BEFORE THE ILLINOIS POLLUTION CONTROL BOARD

IN THE MATTER OF:	**)**	
	)	
PROPOSED AMENDMENTS TO	**)**	**R22-18**
GROUNDWATER QUALITY	**)**	**(Rulemaking – Public Water**
35 ILL. ADM. CODE 620	**)**	**Supply)**
	)	

NOTICE OF FILING

PLEASE TAKE NOTICE that on March 18, 2022, we electronically filed with the Clerk ofthe Pollution Control Board of the State of Illinois, PFAS REGULATORY COALITION'S PRE-FILED FOLLOWUP QUESTIONS TO ILLINOIS EPA, copies of which are attached hereto and served upon you.

Dated: March 18, 2022

Respectfully submitted,

PFAS REGULATORY COALITION

By: */s/ Fredric P. Andes*
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CERTIFICATE OF SERVICE

I, Fredric Andes, hereby certify that I have filed the attached NOTICE OF FILING and PFAS REGULATORY COALITION'S PRE-FILED FOLLOWUP QUESTIONS TO ILLINOIS EPA upon the below service list by electronic mail on March 18, 2022.

Dated: March 18, 2022 */s/ Fredric Andes*

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PROPOSED AMENDMENTS TO	**)**	**R22-18**
GROUNDWATER QUALITY	**)**	**(Rulemaking – Public Water**
35 ILL. ADM. CODE 620	**)**	**Supply)**
	)	

PFAS REGULATORY COALITION'S
PRE-FILED FOLLOWUP QUESTIONS TO ILLINOIS EPA

The PFAS Regulatory Coalition, by and through its attorneys, Barnes & Thornburg, LLP, and pursuant to the Illinois Pollution Control Board's ("Board") Hearing Officer Order dated March 11, 2022, submits the following Pre-Filed Followup Questions to Illinois Environmental Protection Agency ("Agency" or "Illinois EPA") witnesses. The Coalition has no objection to the answers being presented by the most appropriate Illinois EPA witness for each question.

1. Attached as Exhibit A is the set of comments submitted to IEPA by the PFAS Regulatory Coalition (also referred to here as the "Coalition") as to the first version of the proposed standards, which was released in December 2019. Please state how IEPA considered each specific comment, including whether the Coalition's comment was accepted or rejected and the basis for that action.

2. Attached as Exhibit B is the set of comments submitted to IEPA by the PFAS Regulatory Coalition as to the second version of the proposed standards, which was released in May 2021. Please state how IEPA considered each specific comment, including whether the Coalition's comment was accepted or rejected and the basis for that action.

3. The State of Wisconsin has adopted groundwater standards for PFAS substances that are less stringent than the IEPA's proposal. Please explain how the scientific basis for those standards, including assessment of PFAS risks, differs from the scientific basis for the IEPA's proposal, and please explain why IEPA is choosing a different outcome than the State of Wisconsin.

4. The State of Michigan has adopted groundwater standards for PFAS substances that are less stringent than the IEPA's proposal. Please explain how the scientific basis for those standards, including assessment of PFAS risks, differs from the scientific basis for the IEPA's proposal, and please explain why IEPA is choosing a different outcome than the State of Michigan.

5. The State of New Jersey has adopted groundwater standards for PFAS substances that are less stringent than the IEPA's proposal. Please explain how the scientific basis for those standards, including assessment of PFAS risks, differs from the scientific basis for the IEPA's proposal, and please explain why IEPA is choosing a different outcome than the State of New Jersey.

6. Attached as Exhibit C is a report by the Environmental Council of the States ("ECOS"), entitled "Processes & Considerations for Setting State PFAS Standards." The appendices to the report list PFAS standards and criteria issued or proposed by State agencies, and for each of those levels, provides information as to the data, studies, and input values that were used to derive those levels. Many of those State-derived levels for PFAS substances are significantly more stringent than the levels in the IEPA proposal. For each of those levels derived by other States, please explain how the scientific basis for those levels, including assessment of PFAS risks, differs from the scientific basis for the IEPA's proposal, and please explain why IEPA is choosing a different outcome than those other States.

7. Attached as Exhibit D is a set of comments submitted by the PFAS Regulatory Coalition to EPA's Science Advisory Board ("SAB") concerning EPA draft risk assessments for PFAS substances. As to those aspects of the comments that relate to studies or methods that were used in deriving the levels specified in IEPA's proposal, please provide IEPA's response to those comments.

8. Attached as Exhibit E is a set of comments submitted by the American Chemistry Council to EPA's Science Advisory Board ("SAB") concerning EPA draft risk assessments for PFAS substances. As to those aspects of the comments that relate to studies or methods that were used in deriving the levels specified in IEPA's proposal, please provide IEPA's response to those comments.

9. Attached as Exhibits F, G and H are sets of comments submitted by 3M Corporation to EPA's Science Advisory Board ("SAB") concerning EPA draft risk assessments for PFAS substances. As to those aspects of the comments that relate to studies or methods that were used in deriving the levels specified in IEPA's proposal, please provide IEPA's response to those comments.

10. Attached as Exhibit I is a set of comments submitted by the National Council for Air and Stream Improvement, Inc. to EPA's Science Advisory Board ("SAB") concerning EPA draft risk assessments for PFAS substances. As to those aspects of the comments that relate to studies or methods that were used in deriving the levels specified in IEPA's proposal, please provide IEPA's response to those comments.

11. Attached as Exhibit J is a set of comments submitted by Toxicology Excellence for Risk Assessment to EPA's Science Advisory Board ("SAB") concerning EPA draft risk assessments for PFAS substances. As to those aspects of the comments that relate to studies or methods that were used in deriving the levels specified in IEPA's proposal, please provide IEPA's response to those comments.

12. IEPA has stated that the only USEPA-approved method for measuring PFAS in groundwater is SW-846 Method 8327. However, IEPA's proposal requires measurement of PFAS levels in all types of groundwater (including groundwater that is not used for drinking water supply, or which must be treated before drinking water use) with a different method, Method 537.1, which is approved only for use in measuring PFAS levels in drinking water. Please confirm that IEPA is requiring use of a method to measure compliance with all groundwater quality standards for PFAS substances that is not approved for measuring PFAS levels in groundwater.

Dated: March 18, 2022

Respectfully submitted,

PFAS REGULATORY COALITION

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EXHIBIT A

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February 28, 2020

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Re: Comments of the PFAS Regulatory Coalition on Proposed Rulemaking on Section 620.410 Groundwater Quality Standards for Class I Potable Resource Groundwater

Dear Sir or Madam:

The PFAS Regulatory Coalition (Coalition) appreciates the opportunity to file comments regarding the proposed rulemaking on Section 620.410 Groundwater Quality Standards for Class I Potable Resource Groundwater.

I. The Coalition's Interest

The Coalition is a group of industrial companies, municipal entities, agricultural parties, and trade associations that are directly affected by the State's development of policies and regulation related to per- and polyfluoroalkyl substances (PFAS). Coalition membership includes entities in the automobile, coke and coal, iron and steel, municipal, paper, petroleum, and other sectors. None of the Coalition members manufacture PFAS compounds. Coalition members, for purposes of these comments, include: American Coke and Coal Chemicals Institute; American Forest and Paper Association; American Iron and Steel Institute; Barr Engineering; Brown & Caldwell; Gary Sanitary District (IN); Illinois Association of Wastewater Agencies; Lowell, MA; Pueblo, CO; Tempe, AZ; Toyota; Trihydro, and Yucaipa Valley Water District (CA).

Coalition members support the State's efforts to identify potential sources of those individual PFAS that pose risks to human health and the environment, and to prioritize the protection of drinking water sources for vulnerable populations. In the State's pursuit of such regulations, the Coalition urges State regulators to ensure that final standards are scientifically supported, cost-effective, and achievable.

II. Proposed Rulemaking

On December 24, 2019, the Illinois Environmental Protection Agency (IEPA or State) sent letters to a limited number of "stakeholders," proposing changes to the State's groundwater quality standards to protect potential sources of drinking water and proposing to add new contaminants (with related standards), including certain perfluoroalkyl substances (PFAS) compounds. In proposing new standards, the State relied heavily on the "Minimum Risk Levels" drafted by the United States Agency for Toxic Substances and Disease Registry (ATSDR) and the U.S. Environmental Protection Agency's (USEPA) Provisional Peer Reviewed Toxicity Values. The proposed rulemaking designates five PFAS compounds with corresponding groundwater standards, as follows:

- Perfluorobutane Sulfonic Acid (PFBS): 0.14 mg/L
- Perfluorohexane Sulfonic Acid (PFHxS): 0.00014 mg/L
- Perfluorononanoic Acid (PFNA): 0.000021 mg/L
- Perfluorooctanoic Acid (PFOA): 0.000021 mg/L
- Perfluorooctane Sulfonic Acid (PFOS): 0.000014 mg/L

The proposed rulemaking also contains a combined PFOA and PFOS groundwater standard of 0.000021 mg/L. Additionally, Section 620.310 requires preventive response activities, including preventive notification mandates.

The PFAS Regulatory Coalition has general concerns with the State's decision to notice only a limited number of affected stakeholders, as well as the derived standards it is proposing for the various PFAS compounds. Because of the limited outreach insofar as the proposal, the Coalition did not even learn about the proposed standards until almost half way into the short comment period. The Coalition appreciates the comment period was extended but is still concerned that notice of such significant regulatory changes should have been more widely distributed.

Regarding the proposal itself, the proposed standards raise significant questions about their scientific basis and justification. The Coalition does not believe that groundwater monitoring and cleanup standards should be based on the ATSDR oral reference doses, which are derived for purposes other than environmental regulation, such as those being considered and developed by USEPA.

As discussed below, the Coalition requests that the State reconsider its new proposed standards and work more closely with all stakeholders to develop appropriate standards that provide necessary protection of the State's groundwater resources without unreasonably burdening the regulated community with unnecessarily stringent standards.

III. Coalition Analysis and Recommendations

In the comments below, the Coalition recognizes and summarizes some of the challenges that the State faces in attempting to promulgate enforceable regulations, as well as some of the challenges that Coalition members face if states promulgate standards that vary from any existing or future federal standards. The Coalition appreciates the State's desire to act to protect its citizens from potential risks associated with exposure to certain PFAS compounds, but urges Illinois and other states to work with the federal government to develop a cohesive national strategy to help ensure national uniformity. The prospect of a patchwork set of state-specific standards that vary widely is likely to cause significantly more confusion and overwhelming challenges for Coalition members that operate in multiple states or nationwide.

A. The Scientific Community Does Not Agree on Human Health Toxicity Values for PFAS

The term "PFAS" refers to a group of man-made chemicals that include perfluorooctanoic acid (PFOA), perfluorooctane sulfonic acid (PFOS), GenX,[1] and other fluorinated compounds. The most prevalent and available science regarding the incidence and potential health effects of PFAS is based on PFOA and PFOS, two compounds that are no longer manufactured in the United States due to voluntary phase outs. For replacement chemicals, industry has begun using shorter-chain PFAS that have different physical, chemical, and toxicological properties from the long-chain PFOA and PFOS. The scientific understanding of how PFAS impacts people and the environment is still developing and, for thousands of PFAS compounds, much remains unknown. From a toxicological perspective, regulatory agencies must have adequate science for determining health-based values before promulgating individual compound standards, limits, and related regulations.

Toxicologists, whether they work for various state agencies, USEPA, international standards-setting organizations, academia, or in private practice, have not yet established specific methodologies, resources, or even agreed on which of the hundreds of studies of PFAS compounds are the appropriate or critical studies that must or should support appropriate regulatory "standards." Different methodologies, levels of experience, procedural prerequisites to standards-setting, and even local political pressures are leading to consideration of very different standards in various states and at USEPA. Accordingly, the Coalition urges states to work with one another and with USEPA to continue

[1] Note that GenX is a trade name for a specific PFAS compound, ammonium, 2,3,3,3-tetrafluoro-2-(heptafluoropropoxy) propanoate. ITRC "Naming Conventions and Physical and Chemical Properties of Per- and Polyfluoroalkyl Substances (PFAS)," at 12, *available at* https://pfas-1.itrcweb.org/wp-content/uploads/2018/03/pfas_fact_sheet_naming_conventions__3_16_18.pdf (last visited January 23, 2020). More generically, GenX can be denoted by the abbreviation, "HFPO-DA."

developing science and methodologies to inform and encourage a more uniform approach to federal and state PFAS regulatory mandates.

B. Federal Action on PFAS

USEPA has issued "Interim Recommendations for Addressing Groundwater Contaminated with PFOA and PFOS."[2] Those recommendations provide clear and consistent guidance for federal cleanup sites being evaluated and addressed under federal programs, including the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) and the Resource Conservation and Recovery Act (RCRA). The screening levels followed under such cleanups are risk-based values that are used to determine if levels of contamination may warrant further investigation at a site. The recommendations are intended to be used as guidance for states to evaluate state cleanup and corrective action sites. The interim guidance recommends in relevant part:

- Using a screening level of 40 parts per trillion (ppt) to determine if either PFOA, or PFOS, or both, is present at a site and may warrant further attention.
- Using USEPA's PFOA and PFOS Lifetime Drinking Water Health Advisory level of 70 ppt as the preliminary remediation goal (PRG) for contaminated groundwater that is a current or potential source of drinking water, where no state or tribal MCL or other applicable or relevant and appropriate requirements (ARARs) are available or sufficiently protective.

In addition, USEPA is focusing significant resources on developing appropriate regulatory mechanisms specific to various PFAS compounds. For example, USEPA has developed a PFAS Action Plan, which provides a multi-media, multi-program, national research, and risk communication plan to address emerging PFAS challenges.[3] Part of USEPA's PFAS Action Plan involves expanding the scientific foundation for understanding and managing risk from PFAS, including researching improved detection and measurement methods, generating additional information about PFAS presence in the environment and drinking water, improving the understanding of effective treatment and remediation methods, and developing more information regarding the potential toxicity of a broader set of PFAS. In turn, USEPA expects that this information will help states and others better manage PFAS risks.

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[2] USEPA Office of Land and Emergency Management, OLEM Directive No. 9283.1-47 (December 19, 2019), *available at* https://www.epa.gov/sites/production/files/2019-12/text_version_epas_interim_recommendations_for_addressing_groundwater_contaminated_with_pfoa_and_pfos_dec_2019.txt.

[3] *See* USEPA "EPA's Per- and Polyfluoroalkyl Substances (PFAS) Action Plan" (February 2019) *available at* https://www.epa.gov/sites/production/files/2019-02/documents/pfas_action_plan_021319_508compliant_1.pdf.

EPA is also moving towards possible Maximum Contaminant Level (MCL) standards for PFOA and PFOS—two of the most well-known and prevalent PFAS chemicals. On February 20, 2020, EPA released a prepublication version of its Regulatory Determination for Contaminants on the Fourth Drinking Water Contaminant Candidate List. The Regulatory Determination supports regulating under PFOA and PFOS under the Safe Drinking Water Act, meaning EPA is proposing to move forward with setting MCLs for this two PFAS compounds. In making this determination, EPA also relied on the reference dose of 0.00002 mg/kg/day for both compounds.[4] EPA has stated that, "[p]roposing a regulatory determination is the next step in the maximum contaminant level [] rulemaking process under the Safe Drinking Water Act; it enables the USEPA to propose and solicit comment on information critical to regulatory decision-making towards protecting public health and communities across the nation."[5] Additionally, USEPA is gathering and evaluating information to determine if similar regulations are appropriate for a broader number of PFAS compounds.

While USEPA is working through its long-established processes and rulemaking procedures, Congress is considering ways to expedite and fund various national standards-setting approaches. Recently, the U.S. House of Representatives passed the PFAS Action Act (H.R. 535), which would require, among other things, that USEPA promulgate a national primary drinking water regulation for certain PFAS and a health advisory for other PFAS not subject to a national primary drinking water regulation. Also, Congress passed and then the President signed into law the National Defense Authorization Act (NDAA) (P.L. 116-92) that mandates additional federal actions to regulate and manage various risks associated with many PFAS. While we recognize that not all states and stakeholders can agree on specific priorities or approaches to PFAS regulations, these congressional actions, combined with USEPA's efforts, are important national developments that should be supported by the states through their contribution of expertise, resources, and efforts as the Nation works to respond to PFAS exposure risks.

Indeed, a patchwork of 50 different state solutions is unworkable and contrary to how the U.S. has previously addressed similar emerging contaminant issues. While some limited variations related to groundwater, surface water, or soil cleanup levels may be expected and appropriate, the highly variable regulatory health advisories, action levels, and drinking water standards currently being developed or under consideration across the country create unnecessary confusion and complexity for the public and the regulated community.

The Coalition recognizes that states have elected to utilize different methods and processes for communicating risks to their populations. However, standards-setting must reflect more national and uniform collaboration and cohesion. We must work to avoid the

[4] This Regulatory Determination had not yet been published in the *Federal Register* at the time of drafting of these comments, but is available at: https://www.epa.gov/sites/production/files/2020-02/documents/ccl_reg_det_4_preliminary_frn.webposting.pdf.
[5] *Id.*

undesirable solution of 50 separate state rules, particularly with regard to drinking water standards. With this in mind, we urge the states to work closely with USEPA to establish science-based and peer-reviewed federal standards that serve as the basis for comparable state standards. Such an approach is consistent with how USEPA and the states have addressed environmental and human health risks since the creation of USEPA.

In addition, the Coalition can foresee challenges to states that choose to develop their own unique and varying drinking water standards. Many jurisdictions have existing laws or rules that prohibit the state from promulgating regulations that are more stringent than the federal rules. When USEPA does promulgate national primary drinking water regulations, such states may be in conflict with their legislature's clearly stated policy. These states may be required to amend their state-specific PFAS regulations when USEPA completes its work in this regard. And, state antibacksliding provisions may complicate their abilities to change their standards to conform with federal rules.

Considering the above, implementation of any future federal standards likely will be more complex and resource-consuming for states that set their own limits in advance of federal action. Indeed, the purpose of federal law is to protect against a patchwork of state law. Accordingly, the State should clearly articulate how forthcoming federal drinking water standards may impact this State-specific proposed rulemaking, how the State will help to foster consistency and uniformity with neighboring states, and how the State will defer to federal standards or revise standards based on future federal action and improved scientific understanding about exposure, dose, and toxicology.

The Coalition urges the State to use its resources to support the development of sound science upon which USEPA can base its federal standards, heed the non-binding recommendations of USEPA's Federal Health Advisory of 70 ppt (for PFOA and PFOS combined) and, ultimately, work to implement any forthcoming national primary drinking water standards. This will protect the State from expending resources on establishing and enforcing individual PFAS drinking water standards that are inconsistent both with other states and with federal science-based and peer-reviewed standards.

C. Reliance on the ATSDR Values

The ATSDR, part of the federal Center for Disease Control, and many states have reviewed the toxicity information available for PFOA and PFOS and opined on appropriate dosages that reflect highly conservative assumptions designed to protect human health, including the most susceptible subpopulations. ASTDR values are derived through different methods than USEPA's MCL (and Health Advisory) values and the two are not directly comparable.[6] These variabilities in how various health recommendations are

[6] *See* ATSDR Public Health Assessment Guidance Manual (2005) at Appendix F: Derivation of Comparison Values (https://www.atsdr.cdc.gov/hac/phamanual/appf.html) ("MCLs represent more realistic assumptions about toxicity and contain fewer uncertainty factors than the very conservative ATSDR environmental guidelines.")

derived must be considered and addressed to ensure that any final standards are scientifically justified and corroborated. [7]

Moreover, ATSDR has only finalized the Toxicological Profile for two PFAS compounds, PFOA and PFOS. The profiles for two additional PFAS—Hexafluoropropylene Oxide (HFPO) Dimer Acid, more commonly referred to as the "GenX Chemicals," and Perfluorobutane Sulfonic Acid/Potassium Perfluorobutane Sulfonate, referred to as PFBS—are still only in draft form. ATSDR made the Toxicological Profiles for these additional PFAS available for public comment in 2018, and the Profiles have not yet been finalized.

Considering the above, the Coalition recommends that the State base any rulemaking on any forthcoming national primary drinking water standards, rather than the draft ATSDR report. Further, according to Part 620 Subpart F, for substances that USEPA has not established a Maximum Contaminant Level Goal (MCLG), IEPA should base its highest priority approach for calculating the Advisory Concentration on the reference oral dose for humans as derived by USEPA. USEPA has not established MCLGs for any of the five compounds, but it has set a Health Advisory level of 70 ppt for PFOA and PFOS, individually or combined, based on oral reference doses of 0.00002 mg/kg/day for both compounds. Accordingly, IEPA should use the most current USEPA reference doses, such as those used for establishing the Health Advisory level for PFOA and PFOS, rather than establishing standards based on the ATSDR values, some of which are still in draft form.

And, even if the State still seeks to base its rulemaking on the ASTDR reference doses, the Coalition recommends that it wait until ATSDR finalizes its Toxicological Profiles, as the science supporting ATSDR's reference doses is not fully developed nor has the scientific community generally agreed on the science. Moreover, ATSDR has not even drafted profiles for some of the compounds that the State is proposing to regulate.

The State, at best, must avoid underpinning regulations on information that the scientific community is still debating, or using science not yet fully developed enough for ATSDR to draft recommendations. USEPA is actively working on developing its own assessments for these and other PFAS compounds and, consequently, final standards-setting is still premature.

