFOA in drinking water also are available. The results from these studies are conflicting and interpretation is limited by the small number of observed deaths and incident cases." (ACC, p. 2)

Response 10: A finding of 'sufficient evidence in humans' is not a requirement for listing a chemical as causing cancer under the Proposition 65 authoritative bodies listing mechanism and the cited studies are not part of the basis for OEHHA's determination that PFOA meets the criteria for listing pursuant to Section 25306.

Section 25306(e) reads as follows:

> "(e) For purposes of this section, "as causing cancer" means that *either* of the following criteria has been satisfied:
>
> "(1) Sufficient evidence of carcinogenicity exists from studies in humans. For purposes of this paragraph, "sufficient evidence" means studies in humans indicate that there is a causal relationship between the chemical and cancer.
>
> "(2) Sufficient evidence of carcinogenicity exists from studies in experimental animals. For purposes of this paragraph, 'sufficient evidence' means studies in experimental animals indicate that there is an increased incidence of malignant tumors or combined malignant and benign tumors in multiple species or strains, in multiple experiments (e.g., with different routes of administration or using different dose levels), or, to an unusual degree, in a single experiment with regard to high incidence, site or type of tumor, or age at onset." (emphasis added)

Thus, in order to meet the sufficiency of evidence criteria of Section 25306(e), a chemical must satisfy the requirements of either 25306(e)(1) or 25306(e)(2), not both. As indicated in OEHHA's Notice of Intent to List, it is NTP's discussion of data and conclusions from studies in experimental animals that meets the sufficiency of evidence criteria in Section 25306(e)(2).

Regarding the study by Steenland and Wingquist (2021), the conclusion cited by the commenter that "the evidence for an association between PFAS and cancer remains 'sparse'" is referring to the group of PFAS chemicals overall, and not to PFOA specifically. In the summary of evidence section of the paper, the authors state the following regarding testicular cancer:

> "While there are no associations between PFAS and cancer that have been both marked and consistent across studies, there is some evidence for an association of PFOA with testicular cancer. Two studies of this association (one cohort (Barry et al., 2013) and one case-control (Vieira et al., 2013)) coincided in finding a strong positive exposure-response for this cancer, which was also found to be associated with PFOA exposure in rodent studies."

The authors make similar conclusions for kidney cancer:

> "The evidence for kidney cancer, implicated by Barry et al. (2013), Vieira et al. (2013), and Steenland and Woskie, 2012, also is suggestive. The recent large case-control study by Shearer et al. (2020) found a strong exposure-response trend with PFOA, but not other PFAS. Mastrantonio et al. (2018) also found higher kidney cancer mortality rates in PFAS-exposed areas. Combined, these studies strengthen the case for a kidney cancer association with PFOA, although not with other PFAS."

OEHHA (2021) also found the association with kidney cancer to be compelling, concluding that "The association of PFOA and kidney cancer in humans provides strong evidence of carcinogenicity."

Regarding the article by Chang et al. (2014), this review is lacking the most current data, as several additional epidemiological studies were published after this review was completed.

In summary, the reviews and other studies referred to by the commenters do not provide evidence that PFOA is not carcinogenic in humans. Moreover, as explained in the previous comment, OEHHA cannot substitute its scientific opinion for that of NTP.

<u>Comment on human exposure</u>

Comment 11: "OEHHA should not list PFOA as a carcinogen because there is no evidence of Proposition-65 regulable discharges or exposures in California. PFOA has been effectively phased out of the U.S. as is demonstrated by declining, residual PFOA serum levels in California and nationwide." (3M, p. 10)

"In May 2000, 3M announced that it was voluntarily phasing out the production of PFOA. This goal was largely reached by 2002, and fully achieved by 2008." (3M, p. 10)

"California citizens' exposure to PFOA from Proposition 65-regulatable discharges and exposures is essentially non-existent." (3M, p. 11)

"According to the National Health and Nutrition Examination Survey (United States Centers for Disease Control (CDC) National Center for Environmental Health) ("NHANES"), which is a nationally representative sample of the U.S. population (non-institutionalized), the concentration of PFOA in the serum (blood) of the general

population has declined significantly since the phase-out of production activities as reported for the geometric mean and the 95th percentile". (3M, p. 11)

"As a result of the EPA PFOA product stewardship program, it is anticipated that PFOA serum concentrations will continue to decline. Due to this anticipated continued decline, and because there is no showing of any present or foreseeable water discharge of PFOA, further review of PFOA is not necessary to accomplish the goals of Proposition 65." (3M, p. 12)

Response 11: The likelihood of discharge or the level of anticipated exposure to a chemical are not factors used in determining whether a chemical meets the criteria for listing under the Proposition 65 authoritative bodies listing process[39]. Listing of a chemical as causing cancer under Proposition 65 via the authoritative bodies mechanism concerns only a determination that the chemical has been formally identified as causing cancer, as provided in Section 25306.