D. Specificity in the Type of Regulated PFAS

Generally, PFAS regulations should clearly specify the individual compounds of PFAS that they seeks to regulate. Given the wide variations in toxicities and other characteristics exhibited by different PFAS chemicals, it is not scientifically appropriate to

[7] For a thorough discussion on possible confusion created by comparing ATSDR and EPA standards, *see* ECOS White Paper (*Processes & Considerations for Setting State PFAS Standards*) Appendix A, *available at*: https://www.ecos.org/documents/ecos-white-paper-processes-and-considerations-for-setting-state-pfas-standards/ (last accessed Feb. 28, 2020).

group all PFAS together for purposes of risk assessment or to assume that exposures to mixtures of PFAS necessarily bioaccumulate in one's body in interchangeable 1:1 ratios.

Accordingly, the Coalition supports the proposed rulemaking's specificity in identifying which PFAS compounds are regulated and recommends that the regulation of individual PFAS substances reflect peer-reviewed science regarding the physical, chemical, and toxicological properties of each compound. Similarly, the Coalition recommends against including any combined PFAS standards or limits unless science clearly demonstrates that the mixture of the PFAS compounds subject to the combined limit results in bioaccumulation in hazardous concentrations.

E. Validated Test Methods for PFAS

The State should regulate only those PFAS comopounds for which there are validated analytical test methods. USEPA's main validated test methods for PFAS, Methods 537 and 537.1, apply only to 18 PFAS compounds in samples derived from drinking water. USEPA recently issued Method 533 that can be used to measure an additional 11 "short-chain" PFAS compounds (and only 14 of the 18 PFAS covered by Method 537.1), again only for use in testing drinking water. Therefore, the entirety of USEPA's approved test methods can measure no more than 29 different PFAS compounds, and multiple methods would have to be used to obtain results from all 29 compounds.

No validated USEPA test methods exist for testing PFAS compounds in any other environmental media. USEPA has received comments on a draft non-potable water test method (SW-846 Method 8327), but that method is only considered "guidance" at this time. USEPA also is working with the Department of Defense's Naval Seas Systems Command Laboratory Quality and Accreditation Office to validate a solid-phase extraction/isotope dilution method to include solid matrices (*i.e.,* for soil, sediment, fish tissue, biosolids), as well as non-potable water sources, but that effort may not be completed until 2021.[8]

Accordingly, the Coalition recommends that the proposed rulemaking recognize the limits of the available USEPA validated test methods and choose a specific test method to be referenced by any standards being adopted. Limitations on test methods and the lack of any validated method by USEPA for anything except drinking water create major challenges for the State's efforts to regulate non-potable water or other matrices.

[8] *See* PFAS Methods Technical Brief *available at* https://www.epa.gov/sites/production/files/2020-01/documents/pfas_methods-sampling_tech_brief_7jan2020-update.pdf.

F. Testing Capabilities and Reliability

The Coalition urges the State to consider the capabilities and reliability of laboratories that test for PFAS. There is limited capacity nationally to perform all of the analytical laboratory work and limited reliability on any given sample result due to potential lab error, cross contamination, or other factor that could impact results in the very low parts per trillion levels being considered. There is little doubt that the closer the State sets a limit or standard to the detection limit, analytical sampling and related lab results become increasingly unreliable.

For example, Coalition members who have sent split samples to multiple labs report receiving highly variable results. Such anecdotal evidence demonstrates the potential difficulty and unreliability of performing testing at limits that approach the detection limit. Considering that the State can potentially impose fines, costly corrective action, or other penalties for failing to meet regulatory limits, the regulated community must have the ability to accurately measure PFAS to demonstrate compliance. Subjecting the regulated community to fines, corrective action, and other penalties based on potentially unreliable testing raises due process concerns. Accordingly, the Coalition urges the State to consider testing capability and reliability, and set limits and impose a regulatory scheme that accounts for the variability in and limits of current laboratory testing.

G. Availability of Testing and Disposal

A limited number of established laboratories in the country have robust experiecnce testing and reporting PFAS results. The State's rulemaking should account for the limited number of testing laboratories in the region. The Coalition recommends, for example, that in regions where testing capacity is limited that the rule provide for a delayed effective date or phased implementation that allows for laboritories to develop the expertise necessary to reliably accommodate the increased testing that the rule will require.

Similarly, treatment technologies for PFAS are still being developed, and there is limited capacity for the disposal of byproducts from newly-developed technologies. For example, absorption technologies such as granular activated carbon (GAC) are being developed as potential response measures to achieve compliance with new drinking water standards for PFAS. The regulated community will need to safely dispose of the byproducts of such treatment technologies used to treat PFAS in drinking water. Again, this is another area where USEPA is taking action.

Congress, in the NDAA, mandated that USEPA, not later than one year after enactment, "publish interim guidance on the destruction and disposal of perfluoroalkyl and polyfluoroalkyl substances and materials containing perfluoroalkyl and polyfluoroalkyl substances," which includes guidance on "spent filters, membranes, resins, granular

carbon, and other waste from water treatment."[9] The Coalition urges the State to use its resources to support the development of USEPA's interim guidance documents prior to independently establishing MCLs.

H. The State Should Consider the Rulemaking's True Costs

The proposed rulemaking should account for the developing nature of treatment technologies and availability of disposal or other treatment endpoints. Information exists regarding the variable costs of treatment systems installed at locations around the country, and the State should consider that information in establishing remediation standards. Though information exists regarding the costs of treatment alternatives, there is signifcant uncertainty regarding how to handle byproducts from PFAS treatment.

For example, a remediating party may not be able to find a landfill to take the spent media, and incineration of the media is currently subject to criticism and further study. As stated in Section G above, Congress has directed USEPA to develop guidance to specially address these issues.

These remediation standards could also affect sites being remediated under federal programs, such as Superfund. For Department of Defense (DOD) sites, for example, the NDAA requires that cooperative agreements with states include that the DOD "shall meet or exceed the most stringent . . . standards for PFAS in any environmental media." NDAA Sec. 332(a)(2).

The states, municipalities, and private parties that are conducting these cleanups will incur substantial costs as a result. Accordingly, the State should consider the costs to remediate to these proposed standards in its regulatory analysis.

In sum, if this regulation will become final before there is more certainty regarding the underlying questions of treatment and disposal, then the State should conduct a more robust cost analysis to account for the potential costs, including remediation and the range of true disposal and ongoing operation and maintenance costs.

[9] NDAA Sec. 7631(4).

V. Conclusion

The Coalition appreciates the opportunity to submit these comments concerning the proposed rulemaking. We look forward to working closely with the State regarding developing appropriate, reasonable, and scientifically-defensible groundwater protection standards. Please feel free to call or e-mail if you have any questions, or if you would like any additional information concerning the issues raised in these comments.

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EXHIBIT B

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June 25, 2021

VIA ELECTRONIC MAIL
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Re: Comments of the PFAS Regulatory Coalition on Proposed Rulemaking to Revise the Part 620 Groundwater Quality Regulations

Dear Sir or Madam:

The PFAS Regulatory Coalition (Coalition) appreciates the opportunity to file comments regarding the proposed revisions to Illinois' Part 620 groundwater quality regulations.

I. The Coalition's Interest

The Coalition is a group of industrial companies, municipal entities, agricultural parties, and trade associations that are directly affected by the State's development of policies and regulation related to per- and polyfluoroalkyl substances (PFAS). Coalition membership includes entities in the automobile, coke and coal chemicals, iron and steel, municipal, paper, petroleum, and other sectors. None of the Coalition members manufacture PFAS compounds. Coalition members, for purposes of these comments, include: Airports Council International – North America; American Coke and Coal Chemicals Institute; American Forest and Paper Association; American Fuel and Petrochemical Manufacturers; American Iron and Steel Institute; Barr Engineering; Brown & Caldwell; Gary Sanitary District (IN); Illinois Association of Wastewater Agencies; Lowell, MA; Pueblo, CO; Toyota; Trihydro, and Yucaipa Valley Water District (CA).

Coalition members support the State's efforts to set groundwater standards for those individual PFAS that pose risks to human health and the environment. In the State's pursuit of such regulations, the Coalition urges State regulators to ensure that final standards are scientifically supported, cost-effective, and achievable.

II. Proposed Rulemaking

On May 12, 2021, the Illinois Environmental Protection Agency (IEPA or State or Agency) proposed draft language to update 35 Ill. Adm. Code 620. The proposed updates include the addition of nine new chemicals, three new atrazine metabolites, and procedures for selecting toxicity values consistent with current federal guidance. The Coalition's comments address only the proposed revisions relating to PFAS compounds and IEPA's methodologies underlying the groundwater standards for PFAS. Notably, the proposal includes groundwater quality standards for the following PFAS:

- Perfluorobutane Sulfonic Acid (PFBS): 0.0012 mg/L
- Perfluorohexane Sulfonic Acid (PFHxS): 0.000077 mg/L
- Perfluorononanoic Acid (PFNA): 0.000012 mg/L
- Perfluorooctanoic Acid (PFOA): 0.000002 mg/L
- Perfluorooctane Sulfonic Acid (PFOS): 0.0000077 mg/L

Additionally, the proposed revisions to Section 620.310 include preventive response activities, including preventive notification mandates.

The PFAS Coalition has significant concerns and questions relating to the proposed standards, which are orders of magnitude lower than the standards the State initially proposed in December 2019. The Coalition recognizes that IEPA has updated its methodology for developing oral reference doses (RfDs), established a hierarchy for selecting verified RfDs, and updated exposure factors to reflect exposure of a child from 0 to 6 years of age as opposed to exposure of an average adult.[1] The Coalition appreciates IEPA's prioritization of USEPA data, where available, but the Agency's brief discussion of the changes to the rule is insufficient to explain the drastic difference from the standards proposed in December 2019 and the standards proposed currently. The Agency's discussion of the changes do not provide an adequate explanation of IEPA's methodology that would allow the public to independently evaluate the proposal. In this regard, the insufficiency of IEPA's proposal undermines the public's ability to comment and participate meaningfully in the rulemaking process.

As discussed below, the Coalition requests that the State reconsider its new proposal standards, through a more transparent process, towards developing standards that provide necessary protection of the State's groundwater resources without unreasonably burdening the regulated community with unnecessarily stringent standards.

[1] The Coalition disagrees with IEPA's decision to include age-adjusted water intake factors to account for increase cancer risk from childhood exposure for substances suspected of being mutagenic carcinogens. The oral slope factor (SFo) used in calculating the HNTAC is based on a default linear, low-dose extrapolation using a mutagenic mode of action. The Agency does not need to use age-adjusted exposure factors, as that level of conservatism is already included in the SFo derivation.

III. Coalition Analysis and Recommendations

In the comments below, the Coalition discusses some of the challenges that the State faces in attempting to promulgate enforceable regulations, as well as some of the challenges that Coalition members face if states promulgate standards that vary from any existing or future federal standards. The Coalition appreciates the State's desire to act to protect its citizens from potential risks associated with exposure to certain PFAS compounds, but urges Illinois and other states to work with the federal government to develop a cohesive national strategy to help ensure national uniformity. A patchwork set of state-specific standards that vary widely would likely cause significantly more confusion and overwhelming challenges for Coalition members that operate in multiple states or nationwide.

A. The Scientific Community Does Not Agree on Human Health Toxicity Values for PFAS

The term "PFAS" refers to a group of man-made chemicals that include perfluorooctanoic acid (PFOA), perfluorooctane sulfonic acid (PFOS), GenX,[2] and other fluorinated compounds. The most prevalent and available science regarding the incidence and potential health effects of PFAS is based on PFOA and PFOS, two compounds that are no longer manufactured in the United States due to voluntary phase outs over a decade ago. For replacement chemicals, industry has begun using shorter-chain PFAS that have different physical, chemical, and toxicological properties from long-chain PFOA and PFOS. The scientific understanding of how PFAS impacts people and the environment is still developing and, for thousands of PFAS compounds, much remains unknown. From a toxicological perspective, regulatory agencies must have adequate science for determining health-based values before promulgating individual-compound standards, limits, and related regulations.

Toxicologists, whether they work for various state agencies, USEPA, international standards-setting organizations, academia, or in private practice, have not yet established specific methodologies, resources, or even agreed on which of the hundreds of studies of PFAS compounds are the appropriate or critical studies that must or should support appropriate regulatory "standards." Different methodologies, levels of experience, procedural prerequisites to standards-setting, and even local political pressures are leading to consideration of very different standards in various states and at USEPA. The Coalition urges states to work with one another, and with USEPA, to continue developing science and methodologies to inform and encourage a more uniform approach to federal and state PFAS regulatory mandates.

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[2] Note that GenX is a trade name for a specific PFAS compound, ammonium, 2,3,3,3-tetrafluoro-2-(heptafluoropropoxy) propanoate. ITRC "Naming Conventions and Physical and Chemical Properties of Per- and Polyfluoroalkyl Substances (PFAS)," at 12, *available at* https://pfas-1.itrcweb.org/fact_sheets_page/PFAS_Fact_Sheet_Naming_Conventions_April2020.pdf (last visited June 24, 2021). More generically, GenX can be denoted by the abbreviation, "HFPO-DA."

B. Federal Action on PFAS

USEPA issued "Interim Recommendations for Addressing Groundwater Contaminated with PFOA and PFOS" in December 2019[3] Those recommendations provide clear and consistent guidance for federal cleanup sites being evaluated and addressed under federal programs, including the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) and the Resource Conservation and Recovery Act (RCRA). The screening levels recommended for such cleanups are risk-based values that are used to determine if levels of contamination may warrant further investigation at a site. The recommendations are intended to be used as guidance for states to evaluate state cleanup and corrective action sites. The interim guidance recommends in relevant part:

- Using a screening level of 40 parts per trillion (ppt) to determine if either PFOA, or PFOS, or both, are present at a site and may warrant further attention.
- Using USEPA's PFOA and PFOS Lifetime Drinking Water Health Advisory level of 70 ppt as the preliminary remediation goal (PRG) for contaminated groundwater that is a current or potential source of drinking water, where no state or tribal MCL or other applicable or relevant and appropriate requirements (ARARs) are available or sufficiently protective.

In addition, USEPA is focusing significant resources on developing appropriate regulatory mechanisms specific to various PFAS compounds. For example, USEPA has developed a PFAS Action Plan, which provides a multi-media, multi-program, national research and risk communication plan to address emerging PFAS challenges.[4] Part of USEPA's PFAS Action Plan involves expanding the scientific foundation for understanding and managing risk from PFAS, including researching improved detection and measurement methods, generating additional information about PFAS presence in the environment, improving the understanding of effective treatment and remediation methods, and developing more information regarding the potential toxicity of a broader set of PFAS. In turn, USEPA expects that this information will help states and others better manage PFAS risks. To bolster this work, USEPA Administrator Regan established the PFAS Action Council on April 27, 2021.[5]

While we recognize that not all states and stakeholders can agree on specific priorities or approaches to PFAS regulations, USEPA and Congress are leading important

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[3] USEPA Office of Land and Emergency Management, OLEM Directive No. 9283.1-47 (December 19, 2019), *available at* https://www.epa.gov/sites/production/files/2019-12/text_version_epas_interim_recommendations_for_addressing_groundwater_contaminated_with_pfoa_and_pfos_dec_2019.txt.

[4] *See* USEPA "EPA's Per- and Polyfluoroalkyl Substances (PFAS) Action Plan" (February 2019) *available at* https://www.epa.gov/sites/production/files/2019-02/documents/pfas_action_plan_021319_508compliant_1.pdf.

5 *See* Memorandum Regarding Per- and Polyfluoroalkyl Substances (April 27, 2021) *available at* https://www.epa.gov/pfas/memo-epa-council-pfas.

national initiatives that states should support through their contribution of expertise, resources, and efforts as the United States works to respond to PFAS exposure risks. Indeed, a patchwork of 50 different state solutions is unworkable and contrary to how the U.S. has previously addressed similar emerging-contaminant issues. While some limited variations related to groundwater, surface water, or soil cleanup levels may be expected and appropriate, the highly variable regulatory health advisories, action levels, and numeric standards currently being developed or under consideration across the country create unnecessary confusion and complexity for the public and the regulated community.

The Coalition recognizes that states have elected to utilize different methods and processes for communicating risks to their populations. However, standards-setting must reflect more national and uniform collaboration and cohesion. We must work to avoid the undesirable solution of 50 separate state rules. With this in mind, we urge the states to work closely with USEPA to establish science-based and peer-reviewed federal standards that serve as the basis for comparable state standards. Such an approach is consistent with how USEPA and the states have addressed environmental and human health risks since the creation of USEPA.

C. Transparency of IEPA's Proposal

It is not possible to discern from IEPA's proposal how the Agency arrived at the proposed standards. Although the Agency has provided updated equations and values, it does not explain how these updates translate into the new standards proposed. In particular, the proposal does not explain how or why the latest proposed standards are orders of magnitude lower than the standards proposed in December 2019. Not only is IEPA's methodology not clearly explained, the sources from which IEPA has derived its information are different for the various PFAS compounds. The Agency should support USEPA's development of defensible data for each of the PFAS compounds it seeks to regulate and base it groundwater quality standards on updated, sound USEPA-derived values, when available.

IEPA must provide a more detailed methodology, and explanation of how it derived the proposed standards using that methodology, to allow for meaningful public comment. From our review of the proposal and the available support documents, it appears that the Agency is deriving these standards using an assumption that various substances will appear together in mixtures. Then, it is assumed that if several compounds act on the same organ, or produce a similar effect to a given system (e.g, the nervous system), their potential risks as to that organ or effect can be combined. Then, the potential cancer or non-cancer risks to various organs or systems can be combined to yield an overall risk. And somehow, all of those issues are factored in together to result in a specific standard for each substance. However, nowhere does IEPA provide the calculations that yield those proposed standards. Also, the Agency has not provided technical support for the assumptions that provide the basis for the standards, including as to whether (1) it is appropriate to assume that various compounds will occur in mixtures, or (2) that the risks to a given organ or system from several substances can be combined in an additive fashion, or (3) that cancer or non-cancer risks to several different organs or systems can be similarly combined. That information needs to be provided as to

each of the substances covered by the proposal, including as to which studies are being relied on for each toxicity endpoint. Without such information, one cannot determine if the proposed standards are scientifically supported. Stakeholders need to have the opportunity to review that information, and provide comments to the Agency concerning that information, before this proposal can proceed further.

D. Hierarchy of Sources

The Coalition appreciates IEPA's prioritization of USEPA-developed or USEPA-approved sources and values, such as USEPA's IRIS and USEPA's Provisional Peer-Reviewed Toxicity Value (PPRTV). The Coalition disagrees with IEPA reliance on certain of the Tier III sources for toxicity values, including the Agency for Toxic Substances and Disease Registry (ATSDR) and CalEPA. The ATSDR, part of the federal Center for Disease Control, and many states have reviewed the toxicity information available for PFOA and PFOS and opined on appropriate dosages that reflect highly conservative assumptions designed to protect human health, including the most susceptible subpopulations. ATSDR values are derived through different methods than USEPA's MCL (and Health Advisory) values and the two are not directly comparable.[6] These variabilities in how various health recommendations are derived must be considered and addressed to ensure that any final standards are scientifically justified and corroborated. [7]

Accordingly, the Coalition recommends that the State base any rulemaking on the forthcoming national primary drinking water standards, rather than the ATSDR report. Further, according to 35 Ill. Adm. Code Part 620 Subpart F, for substances that USEPA has not established a Maximum Contaminant Level Goal (MCLG), IEPA should base its highest priority approach for calculating the Advisory Concentration on the reference oral dose for humans as derived by USEPA. USEPA has not established MCLGs for any of the five compounds that are the subject of this rulemaking, but it has set a Health Advisory level of 70 ppt for PFOA and PFOS, individually or combined, based on oral reference doses of 0.00002 mg/kg/day for both compounds. IEPA should use the most current USEPA reference doses, such as those used for establishing the Health Advisory level for PFOA and PFOS, rather than establishing standards based on the ATSDR values.

For example, we note that one of five standards for PFAS, PFBS, was based on the PPRTV, which, for the reasons described above, is preferable to the ATSDR value. Notably, the standard for PFBS is also a far higher standard than any of the other PFAS standards. The fact that the PFBS standard, which is the only standard based on the more

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[6] *See* ATSDR Public Health Assessment Guidance Manual (2005) at Appendix F: Derivation of Comparison Values (https://www.atsdr.cdc.gov/hac/phamanual/appf.html) ("MCLs represent more realistic assumptions about toxicity and contain fewer uncertainty factors than the very conservative ATSDR environmental guidelines.")

[7] For a thorough discussion on possible confusion created by comparing ATSDR and EPA standards, *see* ECOS White Paper (*Processes and Considerations for Setting State PFAS Standards*) Appendix A, *available at*: https://www.ecos.org/documents/ecos-white-paper-processes-and-considerations-for-setting-state-pfas-standards/ (last accessed Feb. 28, 2020).

appropriate PPRTV value, is significantly higher than the other PFAS standards further supports the notion that the State should wait for USEPA to develop scientifically substantiated values, rather than promulgating its own standards based on underdeveloped science, which are unnecessary and unduly burdensome.

Additionally, PFOA is the only PFAS compounds for which the State has developed a standard based on cancer risk. USEPA has chosen not to regulate PFOA based on cancer risk. Also, CalEPA's study of PFOA is based on questionable science, which USEPA has not adopted or substantiated. Ultimately, the CalEPA study yields a much more stringent standard that is not derived from a sound or widely-accepted cancer risk assessment.

The State must avoid underpinning regulations on information that the scientific community is still debating, or using science that is not yet fully developed. USEPA is actively working on developing its own assessments for these and other PFAS compounds and, consequently, final standards-setting by the State is still premature. Illinois should not promulgate standards that are unjustifiably much more stringent than the eventual USEPA values.

E. Specificity in the Type of Regulated PFAS

In this current proposal, IEPA appears to have removed the combined PFOS and PFOA limit that the Agency initially included in the December 2019 proposal. The Coalition previously recommended against including any combined PFAS standards or limits and appreciates this revision in the current proposal.

PFAS regulations should clearly specify the individual compounds of PFAS that they seeks to regulate. Given the wide variations in toxicities and other characteristics exhibited by different PFAS chemicals, it is not scientifically appropriate to group all PFAS together for purposes of risk assessment or to assume that exposures to mixtures of PFAS necessarily bioaccumulate in one's body in interchangeable 1:1 ratios. Generally, the Coalition supports the proposed rulemaking's specificity in identifying which PFAS compounds are regulated and recommends that the regulation of individual PFAS substances reflect peer-reviewed science regarding the physical, chemical, and toxicological properties of each compound. Similarly, the Coalition reiterates its recommendation against including any combined PFAS standards or limits unless science clearly demonstrates that the mixture of the PFAS compounds subject to the combined limit results in hazardous concentrations.

F. Validated Test Methods for PFAS in Groundwater

There are no USEPA validated test methods for groundwater. As a general approach, the State should regulate only those PFAS compounds for which there are validated, approved analytical test methods. Here, though, IEPA is seeking to set groundwater limits without a validated test method. USEPA's main validated test methods

for PFAS, Methods 537 and 537.1, apply only to 18 PFAS compounds in samples derived from drinking water. USEPA recently issued Method 533 that can be used to measure an additional 11 "short-chain" PFAS compounds (and only 14 of the 18 PFAS covered by Method 537.1), again only for use in testing drinking water. Therefore, the entirety of USEPA's approved test methods can measure no more than 29 different PFAS compounds, and multiple methods would have to be used to obtain results for all 29 compounds.

No validated, approved USEPA test methods exist for testing PFAS compounds in any other environmental media. USEPA is developing a draft non-potable water test method (SW-846 Method 8327), but that method has not yet been formally incorporated into the SW-846 Compendium. Similarly, USEPA is working with the Department of Defense's (DOD) Naval Seas Systems Command Laboratory Quality and Accreditation Office to validate a solid-phase extraction/isotope dilution method to include solid matrices (*i.e.,* for soil, sediment, fish tissue, biosolids), as well as non-potable water sources, but that effort has not yet been completed.

The Coalition recommends that the proposed rulemaking recognize the limits of the available USEPA validated test methods and choose a specific test method to be referenced by any standards being adopted. Limitations on test methods and the lack of any validated, approved method by USEPA for anything except drinking water creates major challenges for the State's efforts to regulate non-potable water or other matrices. Considering that the State can potentially impose fines, costly corrective action, or other penalties for failing to meet regulatory limits, the regulated community must have the ability to accurately measure PFAS to demonstrate compliance. Subjecting the regulated community to fines, corrective action, and other penalties based on potentially unreliable testing or lack of available testing raises due process concerns. Accordingly, the Coalition urges the State to consider testing capability and reliability, and set limits and impose a regulatory scheme that accounts for the variability in and limits of current laboratory testing.

G. Availability of Treatment and Disposal Options

Similarly, treatment technologies for PFAS are still being developed, and there is limited capacity for the disposal of byproducts from newly-developed technologies. For example, adsorption technologies such as granular activated carbon (GAC) are being developed as potential response measures to achieve compliance with new standards for PFAS. The regulated community will need to safely dispose of the byproducts of such treatment technologies used to treat PFAS. If IEPA issues very low standards based on limited or deficient toxicology data, and the site data is generated by non-validated analytical methods, the regulated community will expend unnecessary resources on already limited remediation options. IEPA should account for the availability, feasibility, and cost of treatment and disposal options in setting standards to ensure that the regulated community has the ability to comply with the regulations.

Again, this is another area where USEPA is taking action. Congress, in the latest National Defense Authorization Act (NDAA), mandated that USEPA, not later than one

year after enactment, "publish interim guidance on the destruction and disposal of perfluoroalkyl and polyfluoroalkyl substances and materials containing perfluoroalkyl and polyfluoroalkyl substances," which includes guidance on "spent filters, membranes, resins, granular carbon, and other waste from water treatment."[8] In December 2020, USEPA released the new interim guidance for public comment, noting that considerable further research must be done to better characterize PFAS-containing materials; to measure and assess the effectiveness of existing methods for destruction; and to develop other technologies that may be employed instead of or with existing technologies.[9] The Coalition urges the State to use its resources to support the development of USEPA's interim guidance documents prior to establishing groundwater quality standards that will require disposal.

H. The State Should Consider the Technical Feasibility and Economic Reasonableness of the Rulemaking

The Illinois Pollution Control Board (Board) ultimately will need to adopt the groundwater quality standards that IEPA issues. The Board's enabling legislation requires that it take into account, among other factors, "the technical feasibility and economic reasonableness of measuring or reducing the particular type of pollution." 415 ILCS 5/27(a). Accordingly, IEPA should specifically address the technical feasibility and economic reasonableness of measuring and reducing PFAS in the environment in this rulemaking. Specifically, the rulemaking should account for the developing nature of treatment technologies and availability of disposal or other treatment endpoints. Information exists regarding the variable costs of treatment systems at locations around the country, and the State should consider that information in establishing remediation standards. Though some information exists regarding the costs of treatment alternatives IEPA must consider the signifcant uncertainty surrounding the handling of byproducts from PFAS treatment.

For example, a remediating party may not be able to find a landfill to take spent media. Additionally, incineration of spent media is thesubject to criticism and requires further study. As discussed in Section G above, Congress has directed USEPA to develop guidance to specially address these issues.

These remediation standards could also affect sites being remediated under federal programs, such as Superfund. For example, at DOD sites, the NDAA requires that cooperative agreements with states include that DOD "shall meet or exceed the most stringent . . . standards for PFAS in any environmental media." NDAA Sec. 332(a)(2). As a result, the states, municipalities, and private parties that are conducting cleanups may

[8] NDAA Sec. 7631(4).
[9] 85 Fed. Reg. 83554 "Interim PFAS Destruction and Disposal Guidance; Notice of Availability for Public Comment" (December 21, 2020).

incur substantial additional costs. The State should consider the costs to remediate to these proposed standards in its regulatory analysis.

Additionally, the rulemaking proposal does not appear to account for background concentrations of PFAS in the environment. Because the Agency has proposed such stringent levels, it is possible that background concentrations of certain PFAS already exceed the standards proposed. Of course, the higher the background concentrations of PFAS, the more costly and technically challenging it will be to remediate to the levels proposed. The rulemaking should include an analysis and determination regarding background levels of PFAS to inform the evaluation of technical feasibility and economic reasonableness of remediating to the levels proposed.

In summary, if this regulation will become final before there is more certainty regarding the underlying questions of treatment, disposal, and background concentrations then the State should conduct a more robust analysis of the technical feasibility and economic reasonableness to account for the potential costs, including remediation and the range of true disposal and ongoing operation and maintenance costs.

V. Conclusion

The Coalition appreciates the opportunity to comment concerning the proposed rulemaking. We look forward to working closely with the State regarding developing appropriate, reasonable, and scientifically-defensible groundwater protection standards. Please feel free to call or e-mail if you have any questions, or if you would like any additional information concerning the issues raised in these comments.

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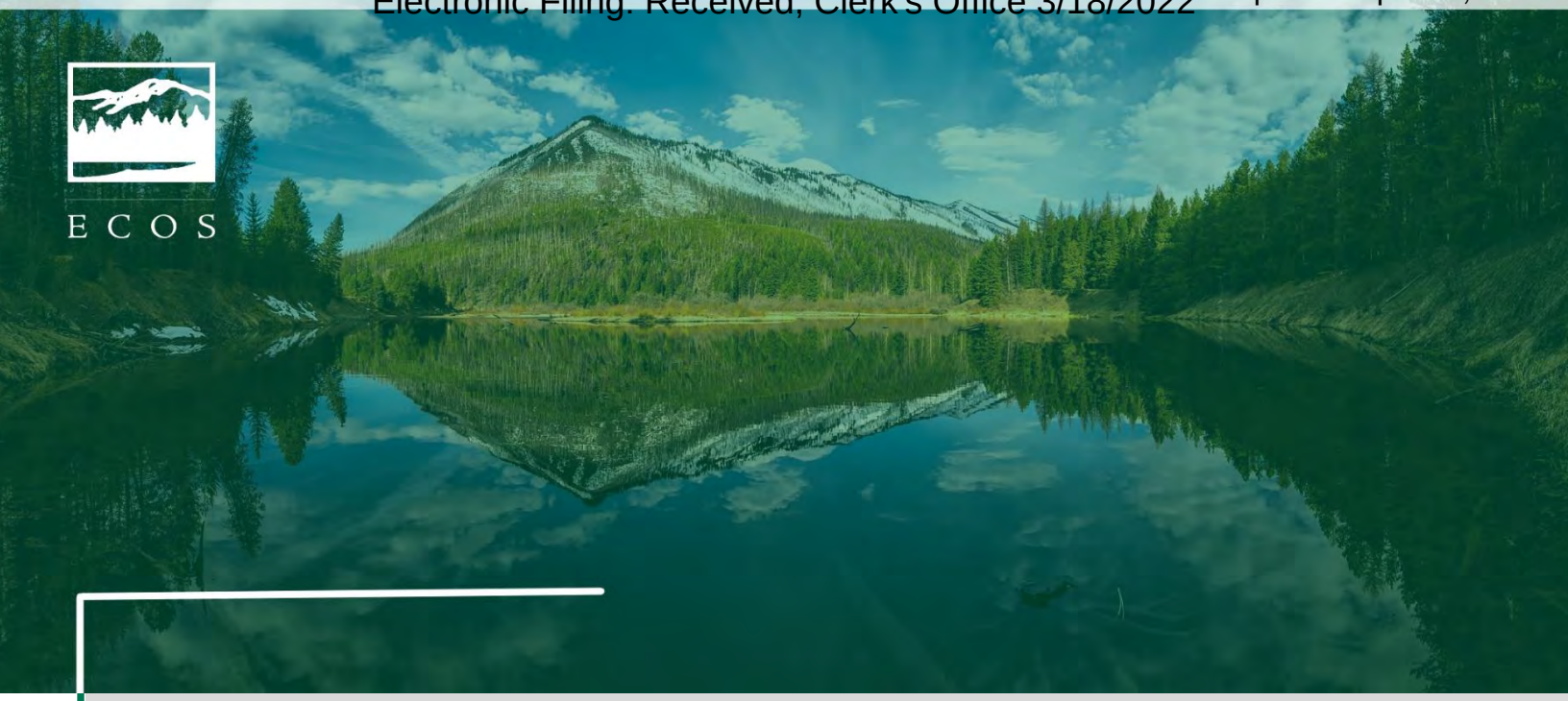
EXHIBIT C

February 2020
Updated April 29, 2021



Processes & Considerations for Setting State PFAS Standards

By Sarah Grace Longsworth, Project Manager, ECOS

Supported by & in conjunction with the ECOS PFAS Caucus

Executive Summary

In recent years, federal, state, and international authorities have established various health-based regulatory values and evaluation criteria for a number of specific per- and polyfluoroalkyl substances (PFAS) in response to growing concerns with contamination. At this time, the U.S. has no federally enforceable PFAS standards, leaving individual states to navigate various avenues for addressing PFAS contamination. Some states have established legally enforceable values for certain PFAS in drinking water, groundwater, surface water, soil, or other environmental media (e.g., drinking water Maximum Contaminant Levels [MCLs]). Other states and regulatory agencies have opted for non-enforceable values such as guidance levels, screening numbers, or advisories that may apply to PFAS for which promulgated standards do not exist.

The Environmental Council of the States (ECOS) in 2019 compiled information on state PFAS standards, advisories, and guidance values (hereinafter referred to as "guidelines"[1]). Sharing data and regulatory approaches helps federal, state, and international authorities avoid unnecessary duplication of efforts, as well as understand and communicate about differences in guidelines. This paper[2] outlines ECOS' findings on state efforts and considerations for future regulatory activities on PFAS.

[1] For the purposes of this white paper, the term "guidelines" will apply to both regulatory (enforceable) standards and non-regulatory (non-enforceable) values.

[2] The white paper was initially published in February 2020. It has been updated with new information and state participants, and will be updated annually as appropriate.

Table of Contents

List of Acronyms

ACRONYM	FULL PHRASE
ACGIH	American Conference of Governmental Industrial Hygienists
ACWA	Association of Clean Water Administrators
AFFF	Aqueous film-forming foam
APFO	Ammonium perfluorooctanoate
ASDWA	Association of State Drinking Water Administrators
ASTM	ASTM International (formerly American Society for Testing and Materials)
ATSDR	Agency for Toxic Substances and Disease Registry
BMDL	Benchmark dose (lower confidence limit)
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CSF	Cancer slope factor
CWA	Clean Water Act
DOD	U.S. Department of Defense
ECOS	Environmental Council of the States
EPA	U.S. Environmental Protection Agency
ESL	Effect Screening Level
FOSA	Perfluorooctane sulfonamide
FTE	Full-time employee
FTS	Fluorotelomer sulfonate
GAC	Granular activated carbon
HBV	Health-Based Value
HED	Human equivalent dose
HFPO-DA	Hexafluoropropylene oxide dimer acid
HRL	Health Risk Limit
ISO	International Organization for Standardization
ITRC	Interstate Technology and Regulatory Council
ITSL	Interim Threshold Screening Level
kg	Kilogram
L	Liter
LHA	U.S. EPA Lifetime Health Advisory
LOAEL	Lowest Observed Adverse Effect Level
MCL	Maximum Contaminant Level

mg	**Milligram**
MLA	**Multi-linear array (SGS Axys method)**
MPART	**Michigan PFAS Action Response Team**
MRL	**Minimal risk level**
NDAA	**National Defense Authorization Act**
NEtFOSA	**N-ethyl perfluorooctane sulfonamide**
NEtFOSAA	**N-Ethyl perfluorooctane sulfonamidoacetic acid**
NEtFOSE	**N-Ethyl perfluorooctane sulfonamidoethanol**
NGO	**Non-governmental organization**
NOAEL	**No Observed Adverse Effect Level**
NPDES	**National Pollutant Discharge Elimination System**
NPDWR	**National Primary Drinking Water Regulation**
NRWQC	**National Recommended Water Quality Criteria**
PFAS	**Per- and polyfluoroalkyl substances**
PFBA	**Perfluorobutanoic acid**
PFBS	**Perfluorobutanesulfonic acid**
PFDA	**Perfluorodecanoic acid**
PFHpA	**Perfluoroheptanoic acid**
PFHxA	**Perfluorohexanoic acid**
PFHxS	**Perfluorohexane sulfonic acid**
PFIB	**Perfluoroisobutylene**
PFNA	**Perfluorononanoic acid**
PFOA	**Perfluorooctanoic acid**
PFOS	**Perfluorooctane sulfonate**
PFOSA	**Perfluorooctanesulfonamide**
POD	**Point of Departure**
ppb	**Parts per billion**
ppm	**Parts per million**
ppt	**Parts per trillion**
PWS	**Public water system**
RCRA	**Resource Conservation and Recovery Act**
RfD	**Reference Dose**
RSC	**Relative Source Contribution**
RSL	**Regional Screening Level**
RCL	**Residual Contaminant Level**
SDWA	**Safe Drinking Water Act**

SOP	**Standard operating procedure**
SPE	**Solid phase extraction**
SPLP	**Synthetic precipitation leaching procedure**
TOF	**Total organic fluorine**
TOP	**Total oxidizable precursor**
TSCA	**Toxic Substances Control Act**
WAX	**Weak anion exchange**

Introduction

PFAS are a group of synthetic chemicals used in a wide array of consumer and industrial products since the 1940s. Several decades later, publicly available studies on certain PFAS risks indicated potential human health concerns related to these chemicals. In 2000, 3M announced a voluntary phase-out of certain legacy PFAS (e.g., perfluorooctanoic acid [PFOA], perfluorooctane sulfonate [PFOS], perfluorohexane sulfonic acid [PFHxS]). In 2006, the U.S. Environmental Protection Agency (EPA) initiated the PFOA Stewardship Program, which encouraged eight major chemical manufacturers to eliminate the use of PFOA and similar long-chain[3] PFAS in their products and in the emissions from their facilities.[4] International signatories of the United Nations' Stockholm Convention on Persistent Organic Pollutants treaty voted in 2009 and 2020 to add PFOS and PFOA, respectively, to the list of substances to be eliminated.[5] In 2020, the EPA issued a rule under the Toxic Substances Control Act (TSCA) prohibiting the manufacturing, processing, and/or importing of products containing certain PFAS without prior agency review and approval. Despite these actions, U.S. manufacturers can with approval still import PFOA, PFOS, and PFHxS for use in consumer goods, and some U.S. sites are legally required to keep PFAS-containing firefighting foams on-site for emergencies.

U.S. manufacturers have developed numerous PFAS to replace long-chain PFAS such as PFOA, PFOS, and perfluorononoanic acid (PFNA). One example is hexafluoropropylene oxide dimer acid (HFPO-DA) and the HFPO-DA ammonium salt, the two chemical substances that are part of the **GenX** technology developed by Chemours (formerly DuPont), that were developed as a PFOA replacement. These replacement chemicals are part of the larger suite of nearly 5,000[6] PFAS, some of which the EPA has approved for manufacture and use in the U.S. This is a problem on many fronts: PFAS do not break down or, in the case of PFAS that are precursors[7], are converted to terminal PFAS that do not break down, and are very hard to remove and/or destroy with treatment. Therefore, there is a persistent "supply" of PFAS in the environment that maintain their carbon-fluorine chemical structures and potential toxicity, in contrast to many other organic compounds. In addition, regulators currently lack routinely available analytical methods for PFAS detection and measurement across most environmental media and have little, if any, toxicological data for the majority of PFAS (especially the precursors) to define risks to human and ecological receptors.

In 2016, the EPA updated its short-term Provisional Health Advisory values for PFOA (400 parts per trillion [ppt]) and PFOS (200 ppt) to a Lifetime Health Advisory (LHA) of 70 ppt for PFOA and PFOS, individually or in combination, in finished drinking water.[8] The EPA states that this LHA was calculated "to provide Americans, including the most sensitive populations, with a margin of protection from a lifetime of exposure to PFOA and PFOS

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[3] Long-chain PFAS are those with carbon chain lengths of 6 or higher for sulfonic acids like PFOS and PFHxS, and carbon chain lengths of 8 or higher for carboxylic acids like PFOA and perfluorononanoic acid (PFNA). In general, perfluoroalkyl acids (sulfonic acids and carboxylates) of all chain lengths do not break down, and long-chain PFAS have been found to bioaccumulate and pose risks to human health and the environment.

[4] **Fact Sheet**, History and Use of Per- and Polyfluoroalkyl Substances (PFAS), ITRC (2020).

[5] For more information on international PFAS regulations, including the European Union's Registration, Evaluation, Authorisation, and Restriction of Chemicals (REACH) regulation, see the **European Chemicals Agency website**.

[6] U.S. Food and Drug Administration's **PFAS website**

[7] Precursor, as used here, are PFAS, known or unknown, which have the potential to degrade to terminal PFAS that do not break down in the environment.

[8] In December 2019, the EPA issued **interim guidance** that recommends a screening level of 40 ppt to assess whether the levels of PFOA and/or PFOS present in groundwater at a federal cleanup site may require further investigation. The EPA will use the LHA of 70 ppt as a preliminary remediation goal for contaminated groundwater. While this may be useful to states, many states have their own guidance for PFAS in groundwater.

from drinking water."[9] The LHA is a non-regulatory and non-legally enforceable value, and is intended to provide guidance to federal, state, and municipal governments for addressing PFOA and PFOS contamination in public water systems and private potable wells. In February 2019, the EPA released its **PFAS Action Plan** in which the agency committed to make a "regulatory determination" for PFOA and PFOS under the Safe Drinking Water Act (SDWA). A regulatory determination is a formal decision on whether the EPA should initiate a process to develop a national primary drinking water regulation for a specific contaminant. The SDWA requires the EPA to make regulatory determinations for at least five contaminants from the most recent drinking water Contaminant Candidate List[10] within five years of the completion of the previous round of regulatory determinations. This determination may initiate the rulemaking process to establish an enforceable National Primary Drinking Water Regulation (i.e., MCL), a process that is likely to take years due to the necessary technical evaluation, public comment, and rulemaking procedures. The EPA sent the regulatory determination for PFOA and PFOS to the Office of Management and Budget in December 2019 for interagency review, and it was released for public comment in February 2020, just after this paper was first published. In January 2021, the EPA announced that it had evaluated more than 11,000 public comments and made a final decision to regulate PFOA and PFOS. This decision was reissued by the new Administration on February 22, 2021. As part of the process of developing a National Primary Drinking Water Regulation (NPDWR) for these PFAS, the EPA will initiate yet another phase of analyses, scientific review, and public comment. The agency also noted that it intends to fast track evaluation of other PFAS for future drinking water regulatory determinations if necessary data and information are available.

In 2018, the U.S. Health and Human Services' Agency for Toxic Substances and Disease Registry (ATSDR) developed provisional **minimal risk levels** (MRLs) for four PFAS: PFOA, PFOS, PFHxS, and PFNA. MRLs are not regulatory values and are not intended to be used as public water or environmental cleanup standards. MRLs are screening tools to identify contaminants of concern at hazardous waste sites. If an exposure is below an MRL, it is not expected to result in adverse health effects, whereas an exposure exceeding an MRL warrants further investigation to determine if the exposure might harm human health. Additionally, MRLs are presented as dosage amounts (a measurement of exposure in units of milligrams/kilogram/day) and not in terms of concentration (the amount of a substance present in a particular media in units of parts per million [ppm], parts per billion [ppb], or ppt). These differences have resulted in public confusion and emphasize the need for improved risk communication, especially in the news media, to explain that MRLs and the EPA's LHAs are used in different situations and are not/should not be considered "equivalent."