Additionally, the population of California is in fact still exposed to PFOA. Although the levels of PFOA detected in human blood samples are declining, there continues to be exposure from products that were made before PFOA was phased out in the US, and from imported products and other sources. Recent data from Biomonitoring California analyses of samples collected from adults in 2018 and 2019 report average serum levels of 1.04 and 0.977 ng/mL, respectively. PFOA was detected in 99.3% (n=425) and 98.6% (n=358) of the individuals studied in 2018 and 2019, respectively[40].

Other comments

Use of new approach methodologies

Comment 12: "Although two-year animal studies are the standard, we would also like to point to the importance of New Approach Methodologies (NAMs) as tools for the future in determining carcinogenicity and regulatory decision-making. There is a great need to develop new tools to rapidly fill data gaps and increase the capacity to efficiently test and identify potential threats to human health. For example, ToxCast program high-throughput screening data provides evidence of carcinogenic mechanisms." (EWG et al., p. 2-3)

Response 12: OEHHA agrees on the importance of new approach methodologies for chemical risk assessment. For listings under the authoritative bodies mechanism, OEHHA relies on the record before the authoritative body and considers the scientific evidence that serves as the basis for the authoritative body's conclusions in light of the criteria in Section 25306.

[39] Section 25306.

[40] https://biomonitoring.ca.gov/results/chemical/all?field_chemical_name_target_id_selective%5B%5D=165 (accessed on January 26, 2022)

Safe harbor levels

Comment 13: "We also urge OEHHA to establish the most protective safe harbor levels consistent with Proposition 65." (EWG et al., p. 3)

Response 13: OEHHA acknowledges the commenter's request for a safe harbor level for PFOA. The Office's general practice is to propose a No Significant Risk Level, when sufficient data and resources are available, for chemicals listed under Proposition 65 within the 12-month grace period before the warning requirement takes effect. This assists businesses in determining whether they must provide a warning for exposures to the chemical their products or activities may cause. Where such a level has not been adopted by OEHHA, the implementing regulations provide guidance for businesses or others to calculate their own no significant risk level.

PFASs should be managed as a class

Comment 14: "Although listing PFOA as a chemical known to cause cancer is a crucial step forward for protecting public health, our organizations urge OEHHA to prioritize review of PFAS beyond the long-chain PFAS compounds to include those still in widespread active use, and most comprehensively, the entire class of chemicals." (EWG et al., p. 2)

"Only listing PFOA as a single substance is not adequate to address the risk. PFOA has been out of production for some time. However, there are dozens of C8 substitute fluorotelomer PFAS in common use that are PFOA precursors that transform to PFOA upon release. This has long been established. All PFOA related compounds must be regarded as of the same risk and concern as PFOA as is now internationally recognised (see UNEP CoP9 recommendation). This includes complex fluorotelomer PFAS such as 8:2, 10:2, 12:2 and 14:2 fluorotelomers commonly used in firefighting foam and materials treatments. These compounds all have long-chain fluorinated carbon backbones as does PFOA with a diversity of functional groups that degrade in the environment to generate end-point carboxylate compounds including PFOA. At a minimum all fluorotelomers with a perfluorinated chain of C8 (8:2Ft etc.) that generate PFOA should be regarded the same as PFOA. Longer chain fluorotelomers can also generate PFOA through progressive transformation." (Queensland)

Response 14: The listing mechanism through which PFOA is being added to the Proposition 65 list requires that a chemical has been "formally identified" by an authoritative body and that it meets the sufficiency of evidence criteria. In this Notice of Intent to List, only the chemical PFOA has been formally identified by NTP. This does not preclude additional PFAS chemicals or groups of chemicals from being listed through the authoritative bodies mechanisms or other mechanisms in the future, in the event they meet the necessary criteria.