Historically, many states relied on the promulgated standards from federal agencies to regulate chemicals, while other states have had the authority to develop their own standards for contaminants of concern. If no federal standard exists, states may rely on toxicity values from the **EPA Tier 3 Toxicity Value Workgroup document** or similar reference documents. Noting the broad range and complexity of PFAS, the need for cross-media consideration, and the absence of promulgated federal standards, states have taken alternative routes to actively address PFAS across a wide range of programs. At least 22 states[11] have developed draft, proposed, or final health-based regulatory and/or guidance values for several PFAS in drinking water, groundwater, and/or surface water.[12] These guidelines may significantly differ from the EPA's LHA and from state-to-state given various legislative and scientific considerations. For example, states may have different mandates (e.g., regulations, policies) that direct them

[9] The **EPA Drinking Water Health Advisories for PFOA and PFOS**

[10] The EPA's **Contaminant Candidate List** is a list of contaminants that are currently not subject to proposed or promulgated national primary drinking water regulations, but are known or anticipated to occur in public water systems.

[11] Several states in addition to those that completed the ECOS survey are known to have drafted, proposed, or finalized health-based regulatory and/or guidance values for PFAS in various environmental media. They are not included in the facts and figures outlined in this report.

[12] See the Interstate Technology and Regulatory Council's [ITRC] **Sections 4 and 5 Tables** in its PFAS regulations fact sheet. The ITRC is a subsidiary of ECOS.

to interpret toxicity data (including considering exposures to sensitive life stages like infants or pregnant women) to develop risk assessments or require them to use the EPA's risk assessments as the basis for their guidelines. Several states have developed drinking water guidelines for PFOA and PFOS that are lower than the EPA's LHA due to considerations of more recent scientific information, more sensitive toxicological endpoints, and/or more stringent exposure parameters. Many of these states have also developed guidelines for various PFAS in addition to PFOA and PFOS. Other states have adopted the EPA's LHA for PFOA and PFOS in drinking water and/or groundwater to guide their efforts upon detection of contamination.[13]

With a growing body of science to inform standard development, an absence of a federally enforceable standard, and pressures from the public and legislative bodies to take regulatory action, it is important to know which states are setting guidelines, understand how the guidelines are developed, and be able to educate legislators on differences between state, federal, and other guidelines. This is essential so that states can make informed decisions when implementing their own regulations and/or risk communication practices.

Overview of States' PFAS Guidelines

ECOS surveyed states on their processes, rulemaking requirements, and other considerations for establishing PFAS guidelines (e.g., occurrence of specific PFAS in drinking water sources or other environmental media). ECOS and its working group of state environmental agency officials (the PFAS Caucus) examined responses from *30 states (Alabama, Alaska, Arizona, California, Colorado, Connecticut, Florida, Hawaii, Illinois, Indiana, Kansas, Maine, Massachusetts, Michigan, Minnesota, Missouri, Nebraska, New Hampshire, New Jersey, New Mexico, New York, North Carolina, Oklahoma, Oregon, Tennessee, Texas, Vermont, Washington, Wisconsin, Wyoming).*[14] Below are findings and conclusions from the 30 states that completed the ECOS survey.

States without PFAS Guidelines

Eight states (Alabama, Arizona, Kansas, Missouri, Nebraska, Oklahoma, Tennessee, Wyoming) indicated that they do not have state guidelines.[15]

Reasoning for Not Establishing State PFAS Guidelines:

- *Six states (Arizona, Indiana, Missouri, New Mexico, North Carolina, Oklahoma*)[16] have restrictions that prohibit them from setting a drinking water or groundwater guideline more stringent (i.e., more protective) than a federal standard in at least one environmental medium. This could dissuade a state from setting a PFAS standard (at any level), or from setting a PFAS standard lower than the EPA's LHA in anticipation that a federal MCL may be enacted at a similar level, forcing the state to amend its guideline(s) in a way that appears to "weaken" it.

[13] The health basis for standards for other contaminants of emerging concern may be as low as those for PFAS, but the actual standards for those other contaminants are often higher because they are based on analytical limitations, while the PFAS standards can be set at the health-based levels.

[14] Individual state PFAS websites can be found in the "Overview" section on ECOS' **PFAS Risk Communication Hub**.

[15] These states may use the EPA's LHA of 70 ppt as guidance, remediation goals, action levels, or for regulatory oversight if PFAS contamination is detected. However, they will likely wait for a federal standard before enacting their own state guidelines.

[16] Indiana, New Mexico, and North Carolina are included in this list because they have such a law governing rule-based standards in at least one environmental medium. However, they have a guideline for at least one PFAS analyte, as indicated below.

- Many states lack the capacity or resources to effectively and individually regulate PFAS. Barriers include lack of technical expertise needed for toxicity interpretation and standard development, labs certified to test for PFAS in the state, interdependence of programs, legislative support, and funding.
- There are still limitations to available toxicity data, approved monitoring or analytical methods, and established federal criteria, all of which may contribute to scientific and regulatory uncertainty. Many states noted the need for more peer-reviewed science to make informed decisions on whether to establish guidance levels for some of the PFAS that have been found in their environmental media.

Without their own state-based guidelines, several of these states are still taking actions to monitor, investigate, and remediate PFAS. Efforts include statewide sampling of Public Water Systems (PWSs) and surface water and groundwater intakes; conducting inventories of facilities that use or have used or produced PFAS; responding to drinking water and fish contamination; notifying local emergency planning committees, fire departments, and industry of the human health and environmental impacts associated with using legacy aqueous film-forming foams (AFFF); and forming interagency task forces to coordinate the messaging for and response to PFAS contamination within the state.

States with PFAS Guidelines

22 states (Alaska, California, Colorado, Connecticut, Florida, Hawaii, Illinois, Indiana, Maine, Massachusetts, Michigan, Minnesota, New Hampshire, New Jersey, New Mexico, New York, North Carolina, Oregon, Texas, Vermont, Washington, Wisconsin) have a guideline for at least one PFAS in at least one environmental medium.[17]

State guidelines specified in ECOS' survey have been incorporated into the ITRC's **Sections 4 and 5 Tables** in its PFAS regulations fact sheet. The tables define to which environmental medium each standard applies, as well as whether the values are promulgated or advisory. States may have slightly different definitions of each medium. For example, most states consider drinking water standards to be finished water from the PWSs, but a state may also include groundwater used as drinking water from a private residential well or similar source. ECOS compiled responses based on how the state categorized each medium in the survey and how it defines it generally for the public. For more detailed state-specific definitions, see **state PFAS websites**.

Of the states that responded to ECOS' survey, the following have different types of guidelines:

Regulatory Standards

- Drinking Water[18]: *Seven states (Massachusetts, Michigan, New Hampshire, New Jersey, New York, Vermont, Washington [proposed])*
- Groundwater: *10 states (Alaska, Colorado, Massachusetts, Michigan, New Hampshire, New Jersey, New Mexico, North Carolina, Texas, Vermont)*
- Surface Water: *Three states (Michigan, Minnesota [site-specific criteria], New Mexico)*
- Soil: *Eight states (Alaska, Massachusetts, Michigan, New Hampshire, New Mexico, Texas, Vermont, Wisconsin)*
- Air: *Three states (Michigan, New Hampshire, Washington)*
- Other: *California* added PFOA and PFOS as developmental toxicants to the Proposition 65 list of chemicals known to cause cancer or reproductive toxicity; *Washington* has regulatory standards for PFAS as halogenated organic compounds in state designated hazardous waste, for PFOA and PFOS in children's products, and

[17] These include promulgated rules and advisories (e.g., action and notification levels, cleanup target levels, initiation levels), and may be determined by the state or may be consistent with EPA's LHA of 70 ppt.
[18] See States with a Final or Proposed MCL (Drinking Water Only) designation below.

regulatory requirements for PFAS in Class B firefighting foams, certain consumer products, and certain food packaging

Advisory Guidelines

- Drinking Water: *Ten states (Alaska, California, Connecticut, Hawaii, Indiana, Maine, Minnesota, North Carolina, Vermont, Wisconsin)*
- Groundwater: *Nine states (California, Colorado, Connecticut, Florida, Hawaii, Illinois, Minnesota, New York, Wisconsin)*
- Surface Water: *Four states (Colorado, Florida, Hawaii, Oregon [wastewater])*
- Soil: *Eight states (California, Connecticut, Florida, Hawaii, Indiana, Maine, Minnesota, New York)*
- Air: *One state (Texas)*
- Water Interface: *One state (Alaska)*
- Fish or Wildlife Consumption Advisories[19]: *Eleven states (California [seafood], Connecticut, Hawaii [in process], Maine [fish, beef, and milk], Michigan [fish and deer], Minnesota, New Hampshire, New Jersey, New York, Washington [in process], Wisconsin [fish and deer])*

States with a Final or Proposed MCL (Drinking Water Only)

- *Massachusetts* (Enacted for six PFAS, Individually and summed)
- *Michigan* (Enacted for seven PFAS, individually)
- *New Hampshire* (Enacted for four PFAS, individually)
- *New Jersey* (Enacted for PFOA, PFOS, and PFNA, individually)
- *New York* (Enacted for PFOA and PFOS, individually)
- *Vermont* (Enacted for five PFAS, individually and summed)
- *Wisconsin* (In process for PFOA and PFOS)

Grouping PFAS

Recently proposed congressional legislation suggested creating a federal MCL for a sum of total PFAS, derived by adding the concentration of each PFAS detected in a sample. This total PFAS concentration depends on which analytical methods are used, as different analytical methods detect different suites of PFAS and have different reporting levels. Given that there are nearly 5,000 PFAS, most of which have little known information about their toxicities, many regulators and subject-matter experts advise against grouping PFAS as an entire class. Some states regulate PFOA, PFOS, and/or other PFAS, individually. Other state guidelines are based on the total concentration of PFOA and PFOS, as the EPA does in its LHA, or on the total concentration of PFOA, PFOS, and several additional long-chain PFAS.

States' approaches for grouping PFAS, and the reasoning provided for grouping PFAS under each method, are as follows:

Individual PFAS

- *18 states*
    - *Alaska*: Soil and groundwater cleanup levels for PFOA, PFOS

[19] Advisories apply to fish only, unless otherwise noted.

- *California*: Non-regulatory notification levels and response levels for PFOA, PFOS, and PFBS in drinking water; Non-regulatory environmental screening levels for PFOA, PFOS in soil, groundwater, aquatic habitat, terrestrial habitat, and leaching to groundwater
- *Florida:* Provisional Soil Cleanup Target Levels for PFOA, PFOS; Provisional Irrigation Water Screening Levels for PFOA, PFOS; Surface Water Screening Levels for fish consumption for PFOA, PFOS
- *Hawaii:* Action levels for PFOA, PFOS, PFNA, PFBS, PFHxS, PFHpS, PFDS, PFBA, PFPeA, PFHxA, PFHpA, PFDA, PFUnDA, PFDoDA, PFTrDA, PFTeDA, PFOSA, HFPO-DA in drinking water, groundwater, surface water, soil
- *Illinois:* Advisory levels for PFOA, PFOS, PFNA, PFBS, PFHxS in groundwater
- *Indiana:* Guidance Remediation Screening Levels for PFBS in drinking water, soil
- *Maine:* Screening levels used as remedial action guidelines for PFOA, PFOS, and PFBS in soil, milk, beef, and fish
- *Michigan*: MCLs for 7 PFAS (PFOA, PFOS, PFNA, PFHxA, PFHxS, PFBS, HFPO-DA); Surface Water Quality Standards for PFOA, PFOS; Groundwater cleanup criteria for PFOA, PFOS (and proposed for PFNA, PFHxA, PFHxS, PFBS, HFPO-DA); Soil criteria for PFOA, PFOS; Consumption advisories for PFOS in fish and deer tissue; Initial Threshold Screening Levels (ITSLs) for PFOA, PFOS, 6:2 fluorotelomer sulfonate (FTS)
- *Minnesota:* Promulgated Health Risk Limits (HRLs) for PFOA, PFOS, PFBA, PFBS in groundwater[20]; Health-Based Values (HBVs) for PFOS, PFBS, PFHxS in groundwater; Rule-based Intervention Limits for PFOA, PFOS, PFBA, PFBS to protect surface water and groundwater at solid waste facilities; Soil Reference Values for PFOA, PFOS, PFBS, PFBA, PFHxS; Site-Specific Criteria for PFOA, PFOS in surface water; Fish Consumption Advice for PFOS
- *New Hampshire:* MCLs and Ambient Groundwater Quality Standards for PFOA, PFOS, PFHxS, PFNA; Soil contact value for PFOA, PFOS, PFHxS, PFNA for evaluating sites; Ambient air limit for APFO
- *New Jersey:* MCLs and Ground Water Quality Standards for PFOA, PFOS, and PFNA; Fish Consumption Advisories for PFOS in some waterbodies
- *New Mexico:* Groundwater and surface water standards for PFOA, PFOS, PFHxS; soil and tap water screening levels for PFOA, PFOS, PFHxS
- *New York:* MCLs and groundwater, soil, and fish advisories for PFOA, PFOS
- *North Carolina:* Groundwater Interim Maximum Allowable Concentration for PFOA[21]; Non-Regulatory Drinking Water Health Goal for HPFO-DA (GenX)
- *Oregon:* Initiation levels for PFOA, PFOS, PFNA, PFHpA, PFOSA in municipal wastewater effluent
- *Texas:* Health-Based Non-Carcinogenic Toxicity Factors and Cleanup Values for 16 PFAS (including PFOA and PFOS) in soil and groundwater; interim short- and long-term Effects Screening Levels (ESLs) for PFOA, PFOS in air permitting
- *Washington:* Draft action levels for PFOA, PFOS, PFNA, PFHxS, PFBS in drinking water; Fish Consumption Advisory for PFOS; Chrome electroplating PFOS National Emission Standards for Hazardous Air; Regulatory standards for PFOA, PFOS in children's products under the Children's Safe Products Act
- *Wisconsin:* Proposed enforcement standards for 12 PFAS in groundwater; proposed standards for PFOA, PFOS in surface water; Residual Contaminant Levels (RCLs) for PFOA, PFOS, PFBS in Soil, based upon the EPA Regional Screening Levels (RSLs) web calculator; Fish consumption advisories for PFOS in some waterbodies

[20] Minnesota's Health Risk Limits and Health-Based Values for groundwater are also used as guidance values for drinking water.
[21] As of February 2021, North Carolina has proposed groundwater standards for the sum of PFOA and PFOS. If adopted, the groundwater standard(s) will eliminate the current groundwater interim maximum allowable concentration.

- Reasoning:
    - Risk assessors evaluate PFAS analytes individually in the regulatory determination process. Regulations are therefore based on conclusions that human health effects, analytical limitations, and removal of drinking water contaminants vary among PFAS.
    - Regulations vary based on the presence of PFAS in a state, availability of chemical guidelines used for testing, and ability of available labs to test for and measure that analyte. States with more limited contamination potential and evaluations of health effects may be waiting to see whether the EPA develops a technical basis for grouping PFAS before summing or regulating additional analytes.
    - Toxicologists have more data on the perfluoroalkyl acids (carboxylates and sulfonates) that are result of the terminal degradation process of PFAS precursors, and less on the PFAS precursors in the same family.
    - Toxicological studies demonstrate differences in the potency and bioaccumulation (i.e., physiological half-lives) among individual PFAS.

PFOA & PFOS, Summed

- *Seven states*
    - *Alaska*: Drinking water action level for PFOA and PFOS
    - *Colorado*: Site-specific groundwater standard for PFOA and PFOS
    - *Connecticut*: Fish tissue consumption criteria for PFOA and PFOS
    - *Florida*: Provisional Groundwater Cleanup Target Level for PFOA and PFOS, individually or combined
    - *New Mexico:* Groundwater standard for PFOA and PFOS; surface water screening level for PFOA and PFOS implemented through CWA Section 401 conditional certification of NPDES permit
    - *North Carolina:* Proposed groundwater standards for PFOA and PFOS
    - *Wisconsin*: Recommended groundwater enforcement standard and recommended groundwater preventive action limit for PFOA and PFOS (individual and summed)[22]

- Reasoning:
    - Regulating PFOA and PFOS aligns with the EPA's LHA. While the EPA has developed draft toxicity factors for a few other PFAS, PFOA and PFOS remain the only analytes with federal health advisories.
    - Regulating PFOA and PFOS together can streamline processes given their similar characteristics and known toxicities. PFOA and PFOS are the most thoroughly studied of the long-chain PFAS, with a large quantity of publicly available toxicity information available, and are considered hazardous substances or listed as a similar toxicant under some states' laws.

More than 2 PFAS, Summed

- *Nine states*
    - *Colorado:* Policy interpreting narrative water quality standards for PFAS sums PFAS constituents based on endpoint toxicity (e.g., PFOA, PFOS, PFNA, and any identified parents are added together based on developmental toxicity; PFHxS and any identified parents are added together based on endocrine toxicity; PFBS and any identified parents are added together based on renal toxicity)

[22] This may eventually be superseded by a recommended combined enforcement standard for PFOA, PFOS, and four precursors.

- *Connecticut:* Advisory drinking water action levels, groundwater protection criteria, groundwater pollutant mobility criteria (soil leaching to groundwater), and soil direct exposure criteria for the sum of 5 PFAS (PFOA, PFOS, PFNA, PFHxS, PFHpA)
- *Maine:* Screening levels used as remedial action guidelines for the sum of 5 PFAS (PFOA, PFOS, PFHxS, PFHpA, PFNA)
- *Massachusetts:* MCL and groundwater cleanup standard for the sum of 6 PFAS (PFOA, PFOS, PFNA, PFHpA, PFHxS, PFDA)
- *Minnesota*: MN's **Health Risk Limits Rules for Groundwater** require evaluation of exposure to multiple contaminants in groundwater. Hazard ratios are summed across contaminants that affect the same health endpoints. For example, PFOA, PFOS, PFHxS, and PFBA all affect the liver and there are hazard ratios for each of these contaminants and would therefore be added together to calculate a multiple contaminant health risk index.
- *New Mexico:* Narrative groundwater standard implemented through risk assessment guidance that provides for summation of PFOS, PFOA, PFHxS
- *Vermont:* MCL and promulgated groundwater standard for the sum of 5 PFAS (PFOA, PFOS, PFNA, PFHpA, PFHxS)
- *Washington:* Regulatory standard for the sum of all PFAS in state-designated hazardous waste when halogenated organic compounds are present; Regulatory standards for the sum of all PFAS in certain consumer products (i.e., carpeting and upholstery treated with PFAS, aftermarket treatments for carpeting and upholstery) under the Safer Products for Washington Act, Class B firefighting foams, and certain food packaging.
- *Wisconsin:* Proposed groundwater enforcement standard for the sum of PFOA, PFOS, and four of their precursors (FOSA, NEtFOSA, NEtFOSAA, and NEtFOSE)

- Reasoning: Many of the summed PFAS analytes are similar as indicated below:

  - They are long-chain compounds with similar chemical structures (+/- two carbons in chain length) to PFOA and PFOS.
  - They are often found together in the environment and have characteristically similar bioaccumulative patterns and fate and transport mechanisms.
  - Human exposures to these PFAS often are correlated, making it difficult to differentiate the contributions of the individual PFAS to health effects observed in humans.
  - Their toxicity is assumed to be additive based on a substantial body of publicly available data indicating that they cause similar toxicological effects, have long serum half-lives in humans (long-chain PFAS only), and are associated with similar health effects in humans.[23]
  - They have similar limits for lab detection via EPA Method 537.1 (see Analytical Methods on page 21), and there is a minimal cost difference between analyzing a few or 18 compounds, so regulating and requiring testing for more analytes does not increase the cost and lessens the potential for the need to resample in the future.
  - PFOA, PFOS, PFNA, PFHxS, PFHpA, and PFBS were the six PFAS included in the EPA's third round of the Unregulated Contaminant Monitoring Rule (UCMR3). These PFAS have been researched to the extent that they are regulated individually by some states. PFHpA has minimal toxicity data available and PFDA was not included in UCMR3, but some states regulate both of these PFAS with the other long-chain PFAS based on close structural similarity and their inclusion as analytes in the EPA's analytical methods for drinking water.

[23] On the other hand, though similar, these PFAS do still present differences (e.g., different levels at which toxicity occurs, different toxicological effects and modes of action) that a state might acknowledge as a reason *not* to group the chemicals, but rather to regulate them individually.

- Regulating more analytes can provide information on conceptual site model development and the potential for PFAS fingerprinting (forensics on the fate and transport of chemicals over time).

Evaluating Differences among States' PFAS Guidelines

One of the most common questions that states are asked to address when communicating risks to the public and co-regulators is why guidelines vary from state-to-state. Many of the states' derived values typically differ within a factor of two to three, indicating that they are similarly protective; however, this is difficult to communicate with audiences who lack a background in the scientific and regulatory basis for the guidelines. Consequently, communicating the rationale for varying guidelines among state and federal entities remains a challenge.

States report that deviations among PFAS guidelines are driven by several main factors:

- Differences in professional judgments regarding the choice of the critical study and endpoint, the method for animal-to-human extrapolation, the uncertainty factors, and exposure parameters such as the Relative Source Contribution. Differences in any one of these choices (described in more detail in the State Trends for the Basis of Guidelines section on page 14) will result in different numerical values for the PFAS standard being developed.[24]
- Differences in timing. *When* guidelines are developed and *when* a state looks at the available scientific information affects *what* the guidelines are. While many technically sound guidelines have been developed from older studies, toxicologists continue to conduct new PFAS research that will provide states with more referential data for deriving values. In this fast-paced field, short timeframes can change what studies relevant to PFAS standard development are available.
- Differences in state legislative or rulemaking requirements. The next section of this paper will explore differences in legislative procedures, but it should also be noted that beyond legislatures, state environmental and health agency programs (e.g., drinking water, surface water, and wastewater) have varying priorities or responsibilities in the standard-setting process.
- Differences in state regulatory processes and histories. States have different histories of developing standard methods, enacting regulations, and setting policy, all of which may direct toxicologists to use specific approaches and require protection of certain human life stages/vulnerable populations or other factors. *Minnesota*, for example, is required to evaluate risks to pregnant women and children in its exposure assumptions. *Washington* chose to regulate PFAS as a class in certain consumer products under the Toxic Pollution law, Class B firefighting foams under the Firefighting Agents and Equipment – Toxic Chemical Use law, and certain food packaging under the Packages Containing Metals and Toxics Chemicals law. These factors, coupled with how well a state's standard-setting methods reflect current and evolving science, can greatly affect how guidelines are calculated and what the resulting values are.

Section I. Legislative Considerations

Rulemaking Capacities

ECOS asked states to describe what authorities and processes they had to set PFAS guidelines. Responses indicate that most state guidelines are adopted/enacted through general rulemaking processes outlined in state administrative policies or acts, while some states have bills or statutes specifically targeted to PFAS. For example, the *California* Department of Toxic Substances Control's Safer Consumer Products Program lists PFAS as Candidate

[24] An August 2020 **critical review** published in the Society of Environmental Toxicology and Chemistry's online journal discusses some of the toxicity and exposure considerations that lead to similarities and differences among state and federal guidelines.

Chemicals and evaluates PFAS in consumer products like carpets in accordance with its Safer Consumer Products Regulations. The California Department of Resources Recycling and Recovery is also adopting regulations that will establish a threshold of 100 ppm PFAS, as measured by total fluorine, in food service packaging used by certain food service facilities, and California legislation amended the state Health and Safety Code to prohibit AFFF beginning January 1, 2022; ban AFFF training classes; restrict unused foam disposal; and track sales of and require notice of PFAS in personal protective equipment. Since 1997, *New Hampshire's* state air toxics regulation has contained annual and 24-hour inhalation standards for APFO, the ammonium salt of PFOA. Additionally, New Hampshire is required by state statute to write rules and require the installation of best available control technology for PFAS and PFAS precursor compound air emissions that may have contributed to ambient groundwater or surface water quality standards. Several states described their active PFAS bills prohibiting AFFF for firefighting, regulating food packaging, and requiring PFAS sampling, among other actions. States active in PFAS regulation are typically backed by their legislators, Attorneys General, and other leadership entities that provide funding and direct the environmental agencies to take action on contamination. Such actions include forming task forces for improved coordination (see Intra-State PFAS Collaboration on page 16), setting guidelines in different media by certain dates (e.g., *Vermont*), or initiating directives or lawsuits against PFAS manufacturers or the DOD (e.g., *Minnesota, New Jersey, New Mexico*).

Enforcement of state regulations is typically a programmatic issue based on the contaminated medium and is conducted in accordance with rules or policies in effect for each regulatory program (e.g., Superfund and hazardous waste, Resource Conservation and Recovery Act [RCRA], SDWA). Consequently, enforcement efforts for PFAS in drinking water, groundwater, surface water, solid waste, biosolids, and other environmental media are led by the state agency with authority to administer the applicable rules, and would be conducted as directed by program rules, unless specific rules for PFAS have been adopted. A couple states indicated that they may rely on the state Attorney General for broader authorities or look to primacy agreements from the EPA. Enforcement may occur if a regulatory standard is exceeded, the contamination is considered hazardous, or there is a requirement for assessment and remediation. Some states noted that PFAS enforcement is a challenge without having adequate toxicity data necessary to establish the criteria on which a permit limit or enforcement/remediation action is based.

Regulating PFAS as Hazardous

16 states (Alaska, Connecticut, Florida, Hawaii, Illinois, Indiana, Maine, Massachusetts, Minnesota, New Hampshire, New Mexico, New York, Vermont, Washington, Wisconsin, and Wyoming) noted that they have emergency rulemaking powers that can be invoked in the event of a PFAS contamination event or if a specific PFAS is declared hazardous at the federal level.

Several states also regulate PFAS as hazardous under certain conditions. For example, *Alaska* includes PFOA and PFOS in a list of hazardous substances for which groundwater and soil cleanup levels are set. *New Jersey* added PFNA to the NJ Hazardous Substance List in 2018, and added PFOA and PFOS to the list in 2020. *New York* regulates PFOA and PFOS as hazardous substances under 6 NYCRR Part 597. Although *New Mexico* cannot adopt rules more stringent than the federal government under its Hazardous Waste Act, it can include PFAS in RCRA corrective action permits and take action in response to a PFAS contamination event of which the quantity, concentration, or other characteristics of the waste threaten human health or the environment. The *Washington* Department of Ecology's Toxics Cleanup Program and the Washington Attorney General's Office concluded that PFAS are hazardous substances under the state's Model Toxics Control Act, a conclusion they will formally announce in 2021.

In its PFAS Action Plan, the EPA outlined its intent to explore hazardous substance definitions for PFOA and PFOS. Similarly, Congress recently considered a number of PFAS issues in its National Defense Authorization Act (NDAA),

including a bill seeking to designate all PFAS as hazardous substances under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). While these provisions were ultimately removed from NDAA for Fiscal Year 2020 (**Senate Bill 1790**, which became law on December 20, 2019), several lawmakers stressed their intent to reconsider it in future rules. In January 2021, the EPA announced an Advance Notice of Proposed Rulemaking for public comment on whether PFOA, PFOS, and/or other PFAS should be designated as CERCLA hazardous substances and/or subject to regulation as hazardous waste under RCRA; however, the new Administration withdrew this activity pending further consideration and it has not yet been posted.

Declaring PFAS (just PFOA and PFOS, or additional analytes) as hazardous under CERCLA would have some, though likely different, impacts on states. *North Carolina* notes that the declaration may provide more information to its rulemaking body, although its environmental agency is unsure if it will speed up the water quality criteria adoption process. Other states note that empowering them to act using existing regulatory CERCLA mechanisms allows for an expedited cleanup process and prevents draining already-strained funds for site investigation and characterization. Kansas said this definition is what it needs to regulate PFAS, as the state's definition of a hazardous substance is based on its inclusion as a CERCLA hazardous substance.

Intra-State PFAS Collaboration

States have varying procedures for designating who regulates PFAS. Many state environmental agencies are coordinating with their health, agriculture, and other state agency counterparts on the state's PFAS response. For example, the *Michigan* PFAS Action Response Team (MPART) was created in 2017 through an executive directive to investigate sources and locations of PFAS and protect drinking water and public health. In 2019, MPART was signed into an executive order as an enduring advisory body of seven state agencies, led by the Michigan Department of Environment, Great Lakes, and Energy. Other states (e.g., *Colorado, Connecticut, Hawaii, Illinois, Maine, Massachusetts, Minnesota, New Mexico, New York, North Carolina, Ohio, Oregon, Pennsylvania, and Wisconsin*) have formed similar task forces and action teams charged with recommending PFAS guidelines and/or conducting other statewide PFAS efforts.

Impacts of Federal Legislative Uncertainty

ECOS asked states that have already established guidelines how they think a federal MCL (as currently being considered by the EPA) or similarly enforceable federal PFAS standard would impact their regulations. A state may be required to modify its guidelines to be "no more stringent than" federal requirements, or a state may be required to "strengthen" its guidelines so that they are as protective as federal standards. *North Carolina* noted that a federal MCL could affect its groundwater programs, and another state noted its concern that a federal MCL may or may not adequately address protection for all populations and impacted communities because MCLs are not strictly risk-based. Numerous states with advisory guidelines expressed their preference for the EPA to have the primary role in setting MCLs, which they argue will facilitate a unified approach to mitigating PFAS contamination in drinking water supplies. These states recognize, however, the timeline associated with setting a nationwide standard and expressed their intentions to move forward with statewide MCLs given the EPA's inaction. Should the EPA enact an enforceable drinking water standard, some states may need to make challenging management decisions regarding how to adjust their existing guidelines and PFAS response efforts.

In the interim, states are pursuing other federal and congressional legislative actions that might make PFAS remediation and regulation more consistent nationwide. In October 2020, a coalition of 20 attorneys general sent a letter to Congress outlining states' PFAS-related priorities for the fiscal year 2021 NDAA. In addition to again encouraging Congress to designate PFAS as hazardous substances under CERCLA, states argued for DOD to meet or exceed the PFOA and/or PFOS standards established in the state in which the military installation is located when

those standards are more stringent than federal standards or health advisory levels. These provisions were not included in the final NDAA bill.

Section II. Risk Assessment

State environmental and public health agencies use quantitative risk assessment to develop health-based criteria for PFAS guidelines. The processes for evaluating exposure and developing these criteria are described across several guidance documents produced by the EPA.[25]

At its core, risk assessment is used to develop the human health basis for guidance values or standards by considering the following:

$$\boldsymbol{Toxicity} \times \boldsymbol{Exposure} = \boldsymbol{Risk}$$

Risk is a function of the toxicity of a chemical and a person's exposure to that chemical. The higher one's exposure, the greater the risk; similarly, the more toxic a chemical is, the more risk there is at the same level of exposure. Both variables are fundamental to the resulting calculation of risk.

As described in more detail below, differences among state PFAS guidelines may arise from differences in toxicity factors, which include Reference Doses (RfDs) for non-cancer effects and Cancer Slope Factors (CSFs) for carcinogenic effects. These toxicity factors are developed based on animal toxicology and/or human epidemiology studies. Choices in the scientific study and toxicity endpoint used, as well as choices made in developing an RfD or CSF from the selected study and endpoint, will result in differences in the numerical values of these toxicity factors.

Different guidelines may also result from variations in exposure factors, which include parameters relating to daily water ingestion, body weight of an individual, duration of exposure, and fraction of total exposure from the medium of concern (e.g., drinking water). As with toxicity factors, state agencies use evidence-based methods to characterize exposure factors.

Scientific Considerations, Professional Judgment, & Peer Review

In general, states prefer to use peer-reviewed, publicly available toxicity studies that meet risk assessment criteria (e.g., study duration, route of exposure) as the basis for their guidelines. In some cases, states will consider non-peer reviewed reports (e.g., contract lab reports or National Toxicology Program data). Regulators review studies to ensure that they were properly conducted and reported, and consider a study's results coupled with its relevance, degree of rigor, and importance to the question on hand. Some states routinely develop their own guidelines for chemicals of interest to their state; however, if the EPA completes this process first, states can review the agency's conclusions and decide whether to use them, saving the state the effort of doing this on its own. When EPA values are not available, some states refer to ATSDR's provisional MRLs (as they would RfDs) or use health-protective values from other agencies like the American Conference of Governmental Industrial Hygienists (ACGIH).

Toxicity Criteria & Methodology

Regulatory agencies may rely on a chemical-by-chemical approach or grouping approaches for developing PFAS toxicity criteria (e.g., RfDs for non-carcinogens and CSFs for carcinogens). Most states conducting their own

[25] Examples of these EPA guidance documents include the Risk Assessment Guidelines, Water Quality Standards Handbook, and Exposure Factors Handbook (2011).

evaluations do not rely solely on EPA or ATSDR risk assessments, for which there are only published documents supporting the EPA's LHA for PFOA and PFOS, draft toxicity documents and RfDs for PFBS and GenX chemicals, and the ATSDR's draft MRLs for PFOA, PFOS, PFHxS, and PFNA. Performing the scientific analysis needed to effectively regulate PFAS is time consuming, and regulators lack toxicological data needed to develop criteria for some PFAS detected in environmental media.

To develop health-based guidelines, agencies conduct risk assessments, which usually follow this sequence of events:

1. Review available studies (e.g., toxicological, epidemiological) to identify critical endpoints that are sensitive and relevant to humans.

   While most scientists prefer human epidemiological information as the basis for guidelines when the data are appropriate, the EPA and states have concluded that currently available human studies are not appropriate to use as the primary basis for PFAS guidelines. As such, all current federal and state PFAS guidelines are based on laboratory animal study data that are then translated.[26] For PFOA and PFOS, the EPA and some states have identified developmental effects (e.g., decreased pup body weight, thyroid effects [PFOS]; accelerated puberty; delayed ossification, delayed mammary gland development, neurobehavioral and skeletal effects [PFOA]; hepatic [liver] toxicity, immune system suppression [PFOA, PFOS]) as critical endpoints. Critical endpoints can vary from state-to-state based on scientific judgment.

2. Determine a point of departure (POD), the spot on the dose-response curve from the animal study at which toxicologists begin to apply uncertainty factors (UFs). PODs can be a No Observed Adverse Effect Level (NOAEL), Lowest Observed Adverse Effect Level (LOAEL), or Benchmark Dose (lower confidence limit; BMDL). BMDL is the preferred POD when available, as it is less dependent on dose selection and sample size.

   Toxicologists typically adjust the POD to account for the much slower excretion rate of PFAS in humans than animals (i.e., calculating human equivalent doses [HEDs] that will result in an equivalent internal dose [serum level] at the POD in animal studies). This dosimetric adjustment can be performed using estimated human clearance values, or the ratio of estimated serum half-lives in humans and animals.[27]

3. Apply UFs to the HED to determine the RfD, an estimate of the daily oral dose at which humans are expected to be without risk from repeated[28] exposure to a chemical, including PFAS. An RfD is expressed as mass of chemical per day on a body weight basis ($mg_{chemical}/kg_{body\ weight}$/day).

   Toxicologists apply UFs of 3 (i.e., the square root of 10, which rounds to 3 if a single such factor is applied; if two such factors are applied, the value equals 10), or 10 to reflect uncertainties associated with the data used.

[26] This may not be true internationally, as the European Food Safety Authority has used **epidemiological studies** to develop acceptable intake rates of PFOA, PFOS, PFNA, and PFHxS in humans.

[27] The dosimetric adjustment is used to determine the human serum PFAS level expected from a given external (oral) dose, and is how toxicologists account for PFAS bioaccumulation in risk assessment. It can be applied to the POD to develop the HED as described, or applied to the ratio of the POD and Total UFs as shown in the RfD equation below. Both methods are mathematically equivalent and the order of operations does not affect the final result.

[28] The length of exposure to which the toxicity factor is intended to apply can vary depending on the chemical and regulatory agency. For example, in its draft toxicity values for **PFBS and GenX chemicals**, the EPA characterizes exposure over a lifetime (chronic RfD) or less (subchronic RfD). For the EPA's LHA for **PFOA and PFOS**, the RfD is defined by a lifetime of exposure and is intended to apply to short-tem (weeks to months) exposure. The ATSDR uses the term MRL instead of RfD to describe the daily dose of a chemical that is not expected to pose a risk to human health. Its PFAS **MRLs** are derived for intermediate (14-364 days) exposure.

Uncertainties include potentially higher sensitivity of some people (intraspecies), extrapolation from animals to humans (interspecies), shorter duration of exposure than the intended timeframe for the RfD in the study used, use of a LOAEL as the POD, and gaps (i.e., potentially more sensitive effects that have not been studied) in the toxicological database. The UFs are applied selectively for each chemical as appropriate for the toxicity data being used as the basis for the RfD.

Toxicologists multiply the UFs together to obtain the total UF, and then divide the selected (NOAEL, LOAEL, or BMDL) POD (or as adjusted, the HED) by the total UF. A dosimetric adjustment is then performed to determine the RfD (as shown in the equation below).[29]

$$\frac{\boldsymbol{POD}}{\boldsymbol{Total\ UFs}} \times \boldsymbol{dosimetric\ adjustment\ factor} = \boldsymbol{RfD}$$

4. Combine the RfD with selected exposure parameters to establish a concentration (i.e., standard or guidance value) for PFAS in a specific medium (e.g., drinking water) that is intended to be protective of human health. Exposure assumptions vary among states and can result in different guidelines despite similar RfDs.

   Some states select exposure parameters for subgroups such as pregnant women or children if they are more sensitive for the toxicological effect of concern. Exposure parameters for health-based guidelines include the exposure rate (e.g., amount of drinking water, fish, or soil assumed to be ingested each day) and representative body weights for the target population. For drinking water guidelines (and groundwater guidelines based on drinking water exposure parameters), states consider the Relative Source Contribution (RSC), which is the percentage of the RfD allocated or allowed to come from drinking water. The default value for the RSC is 20 percent, but states can use chemical specific values from 20 to 80 percent if available data support them. For example, the EPA's LHA allows drinking water to contribute only 20 percent of the RfD and other sources can contribute 80 percent, so the RSC is 20 percent. Furthermore, scientists are still learning about PFAS sources and extents/impacts of exposure levels; as such, states' assumptions about the RSC may change in the future and affect PFAS guidelines.

State Trends on the Basis of Guidelines

ECOS examined states' calculations and factors applied to oral routes of exposure to PFAS that contributed to their standard setting processes.

Appendices A-F of this report include tables of state toxicological information and exposure assumptions for setting guidelines in drinking water, groundwater, surface water, soil, air, and fish and wildlife. Some of the trends in the data are summarized below:

Critical Studies and Endpoints: This is a critical first step in the process, as it indicates the most sensitive health effect identified for which toxicologists are protecting (e.g., fetal/infant growth delays, thyroid dysfunction, infertility, alterations in liver function, and/or impaired immune function). *Eight states* indicated that they use the EPA's preferred critical studies (e.g., Lau et al. [2006] for the PFOA LHA and Luebker et al. [2005] for the PFOS LHA) and pharmacokinetic model for developing a toxicity factor (i.e., modeled average animal serum levels at the POD). *Twelve states* use a variety of critical studies and endpoints based on which PFAS they are evaluating. As discussed in the Human-to-Animal Extrapolation Methods section on page 16, state approaches may differ from the EPA

[29] As stated in Footnote 27, the dosimetric adjustment can alternatively be made on the POD to determine a HED, to which the UFs are applied, yielding the same result for the calculated RfD.

methodology in that the POD is based on serum PFAS levels measured at the end of the animal study rather than serum levels predicted using the EPA pharmacokinetic model.

Points of Departure: The choice of POD depends on the dose response data for the critical endpoint being used as the basis for risk assessment. As previously mentioned, BMDL is the preferred POD when available as it is less dependent on the dose selection and sample size than the NOAEL or LOAEL. If a BMDL cannot be derived, the NOAEL is preferred. If there is no NOAEL in the study (i.e., effects occur at all doses), the LOAEL is used. *Seven states* and the EPA use the LOAEL and NOAEL PODs for PFOA and PFOS in drinking water. Other states indicated that they use a combination of PODs depending on which PFAS they are examining, with LOAEL the most commonly used for PFOA and NOAEL the most commonly used for PFOS. *Five states* reported using a BMDL for various PFAS in drinking water.

Uncertainty Factors: States use a variety of combinations for UFs that differ based on the study used. Some states reported applying a total UF of 300 for PFOA (with a UF of 3 for interspecies; 10 for intraspecies; and other UFs for extrapolation from LOAEL to NOAEL, database limitations, duration of exposure [i.e., subchronic to chronic extrapolation], and/or sensitive developmental endpoints), and a total UF of 30 (with a UF of 3 for interspecies and 10 for intraspecies) for PFOS. Some states have applied higher UFs depending on their interpretations of the relevant scientific data. UFs selected for other PFAS compounds vary.

Exposure Parameters:

- ***Populations at Risk***: States including *Michigan, Minnesota, and New Hampshire* use Minnesota's model (Goeden et al. [2019]) to predict fetal and infant exposure from transplacental transfer, breastmilk, and prepared formula. This model applies the upper-percentile age-adjusted drinking water ingestion rates in the 95th percentile for pregnant women and formula-fed infants, and the upper-percentile ingestion rate for breast-fed infants. Other states account for populations that may be at increased risk by considering their higher intake rates, with infants and lactating women consuming more than typical adults when adjusted for body weight. Examples include, but are not limited to, a 0-1 year old body weight-adjusted drinking water intake rate of 0.175 L/kg/day *(Vermont)*, a 10 kg body weight adjusted drinking water intake rate of 0.1 L/kg/day *(Wisconsin)*, or a lifetime average drinking water intake rate of 0.053 L/kg/day that accounts for increased water consumption relative to body weight at young ages *(California)*, as compared to the default adult water consumption rate (0.029 L/kg/day) *(New Jersey)*. The EPA's LHA assumed the drinking water ingestion rate of the 90th percentile of lactating women to be 0.053 L/kg/day. Several states look at fish consumption rates as well when developing surface water quality criteria and fish consumption advisories; these advisories are more stringent for high risk populations (e.g., infants, children, pregnant and lactating women, women of childbearing age) in some states (e.g., *Connecticut, New Jersey*). Overall, target populations and RSCs differed among states, even if those states used the same critical endpoint or a similar RfD. The different exposure parameters resulted in different final guidelines.[30]

- ***Relative Source Contribution***: *Eleven states* reported using the default value for the RSC of 20 percent (as the EPA does in its LHAs for PFOA and PFOS) for various PFAS in drinking water, indicating that they allow 20 percent of the RfD to come from drinking water and 80 percent to come from other sources of exposure. *Three states* use a chemical-specific RSC of 50 percent in drinking water. No states reported using a less conservative RSC of 80 percent, which would allow 80 percent of the RfD to come from drinking water, allocating only 20 percent to exposure to all other sources like diet or consumer products. While *Wisconsin* uses an RSC of 80 percent in surface water, both *Alaska and Wisconsin* do not use an RSC (i.e., an RSC of 100 percent) in

[30] Some states develop groundwater standards based on the assumption that groundwater is used as drinking water, so the ingestion rates/exposure assumptions used for drinking water standards are applied to the groundwater standards.

groundwater; at that guideline, exposures from other sources would raise the intake above the RfD. Several states reported that the **EPA Decision Tree** (2000) is helpful in establishing an RSC.

Human Epidemiological Data: *Eleven states (California, Connecticut, Florida, Hawaii, Illinois, Massachusetts, Michigan, New Hampshire, New Jersey, North Carolina, Wisconsin)* reported considering both animal and human epidemiological data to support their selections of critical endpoints from animal toxicity studies and guide their risk assessments.[31]

Human-to-Animal Extrapolation Methods: Human toxicity values for PFAS are primarily based on laboratory animal studies and rely on various approaches to account for the much longer half-lives in humans than in animals. Toxicologists consider the interspecies half-life difference in most PFAS risk assessments because the same daily dose of a PFAS results in a higher internal dose (blood serum PFAS level) in humans because of their slower excretion rate. In general, the serum PFAS levels from animal studies are converted to HEDs by applying a chemical-specific clearance factor (based on human half-life and volume of distribution) that relates serum levels to human-administered doses. The interspecies UF is reduced from the default value of 10 to 3 when these approaches are used since interspecies pharmacokinetic differences have already been accounted for.

Seven states (Alaska, Colorado, Connecticut, Maine, Massachusetts, Vermont, Wisconsin) reported using the EPA approach (used in its derivation of the LHA for PFOA and PFOS), which estimates the HED using modeled serum concentrations at the POD in the animal study as the internal dose metric. A few other states, including *New Jersey, New Hampshire, and California*, use measured serum concentrations at the end of the dosing period in the animal study as the POD.

Carcinogenicity: *14 states (Alaska, California, Connecticut, Florida, Hawaii, Illinois, Indiana, Massachusetts, Minnesota, New Hampshire, New Jersey, North Carolina, Vermont, Wisconsin)* reported that they consider carcinogenicity as well as non-cancer endpoints in their evaluations. *Nine of those states (Alaska, California, Connecticut, Florida, Hawaii, Illinois, New Jersey, Vermont, Wisconsin [PFOA only])* quantify cancer risk with a slope factor and a cancer risk level of 1 in 100,000 ($1x10^{-5}$) or 1 in 1,000,000 ($1x10^{-6}$).[32] *California* uses cancer as the critical endpoint for PFOA (pancreatic and liver cancer in male rats) and PFOS (liver cancer in male rats), as does *Illinois* for PFOA.

Section III. Risk Management

Once their toxicologists assess potential health or ecological risks, states take steps to manage those risks and protect public health. This includes analyzing PFAS samples, establishing guidelines, and addressing resource issues. This could also include deciding whether to address PFAS individually or as a group (see Grouping PFAS on page 10), deciding not to act based on their conclusions of the assessed risks, or looking at broader impacts of managing PFAS such as issuing discharge permits and availability of treatment removal technologies.

[31] As with any risk assessment, human epidemiology is considered, at a minimum, to support using an animal study. No state has relied on the human epidemiological data as the quantitative basis of an RfD derivation.

[32] Cancer risk levels used in risk assessments are policy choices that vary among states and may be specified in a state's legislation or regulation.

Analytical Methods & Limitations

States use a variety of methods to test for PFAS in different media. The most widely used are **EPA Method 537** (2009, applies to 14 PFAS in drinking water) and **EPA Method 537.1** (2018/2020, applies to 18 PFAS in drinking water). *Two states (Florida, New Hampshire)* use EPA Method 537 and *ten states (California, Hawaii, Illinois, Michigan, Minnesota, Nebraska, North Carolina, Texas, Vermont, Wisconsin)* use EPA Method 537.1 in drinking water. *Eight states (Alaska, Connecticut, Indiana, Maine, Massachusetts, New Jersey, New Mexico, New York)* reported using both.[33] EPA Method 537.1 analyzes the same 14 PFAS as EPA Method 537, which was used for analysis during UCMR3, and adds four other replacement PFAS, including HFPO-DA. Both methods are designed for drinking water with low total suspended or dissolved solids. Samples are prepared by using a solid phase extraction technique.

Some labs perform modifications to these methods such as using isotope dilution, using a weak anion exchange (WAX) solid-phase extraction (SPE) cartridge, or not evaporating samples to dryness. These changes allow labs to analyze a greater number of analytes in additional matrices and may also allow for lower reporting limits, increased recovery, or greater accuracy. For example, *nine states (Alaska, Connecticut, Indiana, Maine, New Mexico, New York, North Carolina, Texas, Vermont)* reported that they use modifications to EPA Method 537.1 for non-drinking water media.

Other methods and criteria for PFAS analysis include:

- **EPA Solid Waste (SW)-846 Method 8321**: *Washington* has used for fish tissue.
- **DEP SOP LC-001-3**: *Florida* this year moved to its own Department of Environmental Protection standard operating procedure (SOP) method for PFAS in surface water, groundwater, wastewater, soil, and other solids. The DEP SOP LC-001-3 method references the EPA method 8321 and incorporates isotope dilution mass spectrometry to report 30 PFAS analytes, whereas the EPA method does not specifically mention PFAS or isotope dilution, but allows for the addition of non-listed analytes as long as all quality control measures are achieved.
- **EPA SW-846 Method 8327:** *Florida and Illinois* use for surface water, groundwater, and wastewater. This direct injection method for non-drinking water aqueous samples was developed in 2019 for 24 target analytes, 14 of which are also found in EPA Method 537.1. While sensitivity was found in multi-laboratory validation to measure PFOA and PFOS below federal LHA levels for drinking water, this method does not yet provide low-level detection (i.e., single ng/L) and is only intended for testing of non-potable waters. The U.S. Department of Defense (DOD) published a memo stating that this method does not meet its needs to support decision-making and advises its use for screening purposes only. The EPA's Office of Resource Conservation and Recovery anticipates publishing the final version of this method and the associated aqueous sample preparation method 3512 by spring 2021.
- **EPA Method 533**: *Alaska, Hawaii, Maine,* and *Minnesota* allow labs to use this method. Published in 2019, this isotope dilution method uses a WAX SPE cartridge to improve recoveries of 25 short-chain[34] and long-chain PFAS in drinking water. The method targets 25 PFAS, including all 14 PFAS from EPA Method 537 and 11 PFAS unique to this method. Additional stable labeled isotopes are added into this method.
- **DOD Quality Systems Manual** Version 5.1 or later (i.e., 5.2, 5.3): *California, Colorado, Hawaii, Maine, and North Carolina* use for consideration as additional guidance and quality control requirements. *Washington* specifies

[33] Methods can be applied to analyze one, some, or all applicable PFAS for which the methods apply, depending on which PFAS a state considers.

[34] Short-chain PFAS are those with carbon chain lengths of 5 or lower for sulfonic acids like PFBS, and carbon chain lengths of 7 or lower for carboxylic acids like PFHxA.

that labs must use their preferred isotopic dilution method that is compliant with the DOD Quality Systems Manual PFAS criteria when analyzing groundwater, surface water, and sediments.
- Total Oxidizable Precursor (TOP) Assay: *Connecticut* uses for groundwater, surface water, AFFF, and fluorine-free foam; *Hawaii* uses for soil and groundwater; *Maine* uses for all matrices; *New York* uses for soil; *Vermont* uses for soil and groundwater; *Washington* has used for surface water and sediments.
- EPA SW-846 Method 1312, Synthetic Precipitation Leaching Procedure (SPLP): *New York* uses for soil; *Vermont* uses for soil and sludge.
- SGS Axys Analytical, SOP MLA 110: *Connecticut* uses for fish tissue; *Hawaii* uses for soil and groundwater; *Maine* uses for all matrices; *Minnesota* uses for water/effluent, soil/sediment, biosolids, and tissue; *New York* uses for biota; *Vermont* uses for sludge; *Washington* has used for surface water and sediments.
- ASTM D7979-17: *Florida* uses for surface water and sludge.
- ASTM D7968-17a: *Florida* uses for soil.
- ISO 25101: *New York* uses for drinking water.
- As long as the method meets program requirements and project objectives, some states defer to each lab's preferred methods[35]: *six states (Maine [all matrices except drinking water, requires use of isotope dilution], Minnesota [drinking water], New Jersey, New York, Wisconsin, Texas [remediation]).*

Several methods were not final when ECOS conducted the survey[36], so it is unknown if or which states may already use them:

- EPA Clean Water Act and SW-846 Isotope Dilution Methods: In collaboration with the DOD, the EPA is developing test methods for PFAS in wastewater, groundwater, surface water, leachate, soil, sediment, biosolids, and fish tissue. These methods are currently undergoing single-lab validation, and planning is underway for a multi-lab validation study. A list of PFAS are being evaluated for potential inclusion in the methods. This method has undergone single-lab validation and will now undergo validation in ten labs. If its final version is approved, this method will encompass 40 PFAS. The EPA's goal is to publish a 1600 series Clean Water Act method and SW-846 guidance methods for preparation, cleanup, and analysis using the same validation study. The methods will be similar, but Clean Water Act methods are written in a more prescriptive manner than the SW-846 guidance methods. A state noted that isotope dilution is the gold standard for quantitation and is the only method that corrects results for potential matrix effects.
- EPA Other Test Method-45: This method will be used to test for 50 specific PFAS at stationary sources, as well as identify other PFAS that may be present in the air sample, which will help improve emissions characterizations and inform the need for further testing.
- The EPA is developing a number of source emission methods for measurements from industrial and combustion/incineration sources. The EPA will apply what they learn in the source sampling (stack testing) efforts to ambient measurement techniques anticipated in 2022-2024.
- Some states and the EPA are considering validating supplemental analysis (e.g., Total Organic Fluorine (TOF) and TOP assays) to more completely characterize total PFAS in various media including consumer and industrial products.

Challenges that confound PFAS analysis include:

- There are no low-level detection methods that are applicable to most PFAS in complex media.

[35] State agencies have method performance expectations that they use to approve labs and determine whether or not the lab's own method is considered suitable by state program standards.
[36] The EPA in 2020 created a PFAS Innovative Treatment Team that is working to develop and validate new methods, many of which are expected to be completed by mid-2021.

- Sample collection and analytical interference/contamination due to the presence of PFAS in common consumer products, sampling equipment, and lab materials can create challenges concerning quality control procedures in the laboratories.
- Matrix effects can interfere with accurate PFAS quantitation, as natural biological components and coexisting chemicals are often present in environmental samples but not in the solvent standards, leading to a difference in instrument response for equal concentration standards and samples.
- There are new challenges associated with emerging PFAS. For example there is a lack of availability for analytical standards and the stable isotope-labeled internal standards, which help optimize method accuracy, for emerging PFAS. Several emerging PFAS have also been found to be diprotic (meaning the molecule contains two acid functional groups can cause varying charge states) or to be early eluting PFAS (meaning the compounds elute off of the high performance liquid chromatography columns too quickly), and many require lower mass spectrometer source temperatures and capillary voltage for ionization for optimum instrument signal and enhanced analytical accuracy. In addition, trifluoroacetic acid (TFA, a common environmental contaminant) interferes in the analysis of early eluters by suppressing the ionization of other coeluting PFAS. Lastly, several PFAS have been found to contain isomer forms (with more isomer forms present with increasing PFAS chain length), complicating analysis.
- There are financial and time constraints for existing lab methods. The Minnesota Department of Health reports that the turnaround time for their samples is 45 days and each water sample costs more than $300.
- There are different and sometimes inconsistent laboratory procedures for non-EPA approved methods. Not every state has a state lab, and some labs are government contracted or private. Each could result in different costs, time constraints, and sampling procedures. State agencies verify labs for use based on their own criteria.

ECOS recommends conferring with other states and using resources like the ITRC's **Sampling and Analytical Methods fact sheet**, or the Association of State Drinking Water Administrators' (ASDWA) **PFAS Laboratory Testing Primer** for guidance on selecting an analytical method, finding a qualified laboratory, specifying PFAS analytes and reporting limits, understanding sample collection procedures, and interpreting testing results and variability.

Establishing Guidelines

States consider the health-based criteria from risk assessment and other technical factors in the establishment of their guidelines. Some states' risk assessment approaches and conclusions have resulted in the development and adoption of PFAS guidelines that are lower than guidelines for most other contaminants. Scientific considerations that may contribute to these values include:

- PFAS cause toxicological effects at very low doses.
- Risk assessments account for the higher bioaccumulation of certain PFAS in humans than in animals. The same dose given to a human will result in a much higher blood serum level than in a lab animal.
- Low levels of certain PFAS in blood serum are associated with human health effects, and some states will consider how much a certain level in drinking water will increase blood serum PFAS levels. Even low levels of PFAS in drinking water can cause considerable increases in blood serum PFAS levels.
- As mentioned in footnote 9, the health basis for standards for other contaminants of emerging concern may be as low as those for PFAS, but the final guideline is set at the analytical quantitation levels, which may be up to several orders of magnitude higher than the health-based levels. For PFAS, analytical quantitation levels are very low, such that the final standard or guidance can be set at the health-based criterion.

Additionally, some states are required to perform a cost-benefit analysis in setting their final standards.

PFAS Resource (Cost) Issues

13 states (Alaska, California, Illinois, Indiana, Maine, Massachusetts, Michigan, New Jersey, New Mexico, New York, North Carolina, Washington, Wisconsin) have conducted, are required by a state or federal law to conduct, or plan to consider costs or conduct cost-benefit analyses to define the economic impact of establishing guidelines for certain PFAS. Some states (e.g., *New Mexico, North Carolina*) require a cost-benefit analysis as part of their administrative procedures for developing MCLs or water quality criteria, or release compliance costs through rulemaking (*New York*). Other states are not required to conduct a cost-benefit analysis prior to adopting guidelines into state regulation but plan to factor costs into decision-making. One state noted that the operations and management costs for treatment (e.g., Granular Activated Carbon [GAC]) are detrimental to its and others' budgets, especially for small public water systems that perform carbon changeouts regularly to ensure no arsenic MCL exceedances or other background factors when undergoing PFAS treatment procedures.[37]

Seven states (California, Connecticut, Maine, Michigan, Minnesota, New Jersey, New Mexico) have conducted cost estimates for some PFAS efforts. Some actions may fall under a state's normal agency programmatic activity; others require more staff and time. For example, in 2019, *Michigan* had allocated $3 million for testing its PWSs and three full-time employees (FTEs) for oversight of the testing and rulemaking, and estimated rulemaking costs to exceed $250,000. Michigan's overall costs for the investigation and response exceed $100 million since 2018. *New Mexico* estimated 2020 and 2021 drinking water sampling efforts to total $1.2 million, and the state legislature has authorized $4 million for communities in two counties to plan, design, and construct improvements to water systems with PFAS contamination. *Maine* expended approximately $0.5 million through the end of 2020 on personnel and other (mainly laboratory) expenses, not including for senior manager FTEs. The state has a significant PFAS investigation underway at several sites it notes will add significantly to this total. *New Jersey* utilizes five FTEs for PFAS standard-setting efforts. *California* has FTEs dedicated to enforcement of the regulation but does not consider FTEs for rule development in its cost estimates. In 2020, *Connecticut* estimated it needed $5 million to implement a 5-year statewide monitoring plan to study surface water and fish tissue (not including staff time); $75,000 to evaluate influent and effluent PFAS values at approximately 30 publicly-owned treatment works for 1 year; and $90,000 to support the development of a geographic information system for risk assessment of groundwater, surface water, and drinking water. A couple of states noted that PFAS has required a somewhat swift and significant rebalancing of staff member projects; for example, a state may have difficulty hiring new employees to fill the previous positions of those now assigned to work on PFAS, or a state's other projects may fall by the wayside due to the demand of this issue.

Incurred costs extend beyond regulating PFAS and should factor in: expenditures for states to initially investigate whether and to what degree there are PFAS releases or contaminated media; removal methods for contaminated media; disposal or long-term storage of AFFF; lab certification process development and equipment acquisition; chemical analysis; liabilities and legal fees; risk communication; and tracking the fate and transport of PFAS once released from an active source to the environment, requiring (re)sampling and treatment. For example, *Minnesota* is still calculating its costs (the total for past, ongoing, and potential future PFAS efforts will be estimated in its pending PFAS report), but noted that an industrial facility in the state allocated about $750,000 to retrofit its operations where PFAS were used and had contaminated a nearby waterbody. *New Jersey* estimates that the average cost for lab analysis is $300 per PFAS sample at each point of entry, and that this cost is expected to decrease as additional laboratories are certified for PFAS analysis and as market competition increases. The state also estimates that the cost of installing PFAS-specific GAC treatment for a PWS treating one million gallons per day (serving about 10,000 people) ranges from $500,000 to $1,000,000, with estimated operating costs of approximately $80,000 per year.

[37] Small public water systems usually contain contaminants other than PFAS, including arsenic, manganese, nitrate, or bacteria that present health risks and are naturally occurring or originate from nearby land uses. Effectiveness of PFAS treatment will depend on how often filters are replaced and what levels of these other contaminants are present in the system. See more **here**.

New Jersey notes that operating costs could increase depending on the number of wells requiring treatment and the level of contamination. Given PFAS ubiquity, the ability for precursors (e.g., fluorotelomers) to transform to perfluoroalkyl compounds and complicate site models, and complex transport mechanisms, especially at the air-water interface, states will need to use more resources to test process-based conceptual site models and fully understand the size and source of PFAS plumes.

States identified several cost implications of regulating PFAS:

- Resource availability is driven by dedicated government appropriations. For most states, resources to investigate and address PFAS come from existing program budgets (i.e., no new funds). Some states like *Colorado* and *Michigan* have received funding from bills signed by their Governors, and *Connecticut* received $2 million in bond funding to support the development and implementation of an AFFF take-back program, limited private well sampling, and treatment where needed. But these exemplify state-specific resources based on legislative priorities. Other states have received funding from settlements with PFAS manufacturers to use on regulation and/or restoration of contaminated sites.
- Resource disparity exists – States with the fewest resources to address PFAS may be more significantly impacted by PFAS than others. Similarly, they may only have resources to address PFAS-related risks that are most studied in existing science and most salient among the public, rather than addressing risks unique to that state. The complexities of PFAS scientific information also create a barrier to understanding risk in a public forum.
- Data gaps prevent confident decision-making on how resources are used to address PFAS. States want to develop regulations based on a sound understanding of the problem in their state and to be able to communicate that understanding to their constituents. However, various factors – the lack of information on the sources and fates of PFAS, how they can be removed from drinking water and aquifers, and resulting waste management issues – create barriers to state time and financial investment.

A few states identified the need for water quality-based effluent limits, as well as the need for a cost conversation through national MCL or National Recommended Water Quality Criteria (NRWQC) processes, as many states do not have the resources to regulate PFAS on their own. These are SDWA and CWA processes driven by the EPA and involving states as co-regulators, and are one example of how the EPA is assessing potential changes to its regulatory processes to better respond to contaminants of emerging concern and be more inclusive of state priorities.[38]

Conclusion

ECOS asked states to list considerations and unanswered questions that will affect their PFAS guidelines in the future. States noted that the greatest impacts on state PFAS regulations will be:

- How can regulators apply or develop guidelines to PFAS in less-explored media (e.g., food and agriculture, biosolids, landfills, foam, and air emissions), if at all? For example, *eleven states* have or are developing guidelines or consumption advisories for fish tissue and/or deer meat.
- How can labs detect lower concentrations of PFAS for media other than drinking water?
- What new information on sensitive human subpopulations, bioaccumulation in fish and shellfish, etc. will affect PFAS regulation?
- How will shifting use and chemistries of PFAS that have yet to be addressed complicate the responses? How many PFAS exist but are unknown to regulators due to confidentiality from manufacturers, etc.?

[38] For more information on states' recommendations for contaminants of emerging concern, see the Association of Clean Water Administrators (ACWA) and ASDWA joint **Recommendations Report for Contaminants of Emerging Concern**.

- How will developing information about PFAS migration from soil into animal feed, food crops, etc. affect the need for guidance values and state actions in response?
- What analytical approaches and health effects data will be available to develop guidelines for replacement PFAS?
- What will happen to current and pending state guidelines if federally enforceable standards (MCLs, NRWQCs) are enacted?
- What kinds of new science are needed to more effectively regulate PFAS?
- How will guidelines affect PFAS management/cleanup liability, disposal, and other considerations? For example, what will be the impact of designating PFAS as hazardous substances or regulating discharges through the National Pollutant Discharge Elimination System (NPDES) and remediation programs? Who will pay for mitigation or remediation? What role does pollution prevention play in prohibiting PFAS in consumer goods from passing through regulated facilities and entering the environment?

PFAS pose complex challenges that are new (e.g., drinking water contamination is not a major issue for other persistent, bioaccumulative, and toxic chemicals) and especially daunting. Their unique characteristics include mobility; persistence in the environment and the human body; animal and health effects at low doses; a lack of toxicological data for most PFAS detected in the environment and used in commerce; ubiquitous detection in human blood; and technical obstacles for remediation. These challenges are compounded by regulatory and policy developments that vary by state and are uncertain at the federal level. There is also heightened public pressure for swift risk management, encouraged through social media and news reports. For example, there have been large settlements of high-profile lawsuits (e.g., $850 million from 3M to Minnesota in 2018, $671 million from DuPont to plaintiffs in West Virginia and Ohio in 2017). Advocacy groups have convened community events and produced films inspired by PFAS contamination in cities like Parchment, Michigan; Decatur, Alabama; and Parkersburg, West Virginia. And public data from the UCMR3 reported that PFAS were detected in water supplies serving 16.5 million people in the U.S. and that more than six million people consumed water with PFAS concentrations above the EPA's LHA in 2015.[39]

A few states followed the emerging scientific information on, evaluated occurrence of, and developed guidelines for PFAS for many years before they were widely known to the public. Some states are actively responding to the recent events mentioned above by establishing programs and guidelines to regulate PFAS-contaminated sites. Other states are aware of PFAS as a contaminant of emerging concern and addressing it as they can. Given these circumstances, risk communication is going to be an increasingly important function. Regulators need more transparency about the uses of existing PFAS, the ongoing development of new PFAS by industry, and PFAS approval by the EPA under statutes like TSCA. As states seek to independently regulate PFAS, it is critical to coordinate with and learn from other states that have established and are establishing their own guidelines.

This compilation of state-developed PFAS guidelines is a moving target, as regulators are acting quickly to develop and/or update guidelines for PFAS in various environmental media. Some states are waiting to set guidelines in the hopes that the EPA will establish a federally-enforceable MCL, and other states are establishing guidance at levels below the EPA's LHA and/or for PFAS other than PFOA and PFOS, indicating that some regulators and toxicologists view the federal approach[40] as insufficiently protective. As not all states completed the survey (including some states known to have developed guidelines) and there will likely continue to be state standard setting at concentrations below the EPA's LHA and for PFAS other than PFOA and PFOS, ECOS hopes to compile additional information in the future.

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[39] Hu et al., 2016. "Detection of Poly- and Perfluoroalkyl Substances (PFASs) in U.S. Drinking Water Linked to Industrial Sites, Military Fire Training Areas, and Wastewater Treatment Plants." *Environmental Science & Technology Letters,* vol. 3, no. 10, 2016, pp. 344-350. *ACS Publications*, https://doi.org/10.1021/acs.estlett.6b00260.

[40] I.e., its process as a whole, or in its choice of critical studies or factors for calculation.

This white paper is not intended to be a comprehensive compendium of state PFAS regulations. Rather, it aims to lay the foundation for states to dig deeper into the issue. ECOS hopes this paper will serve as a basis for future conversations, and encourages state-to-state, state-federal, and state-NGO partnerships and collaboration. In June 2020, the ASDWA published a **toolkit** of modules on assessing state resources, characterizing health impacts, identifying treatment, analyzing costs and benefits, and other considerations surrounding PFAS in source water. ECOS is also compiling a spreadsheet of PFAS that states monitor for, including those for which the state does not have guidelines. The spreadsheet will be available on ECOS' **PFAS webpage** and will be updated as often as states submit new data. ECOS encourages states to use this white paper in combination with its additional PFAS resources, the ASDWA's numerous reports, the ITRC **fact sheets** and **Technical/Regulatory Guidance document**, and other relevant documents to fully understand the current status on PFAS regulation.

State Agency Reports on PFAS Guidelines

These reports/resources were provided by state environmental and health agencies that responded to the ECOS survey. For a full list of individual state PFAS websites with information on how they developed their guidelines and on other PFAS efforts, see the "Overview" section of ECOS' **PFAS Risk Communication Hub**.

- **California**
- **Colorado**
- **Connecticut**
- **Florida**
- **Hawaii**
- **Illinois**
- **Indiana**
- **Maine**
- **Massachusetts**
- **Michigan**
- **Minnesota**
- **New Hampshire**
- **New Jersey**
- **New York**
- **Texas**
- **Vermont**
- **Washington**

Appendix A: State Drinking Water PFAS Guideline Criteria

State	PFAS Analyte(s)	Guideline Level (ug/L)	Toxicity Data	Critical Effect Study	Endpoint	RSC (%)	POD	HED (mg/kg/day)	UFs							RfD (mg/kg/day)	Drinking Water Intake Rate (L/day unless otherwise specified)	Exposure assumptions	Target Populations	Resources
									Total	Interspecies	Intraspecies	LOAEL to NOAEL	Database Limitation	Duration of Exposure (i.e., Subchronic to Chronic)	Sensative Developmental Endpoints					
CA	PFOA	0.0051 (based on health-based reference level of 0.1 ppt for cancer effects, 2 ppt for non-cancer effects [liver])	Animals (mice/liver, rats/cancer)	Li et al., 2017; NTP, 2018	Hepatotoxicity in female mice; Cancer (pancreatic and liver) in male rats	20	LOAEL (0.97 mg/L)		300	3	10	3			3		Lifetime average of 0.053 L/kg/day	Oral ingestion as significant route of exposure		https://www.waterboards.ca.gov/pfas/ https://oehha.ca.gov/water/notification-level/notification-level-recommendations-perfluorooctanoic-acid-pfoa https://www.waterboards.ca.gov/drinking_water/certlic/drinkingwater/PFOA_PFOS.html
	PFOS	0.0065 (based on health-based reference level of 0.4 ppt for cancer effects, 7 ppt for non-cancer effects [immune system])	Animals (mice/liver, rats/cancer)	Dong et al., 2009 Butenhoff et al., 2012	Immunotoxicity in male mice; Cancer (liver, structural similarity to PFOA) in male rats	20	NOAEL (0.674 mg/L)		30	3	10						Lifetime average of 0.053 L/kg/day			
	PFBS	0.5	Animals	Feng et al., 2017	Reduction of thyroid hormone, pregnant mice	20	6 mg/kg/day	0.06	100	3	10		3			0.0006	0.237 L/kg/day	0-6 month infant drinking water intake rate		https://oehha.ca.gov/media/downloads/water/chemicals/nl/pfbsnl011321.pdf
CT	PFOA, PFOS, PFHxS, PFHpA, PFNA	0.07*	Animals (mice)	EPA (2016)	EPA (2016)	20	EPA (2016)		EPA (2016)											
HI	PFOA-	0.040	Animals (mice)	EPA (2016)	Based on noncarcinogenic effects	20	EPA (2016)		EPA (2016)							0.54 L/kg/day				https://health.hawaii.gov/heer/files/2020/12/PFASs-Techncal-Memo-HDOH-Dec-2020.pdf
	PFOS-	0.040	Animals (mice)	EPA (2016)	Based on noncarcinogenic effects	20	EPA (2016)		EPA (2016)							0.54 L/kg/day				
	PFNA-	0.004	Animals (mice)	EPA (2016)	Based on noncarcinogenic effects	20	EPA (2016)		EPA (2016)							0.54 L/kg/day				
	PFBS-	0.600	Animals (mice)	EPA (2016)	Based on noncarcinogenic effects	20	EPA (2016)		EPA (2016)							0.54 L/kg/day				
	PFHxS-	0.019	Animals (mice)	EPA (2016)	Based on noncarcinogenic effects	20	EPA (2016)		EPA (2016)							0.54 L/kg/day				

State	PFAS Analyte(s)	Guideline Level (ug/L)	Toxicity Data	Critical Effect Study	Endpoint	RSC (%)	POD	HED (mg/kg/day)	UFs							RfD (mg/kg/day)	Drinking Water Intake Rate (L/day unless otherwise specified)	Exposure assumptions	Target Populations	Resources
									Total	Interspecies	Intraspecies	LOAEL to NOAEL	Database Limitation	Duration of Exposure (i.e., Subchronic to Chronic)	Sensative Developmental Endpoints					
HI	$PFHpS^-$	0.020	Animals (mice)	EPA (2016)	Based on noncarcinogenic effects	20	EPA (2016)		EPA (2016)							0.54 L/kg/day				https://health.hawaii.gov/heer/files/2020/12/PFASs-Techncal-Memo-HDOH-Dec-2020.pdf
	$PFDS^-$	0.020	Animals (mice)	EPA (2016)	Based on noncarcinogenic effects	20	EPA (2016)		EPA (2016)							0.54 L/kg/day				
	$PFBA^-$	7.6	Animals (mice)	EPA (2016)	Based on noncarcinogenic effects	20	EPA (2016)		EPA (2016)							0.54 L/kg/day				
	$PFPeA^-$	0.800	Animals (mice)	EPA (2016)	Based on noncarcinogenic effects	20	EPA (2016)		EPA (2016)							0.54 L/kg/day				
	$PFHxA^-$	4.0	Animals (mice)	EPA (2016)	Based on noncarcinogenic effects	20	EPA (2016)		EPA (2016)							0.54 L/kg/day				
	$PFHpA^-$	0.040	Animals (mice)	EPA (2016)	Based on noncarcinogenic effects	20	EPA (2016)		EPA (2016)							0.54 L/kg/day				
	$PFDA^-$	0.004	Animals (mice)	EPA (2016)	Based on noncarcinogenic effects	20	EPA (2016)		EPA (2016)							0.54 L/kg/day				
	$PFUnDA^-$	0.010	Animals (mice)	EPA (2016)	Based on noncarcinogenic effects	20	EPA (2016)		EPA (2016)							0.54 L/kg/day				
	$PFDoDA^-$	0.013	Animals (mice)	EPA (2016)	Based on noncarcinogenic effects	20	EPA (2016)		EPA (2016)							0.54 L/kg/day				
	$PFTrDA^-$	0.013	Animals (mice)	EPA (2016)	Based on noncarcinogenic effects	20	EPA (2016)		EPA (2016)							0.54 L/kg/day				
	$PFTeDA^-$	0.130	Animals (mice)	EPA (2016)	Based on noncarcinogenic effects	20	EPA (2016)		EPA (2016)							0.54 L/kg/day				
	$PFOSA^-$	0.024	Animals (mice)	EPA (2016)	Based on noncarcinogenic effects	20	EPA (2016)		EPA (2016)							0.54 L/kg/day				
	$HFPO\text{-}DA^-$	0.160	Animals (mice)	EPA (2016)	Based on noncarcinogenic effects	20	EPA (2016)		EPA (2016)							0.54 L/kg/day				
IN	PFBS	140	Animals (mice)	EPA RSL Tables					400											
MA	PFOS, PFOA, PFNA, PFHpA, PFHxS, PFDA	0.020*	Animals	Multiple	Based on mulitple endpoints and evidence of effects below EPA PODs for PFOA and PFOS; including: immunotoxicity, hepatotoxicity, thyroid effects, developmental effects.	20; to account for dietary and other exposures to PFAS subgroup addressed as well as potentially higher infant exposures.	NOAEL for PFOS, LOAEL for PFOA, equivalent to EPA values.	Equivalent to EPA values for PFOA and PFOS	1000 for PFOA, 100 for PFOS	3	10	10 for PFOA	3 for both PFOA and PFOS			$5x10^{-6}$ based on PFOS and PFOA value, which is applied to subgroup based on similarity in chemical strutures, toxicities, long serum half-lives.	0.054 L/kg/day (same as EPA value used in LHA derivation)	Body weight and water intake of lactating women (same as EPA value used in LHA derivation)	Lactating and pregnant women; fetus; nursing infants	https://www.mass.gov/lists/development-of-a-pfas-drinking-water-standard-mcl
ME	PFOA, PFOS, PFHxS, PFHpA, PFNA	0.07*	Animals (mice)	EPA (2016)	EPA (2016)	20	EPA (2016)		EPA (2016)											

State	PFAS Analyte(s)	Guideline Level (ug/L)	Toxicity Data	Critical Effect Study	Endpoint	RSC (%)	POD	HED (mg/kg/day)	UFs							RfD (mg/kg/day)	Drinking Water Intake Rate (L/day unless otherwise specified)	Exposure assumptions	Target Populations	Resources
									Total	Interspecies	Intraspecies	LOAEL to NOAEL	Database Limitation	Duration of Exposure (i.e., Subchronic to Chronic)	Sensative Developmental Endpoints					
MI	PFOA	0.008	Animals (mice)	Onishchenko et al., 2011 and Koskela et al., 2016	Neurobehavioral effects and skeletal alterations	50	LOAEL		300	3	10	3	3	1			95th percentile, 50% RSC			https://dtmb.state.mi.us/ARS_Public/Transaction/RFRTransaction?TransactionID=29
	PFOS	0.016	Animals (mice)	Dong et al., 2009	Immunotoxicity and Hepatotoxicity	50	NOAEL		30	3	10	1	1	1			95th percentile, 50% RSC			
	PFNA	0.006	Animals (mice)	Das et al., 2015	Reduced pup body weight	50	NOAEL		300	3	10	1	10	1			95th percentile, 50% RSC			
	PFHxA	400	Animals (rats)	Klaunig et al., 2015	Renal effects	20	BMDL		300	3	10	1	10	1			95th percentile, 20% RSC			
	PFHxS	0.051	Animals (rats)	NTP 2018 Tox-96 Report	Thyroid effects	50	BMDL		300	3	10	1	10	1			95th percentile, 50% RSC			
	PFBS	0.42	Animals (mice)	Feng et al., 2017	Thyroid effects	20	BMDL		300	3	10	1	10	1			95th percentile, 20% RSC			
	Gen X	0.37	Animals (mice)	DuPont 18405-1037, 2010	Reduced pup body weight, Hepatotoxicity	20	BMDL		300	3	10	1	3	3			95th percentile, 20% RSC			
MN	PFOA (Short-term, Subchronic and chronic)	0.035	Animals (mice)	Lau et al., 2006	Developmental and liver effects, kidney effects, Immunotoxicity	50	38 mg/L serum concentration	0.0053	300	3	10	3	3			$1.8x10^{-5}$	95th percentile	Half-life 840 days; placental transfer 87%, 5.2% breastmilk transfer	Fetus and Breastfeeding Infants	https://www.health.state.mn.us/communities/environment/risk/docs/guidance/gw/pfoa.pdf
	PFOS (Short-term, Subchronic and chronic)	0.015	Animals (mice)	Dong et al., 2011	Immunotoxicity, adrenal, developmental effects, liver effects, thyroid effects	20 for older children and adults, 50 for infants/ young children	2.36 mg/L serum concentration	0.000307	100	3	10		3			$3.1x10^{-6}$	95th percentile	Half-life 1241 days; placental transfer 40%; 1.7% breastmilk transfer	Fetus and Breastfeeding Infants	https://www.health.state.mn.us/communities/environment/risk/docs/guidance/gw/pfos.pdf
	PFBA (Short-term, Subchronic and chronic)	7	Animals (rats)	NOTOX, 2007 and Butenhoff, 2007	Liver effects, Thyroid effects	50	3.01 mg/kg/day	0.38	100	3	10		3			$3.8x10^{-3}$	95th percentile	Half-life 72 hrs; placental transfer ND; breastmilk transfer ND	Infants and Adults	https://www.health.state.mn.us/communities/environment/risk/docs/guidance/gw/pfba2summ.pdf
	PFBS (Short-term and Subchronic)	3	Animals (mice)	Feng, 2017	Developmental effects, Thyroid effects, Reproduction	50	50 mg/kg/day	0.158	100	3	10		3			$1.6x10^{-3}$	95th percentile	Half-life 665 hrs; placental transfer ND; breastmilk transfer ND	Infants and Adults	https://www.health.state.mn.us/communities/environment/risk/docs/guidance/gw/pfbssummary.pdf
	PFBS (Chronic)	2	Animals (rats)	Lieder, 2009 and York, 2003	Kidney	20	45 mg/kg/day	0.129	300	3	10		3	3		$4.3x10^{-4}$	95th percentile	Half-life 665 hrs; placental transfer ND; breastmilk transfer ND	General Population	https://www.health.state.mn.us/communities/environment/risk/docs/guidance/gw/pfbssummary.pdf
	PFHxS (Short-term, Subchronic and chronic)	0.047	Animals (rats)	NTP, 2018	Thyroid effects, Liver effects	20 for older children and adults, 50 for infants/ young children	32.4 mg/L	0.00292	300	3	10		10			$9.7x10^{-6}$	95th percentile	Half-life 1935 days; placental transfer 70%; breastmilk transfer 1.4%	Fetus and Breastfeeding Infants	https://www.health.state.mn.us/communities/environment/risk/docs/guidance/gw/pfhxs.pdf

State	PFAS Analyte(s)	Guideline Level (ug/L)	Toxicity Data	Critical Effect Study	Endpoint	RSC (%)	POD	HED (mg/kg/day)	UFs							RfD (mg/kg/day)	Drinking Water Intake Rate (L/day unless otherwise specified)	Exposure assumptions	Target Populations	Resources
									Total	Interspecies	Intraspecies	LOAEL to NOAEL	Database Limitation	Duration of Exposure (i.e., Subchronic to Chronic)	Sensative Developmental Endpoints					
NC	GenX	0.14	Animals (mice)	DuPont-24459, 2008; DuPont-18405-1037, 2010	Hepatotoxicity	20	0.1 mg/kg/day (NOAEL)		1000	10	10			10		0.0001	1.1 L/day (95th percentile infant)	Bottle-fed infants of median weight	Infants	https://epi.dph.ncdhhs.gov/oee/pfas/NC%20DHHS%20Health%20Goal%20Q&A.pdf
NH	PFOA	0.012	Animals (mice)	Loveless et al., 2007	Hepatotoxicity	50	BMDL10		100	3	10		3				95th percentile	MDH Model	Fetus and Breastfeeding Infants	
	PFOS	0.015	Animals (mice)	Dong et al., 2011	Immunosuppression	50	NOAEL		100	3	10		3				95th percentile	MDH Model	Fetus and Breastfeeding Infants	
	PFNA	0.011	Animals (mice)	Das et al., 2015	Hepatotoxicity	50	BMDL10		100	3	10		3				95th percentile	MDH Model	Fetus and Breastfeeding Infants	
	PFHxS	0.018	Animals (mice)	Chang et al., 2018 and Ali et al.	Infertility	50	BMDLSD		300	3	10		10				95th percentile	MDH Model	Fetus and Breastfeeding Infants	https://pubmed.ncbi.nlm.nih.gov/31487490/
NJ	PFOA	0.014	Animals (mice)	Loveless et al., 2006	Hepatotoxicity	20	BMDL		30	3	10				10		2 (70 kg body wt)		Infants	https://www.state.nj.us/dep/watersupply/pdf/pfoa-appendixa.pdf
	PFOS	0.013	Animals (mice)	Dong et al., 2009	Immunotoxicity	20	NOAEL		30	3	10						2 (70 kg body wt)		Infants	https://www.state.nj.us/dep/watersupply/pdf/pfos-recommendation-appendix-a.pdf
	PFNA	0.013	Animals (mice)	Das et al., 2015	Hepatotoxicity	50	BMDL		1000	3	10		3	10	3			200:1 serum: drinking water ratio		https://www.state.nj.us/dep/watersupply/pdf/pfna-health-effects.pdf
NY	PFOA	0.01																		
	PFOS	0.01																		
VT	PFOA, PFOS, PFHxS, PFHpA, PFNA	0.02*	Animals (mice)	EPA (2016)	EPA (2016)	20	EPA (2016)		EPA (2016)								0.175 L/kg/day		0-1 year old	

*= Advisory level is based on the total of more than one PFAS

Appendix B: State Groundwater PFAS Guideline Criteria

State	PFAS Analyte(s)	Guideline Level (ug/L)	Toxicity Data	Critical Effect Study	Endpoint	RSC (%)	POD	HED (mg/kg/day)	UFs								RfD (mg/kg/day)	Drinking Water Intake Rate (L/day unless otherwise specified)	Exposure assumptions	Target Populations	Resources & Notes
									Total	Interspecies	Intraspecies	LOAEL to NOAEL	Database Limitation	Duration of Exposure (i.e., Subchronic to Chronic)	Sensative Developmental Endpoints/ Subpopulations	Modifying Factor					
AK	PFOA	0.4	Animals (mice)	Lau et al., 2006	Decreased ossification of pup proximal phalanges, accelerated preputial separation	None (but does not include an RSC in cleanup level calculations, so essenitally use an RSC of 100)	EPA (2016)		EPA (2016)								EPA (2016)	0.78	Residential exposure for 6 yrs old child receptor	Child	http://dec.alaska.gov/media/7543/20180201_pccl.pdf
	PFOS	0.4	Animals (mice)	Luebker et al., 2005	Reduced pup body weight	None (but does not include an RSC in cleanup level calculations, so essenitally use an RSC of 100)	EPA (2016)		EPA (2016)								EPA (2016)	0.78	Residential exposure for 6 yrs old child receptor	Child	http://dec.alaska.gov/media/7543/20180201_pccl.pdf
CO	PFOA, PFOS	0.07*	Animals (mice)	EPA (2016)	EPA (2016)	20	EPA (2016)		EPA (2016)								EPA (2016)	EPA (2016)	EPA (2016)	EPA (2016)	
	PFBS	400	Animals (mice)	EPA RSL	EPA RSL	EPA RSL	EPA RSL		EPA RSL								EPA RSL	EPA RSL	EPA RSL	EPA RSL	
	PFHxS	0.7	Animals (mice)																		
CT	PFOA, PFOS, PFHxS, PFHpA, PFNA	0.07*																			
FL	PFOA	0.07	Animals (mice)	Lau et al., 2006	Decreased ossification of pup proximal phalanges, accelerated preputial separation	20	EPA (2016)		300	3		10			10		$2x10^{-5}$	0.054 L/kg/day		Prengant/ lactating women	
	PFOS	0.07	Animals (mice)	Luebker et al., 2005	Decreased offspring body weight	20	EPA (2016)		30	3					10		$2x10^{-5}$	0.054 L/kg/day		Prengant/ lactating women	
HI	PFOA^	0.04 (drinking water [DW] toxicity), 8.5 (chronic aquatic [CA] toxicity), 120 (acute aquatic [AA]																			Applicable to groundwater that is a current or potential drinking water resource, where the surface water body is located within 150 meters of a release site. See other action levels and more information: https://health.hawaii.gov/heer/guidance/ehe-and-eals/
	PFOS^	0.04 (DW), 1.1 (CA), 31 (AA)																			
	PFNA^	0.004 (DW) 8.0 (CA) 8.0 (AA)																			
	PFBS^	0.600 (DW), 130000 (CA), 130000 (AA)																			

State	PFAS Analyte(s)	Guideline Level (ug/L)	Toxicity Data	Critical Effect Study	Endpoint	RSC (%)	POD	HED (mg/kg/day)	UFs								RfD (mg/kg/day)	Drinking Water Intake Rate (L/day unless otherwise specified)	Exposure assumptions	Target Populations	Resources & Notes
									Total	Interspecies	Intraspecies	LOAEL to NOAEL	Database Limitation	Duration of Exposure (i.e., Subchronic to Chronic)	Sensative Developmental Endpoints/ Subpopulations	Modifying Factor					
HI	PFHxS-	0.019 (DW), 10 (CA), 10 (AA)																			Applicable to groundwater that is a current or potential drinking water resource, where the surface water body is located within 150 meters of a release site. See other action levels and more information: https://health.hawaii.gov/heer/guidance/ehe-and-eals/
	PFHpS-	0.020 (DW) 0.020 (CA) 0.020 (AA)																			
	PFDS-	0.020 (DW) 0.020 (CA) 0.020 (AA)																			
	PFBA-	7.6 (DW) 830 (CA) 830 (AA)																			
	PFPeA-	0.800 (DW) 0.800 (CA) 0.800 (AA)																			
	PFHxA-	4.0 (DW), 6300 (CA) 48000 (AA)																			
	PFHpA-	0.040 (DW) 0.040 (CA) 0.040 (AA)																			
	PFDA-	0.004 (DW) 10 (CA) 10 (AA)																			
	PFUnDA-	0.010 (DW) 0.010 (CA) 0.010 (AA)																			
	PFDoDA-	0.013 (DW) 20 (CA) 20 (AA)																			
	PFTrDA-	0.013 (DW) 0.013 (CA) 0.013 (AA)																			
	PFTeDA-	0.130 (DW) 0.130 (CA) 0.130 (AA)																			
	PFOSA-	0.024 (DW) 0.024 (CA) 0.024 (AA)																			
	HFPO-DA-	0.160 (DW) 0.160 (CA) 0.160 (AA)																			
IL	PFOA	0.002 (MRL)	Animals (Rats/Cancer)	NTP 2018. TR-598	Liver/Pancreatic Tumors		Slope Factor 143 mg/kg/day	0.00035									143 (SF)	2	Duration: 30 years. Frequency: 350 days/year	Average adult	https://www2qa.illinois.gov/epa/topics/water-quality/pfas/Pages/pfas-statewide-investigation-network.aspx
	PFOS	0.014	Animals (Rats/Developmental)	Luebker et al., 2005	Decreased bodyweight/delayed eye opening	20	NOAEL 0.1 mg/kg/day	0.000515	300	3	10	1			1100		0.000002	2	Oral ingestion as significant route of exposure	Average adult	
	PFBS	140	Animals (Rats/Kidney)	Lieder et al. 2009	Hyperplasia	20	$BMDL_{10}$ 78.7 mg/kg/day	18.9	1000	3	10	1	3	10			0.02	2	Oral ingestion as significant route of exposure	Average adult	

State	PFAS Analyte(s)	Guideline Level (ug/L)	Toxicity Data	Critical Effect Study	Endpoint	RSC (%)	POD	HED (mg/kg/day)	UFs								RfD (mg/kg/day)	Drinking Water Intake Rate (L/day unless otherwise specified)	Exposure assumptions	Target Populations	Resources & Notes
									Total	Interspecies	Intraspecies	LOAEL to NOAEL	Database Limitation	Duration of Exposure (i.e., Subchronic to Chronic)	Sensative Developmental Endpoints/ Subpopulations	Modifying Factor					
IL	PFHxS	0.14	Animals (Rats/Thyroid)	Butenhoff et al. 2009	Thyroid follicular damage	20	NOAEL 1 mg/kg/day	0.0047	300	3	10	1				10	0.00002	2	Oral ingestion as significant route of exposure	Average adult	https://www2qa.illinois.gov/epa/topics/water-quality/pfas/Pages/pfas-statewide-investigation-network.aspx
	PFNA	0.021	Animals (Mice/Developmental)	Das et al. 2015	Decreased bodyweight/developmental delays	20	NOAEL 1 mg/kg/day	0.001	300	3	10	1				10	0.000003	2	Oral ingestion as significant route of exposure	Average adult	
MA	PFOS, PFOA, PFNA, PFHpA, PFHxS, PFDA	0.020*	Animals	Multiple	Based on mulitple endpoints and evidence of effects below EPA PODs for PFOA and PFOS; including: immunotoxicity, hepatotoxicity, thyroid effects, developmental effects.	20; to account for dietary and other exposures to PFAS subgroup addressed as well as potentially higher infant exposures.	NOAEL for PFOS, LOAEL for PFOA, equivalent to EPA values.	Equivalent to EPA values for PFOA and PFOS	1000 for PFOA, 100 for PFOS	3	10	10 for PFOA	3 for both PFOA and PFOS				$5x10^{-6}$ based on PFOS and PFOA value, which is applied to subgroup based on similarity in chemical strutures, toxicities, long serum half-lives.	0.054 L/kg/day (same as EPA value used in LHA derivation)	Body weight and water intake of lactating women (same as EPA value used in LHA derivation)	Lactating and pregnant women; fetus; nursing infants	https://www.mass.gov/lists/development-of-a-pfas-drinking-water-standard-mcl
MI	PFOA	0.008	Animals (mice)	Onishchenko et al., 2011 and Koskela et al., 2016	Neurobehavioral effects and skeletal alterations	50	LOAEL		300	3	10	3	3	1			95th percentile, 50% RSC			https://dtmb.state.mi.us/ARS_Public/Transaction/RFRTransaction?TransactionID=29	
	PFOS	0.016	Animals (mice)	Dong et al., 2009	Immunotoxicity and Hepatotoxicity	50	NOAEL		30	3	10	1	1	1			95th percentile, 50% RSC				
	PFNA	0.006	Animals (mice)	Das et al., 2015	Reduced pup body weight	50	NOAEL		300	3	10	1	10	1			95th percentile, 50% RSC				
	PFHxA	400	Animals (rats)	Klaunig et al., 2015	Renal effects	20	BMDL		300	3	10	1	10	1			95th percentile, 20% RSC				
	PFHxS	0.051	Animals (rats)	NTP 2018 Tox-96 Report	Thyroid effects	50	BMDL		300	3	10	1	10	1			95th percentile, 50% RSC				
	PFBS	0.42	Animals (mice)	Feng et al., 2017	Thyroid effects	20	BMDL		300	3	10	1	10	1			95th percentile, 20% RSC				
	Gen X	0.37	Animals (mice)	DuPont 18405-1037, 2010	Reduced pup body weight, Hepatotoxicity	20	BMDL		300	3	10	1	3	3			95th percentile, 20% RSC				
	PFOA (GSI for drinking water source)	0.42	Animals (primates)	Butenhoff et al., 2002	Hepatotoxicity	n/a	LOAEL		3000	3	10	10		10			$1.53x10^{-5}$	2			https://www.michigan.gov/egle/0,9429,7-135-3311_4109-251790--,00.html
	PFOA (GSI)	12	Animals (primates)	Butenhoff et al., 2002	Hepatotoxicity	n/a	LOAEL		3000	3	10	10		10			$1.53x10^{-5}$	0.01			
	PFOS (GSI for drinking water source)	0.011	Animals (primates)	Seacat et al., 2002	Decreased body weight, hepatoxicity, thyroid toxicity	n/a	NOAEL		30	3	10						$1.3667x10^{-5}$	2			
	PFOS (GSI)	0.012	Animals (primates)	Seacat et al., 2002	Decreased body weight, hepatoxicity, thyroid toxicity	n/a	NOAEL		30	3	10						$1.3367x10^{-5}$	0.01			

State	PFAS Analyte(s)	Guideline Level (ug/L)	Toxicity Data	Critical Effect Study	Endpoint	RSC (%)	POD	HED (mg/kg/day)	UFs								RfD (mg/kg/day)	Drinking Water Intake Rate (L/day unless otherwise specified)	Exposure assumptions	Target Populations	Resources & Notes
									Total	Interspecies	Intraspecies	LOAEL to NOAEL	Database Limitation	Duration of Exposure (i.e., Subchronic to Chronic)	Sensative Developmental Endpoints/ Subpopulations	Modifying Factor					
MN	PFOA (Short-term, Subchronic and chronic)	0.035	Animals (mice)	Lau et al., 2006	Developmental and liver effects, kidney effects, Immunotoxicity	50	38 mg/L serum concentration	0.0053	300	3	10	3	3				$1.8x10^{-5}$	95th percentile	Half-life 840 days; placental transfer 87%, 5.2% breastmilk transfer	Fetus and Breastfeeding Infants	https://www.health.state.mn.us/communities/environment/risk/docs/guidance/gw/pfoa.pdf
	PFOS (Short-term, Subchronic and chronic)	0.015	Animals (mice)	Dong et al., 2011	Immunotoxicity, adrenal, developmental effects, liver effects, thyroid effects	20 for older children and adults, 50 for infants/ young children	2.36 mg/L serum concentration	0.000307	100	3	10		3				$3.1x10^{-6}$	95th percentile	Half-life 1241 days; placental transfer 40%; 1.7% breastmilk transfer	Fetus and Breastfeeding Infants	https://www.health.state.mn.us/communities/environment/risk/docs/guidance/gw/pfos.pdf
	PFBA (Short-term, Subchronic and chronic)	7	Animals (rats)	NOTOX, 2007 and Butenhoff, 2007	Liver effects, Thyroid effects	50	3.01 mg/kg/day	0.38	100	3	10		3				$3.8x10^{-3}$	95th percentile	Half-life 72 hrs; placental transfer ND; breastmilk transfer ND	Infants and Adults	https://www.health.state.mn.us/communities/environment/risk/docs/guidance/gw/pfba2summ.pdf
	PFBS (Short-term and Subchronic)	3	Animals (mice)	Feng, 2017	Developmental effects, Thyroid effects, Reproduction	50	50 mg/kg/day	0.158	100	3	10		3				$1.6x10^{-3}$	95th percentile	Half-life 665 hrs; placental transfer ND; breastmilk transfer ND	Infants and Adults	https://www.health.state.mn.us/communities/environment/risk/docs/guidance/gw/pfbssummary.pdf
	PFBS (Chronic)	2	Animals (rats)	Lieder, 2009 and York, 2003	Kidney	20	45 mg/kg/day	0.129	300	3	10		3	3			$4.3x10^{-4}$	95th percentile	Half-life 665 hrs; placental transfer ND; breastmilk transfer ND	General Population	https://www.health.state.mn.us/communities/environment/risk/docs/guidance/gw/pfbssummary.pdf
	PFHxS (Short-term, Subchronic and chronic)	0.047	Animals (rats)	NTP, 2018	Thyroid effects, Liver effects	20 for older children and adults, 50 for infants/ young children	32.4 mg/L	0.00292	300	3	10		10				$9.7x10^{-6}$	95th percentile	Half-life 1935 days; placental transfer 70%; breastmilk transfer 1.4%	Fetus and Breastfeeding Infants	https://www.health.state.mn.us/communities/environment/risk/docs/guidance/gw/pfhxs.pdf
NC	PFOA	2	Animals (rats)	York et al., 2002, Butenhoff et al., 2004	Reduced pup body weight	20	LOAEL		3000	10	10	10	3	1				Assumed body weight and water consumption of adult	Daily exposure to human population	Adults	
NH	PFOA	0.012	Animal (mice)	Loveless et al., 2007	Hepatotoxicity	50	BMDL10		100	3	10		3					95th percentile	MDH Model	Fetus and Breastfeeding Infants	
	PFOS	0.015	Animal (mice)	Dong et al., 2011	Immunosuppression	50	NOAEL		100	3	10		3					95th percentile	MDH Model	Fetus and Breastfeeding Infants	
	PFNA	0.011	Animal (mice)	Das et al., 2015	Hepatotoxicity	50	BMDL10		100	3	10		3					95th percentile	MDH Model	Fetus and Breastfeeding Infants	
	PFHxS	0.018	Animal (mice)	Chang et al., 2018 and Ali et al.	Infertility	50	BMDLSD (under peer review)		300	3	10		3	3				95th percentile	MDH Model	Fetus and Breastfeeding Infants	

State	PFAS Analyte(s)	Guideline Level (ug/L)	Toxicity Data	Critical Effect Study	Endpoint	RSC (%)	POD	HED (mg/kg/day)	UFs								RfD (mg/kg/day)	Drinking Water Intake Rate (L/day unless otherwise specified)	Exposure assumptions	Target Populations	Resources & Notes
									Total	Interspecies	Intraspecies	LOAEL to NOAEL	Database Limitation	Duration of Exposure (i.e., Subchronic to Chronic)	Sensative Developmental Endpoints/ Subpopulations	Modifying Factor					
NJ	PFOA	0.014	Animals (mice)	Loveless et al., 2006	Hepatotoxicity	20	BMDL		30	3	10				10			2 (70 kg body wt)		Infants	Note: MCLs for PFOA, PFOS, and PFNA are also used as Groundwater Quality Standards.
	PFOS	0.013	Animals (mice)	Dong et al., 2009	Immunotoxicity	20	NOAEL		30	3	10							2 (70 kg body wt)		Infants	Note: MCLs for PFOA, PFOS, and PFNA are also used as Groundwater Quality Standards.
	PFNA	0.013	Animals (mice)	Das et al., 2015	Hepatotoxicity	50	BMDL		1000	3	10		3	10	3				200:1 serum: drinking water ratio		Note: MCLs for PFOA, PFOS, and PFNA are also used as Groundwater Quality Standards.
NM	PFOA	0.07*																			
	PFOS	0.07*																			
	PFHxS	0.07*																			
NY	PFOA	0.01																			
	PFOS	0.01																			
TX	PFBA	71	Animals (mice)	MDH	Hepatotoxicity		NOAEL (6.9 mg/kg/d)		2400	1	10		10	3			$2.9x10^{-3}$				Note: oral dose, 0.5 acre source area) (Res GWGWIng PCLs) https://www.tceq.texas.gov/assets/public/implementation/tox/evaluations/pfcs.pdf
	PFBuS	34	Animals (mice)	Leider et al., 2009, York et al., 2002	Systemic Toxicity		NOAEL (60 mg/kg/d)		42600	1	10		10	3			$1.4x10^{-3}$				
	PFPeA	0.093	Animals (mice)	Surrogate: PFHxS	Hematotoxicity		NOAEL (0.3 mg/kg/d)		78900	1	10	3	10				$3.8x10^{-6}$				
	PFHxS	0.093	Animals (mice)	Hoberman and York, 2003	Hematotoxicity		NOAEL (0.3 mg/kg/d)		78900	1	10	3	10				$3.8x10^{-6}$				
	PFHxA	0.093	Animals (mice)	Surrogate: PFHxS	Hematotoxicity		NOAEL (0.3 mg/kg/d)		78900	1	10	3	10				$3.8x10^{-6}$				
	PFHpA	0.56	Animals (mice)	Surrogate: PFOS	Neurodevelopment		NOAEL (0.6 mg/kg/d)		26300	1	10	10	1				$2.3x10^{-5}$				
	PFOS	0.56	Animals (mice)	Zeng et al., 2011	Neurodevelopment		NOAEL (0.6 mg/kg/d)		26300	1	10	10	1				$2.3x10^{-5}$				
	PFOA	0.29	Animals (mice)	Macon et al., 2011	Mammary gland development		NOAEL (0.3 mg/kg/d)		24300	1	10	30	1				$1.2x10^{-5}$				
	PFOSA	0.29	Animals (mice)	Surrogate: PFOA	Mammary gland development		NOAEL (0.3 mg/kg/d)		24300	1	10	30	1				$1.2x10^{-5}$				
	PFNA	0.29	Animals (mice)	Fang et al., 2010	Spleen Cell Death		NOAEL (1 mg/kg/d)		81000	1	10		10	10			$1.2x10^{-5}$				
	PFDeA	0.37	Animals (mice)	Kawashima et al., 1995	Hepatotoxicity		NOAEL (1.2 mg/kg/d)		81000	1	10		10	10			$1.5x10^{-5}$				
	PFDS	0.29	Animals (mice)	Surrogate: PFDoA	Reduced Body Weight		NOAEL (1 mg/kg/d)		81000	1	10		10	10			$1.2x10^{-5}$				
	PFUA	0.29	Animals (mice)	Surrogate: PFDoA	Reduced Body Weight		NOAEL (1 mg/kg/d)		81000	1	10		10	10			$1.2x10^{-5}$				

State	PFAS Analyte(s)	Guideline Level (ug/L)	Toxicity Data	Critical Effect Study	Endpoint	RSC (%)	POD	HED (mg/kg/day)	UFs								RfD (mg/kg/day)	Drinking Water Intake Rate (L/day unless otherwise specified)	Exposure assumptions	Target Populations	Resources & Notes
									Total	Interspecies	Intraspecies	LOAEL to NOAEL	Database Limitation	Duration of Exposure (i.e., Subchronic to Chronic)	Sensative Developmental Endpoints/ Subpopulations	Modifying Factor					
TX	PFDoA	0.29	Animals (mice)	Shi et al., 2007	Reduced Body Weight		NOAEL (1 mg/kg/d)		81000	1	10		10	10			$1.2x10^{-5}$				
	PFTrDA	0.29	Animals (mice)	Surrogate: PFDoA	Reduced Body Weight		NOAEL (1 mg/kg/d)		81000	1	10		10	10			$1.2x10^{-5}$				
	PFTeDA	0.29	Animals (mice)	Surrogate: PFDoA	Reduced Body Weight		NOAEL (1 mg/kg/d)		81000	1	10		10	10			$1.2x10^{-5}$				
VT	PFOA, PFOS, PFHxS, PFHpA, PFNA	0.02*	Animals (mice)	EPA (2016)	EPA (2016)	20	EPA (2016)		EPA (2016)									0.175 L/kg/day		0-1 year old	
WI	PFOA	0.02 (combined)*	Animals (mice)	Lau et al., 2006	Developmental (reduced ossification)	100	LOAEL		300	10	3	10									https://www.dhs.wisconsin.gov/water/gws.htm
	PFOS	0.02 (combined)*	Animals (mice)	Luebker et al., 2005	Reduced pup body weight	100	NOAEL		30	3	10				10			1 (10 kg body wt)	Gestation and infancy (including breastfeeding)		
	FOSA, NEtFOSA, NEtFOSAA, NEtFOSE	0.02 (combined)*	PFOA and PFOS Precursor		Combined standard for PFOS, PFOA, FOSA, NEtFOSE, NEtFOSA, and NEtFOSAA	100												Combined			https://www.dhs.wisconsin.gov/water/gws-cycle11.htm
	PFTeA	10	Animals (rats)	Hirata-Koizumi et al., 2015	Body weight	100	NOAEL (1 mg/kg/day)		1000	10	10	1	10	1	1		0.001	1			https://www.dhs.wisconsin.gov/water/gws-cycle11.htm
	PFHxA	150	Animals (rats)	Klaunig, 2015	Clinical effects	100	NOAEL (15 mg/kg/day)		1000	10	10	1	10	1	1		0.015	1			https://www.dhs.wisconsin.gov/water/gws-cycle11.htm
	PFUnA	3	Animals (rats)	Takahashi et al., 2014	Body weight	100	NOAEL (0.3 mg/kg/day)		1000	10	10	1	10	1	1		0.0003	1			https://www.dhs.wisconsin.gov/water/gws-cycle11.htm
	PFDoA	0.5	Animals (rats)	Shi, 2009	Body weight and testosterone levels	100	NOAEL (0.05 mg/kg/day)		1000	10	10	1	10	1	1		$5x10^{-5}$	1			https://www.dhs.wisconsin.gov/water/gws-cycle11.htm
	PFBA	10	Animals (rats)	van Otterdyk, Buttenholf 2012b	Hemotoxicity, hepatotoxicity, and thyroid toxicity	100	BMDL (MN) (3 mg/kg/day)		3000	10	10	1	10	3	1		0.001	1			https://www.dhs.wisconsin.gov/water/gws-cycle11.htm
	PFBS	450	Animals (rats)	Lieder, 2009b	Nephrotoxicity	100	BMDL (MN) (45 mg/kg/day)		1000	10	10	1	10	1	1		0.045	1			https://www.dhs.wisconsin.gov/water/gws-cycle11.htm
	PFNA	0.03	Animals (mice)	Das, 2015	Reproductive toxicty	100	NOAEL (1 mg/kg/day)	0.0011	300	3	10	1	1	1	10		$3x10^{-6}$	1			https://www.dhs.wisconsin.gov/water/gws-cycle11.htm
	PFDA	0.3	Animals (mice)	Harris and Birnbaum 1989	Deveolpmental (Fetal growth)	100	NOAEL (0.03 mg/kg/day)		1000	10	10	1	10	1	1		$3x10^{-5}$	1			https://www.dhs.wisconsin.gov/water/gws-cycle11.htm
	PFHxS	0.04	Animals (rats)	Cheng, 2018	Developmental and repoductive toxicity (Maternal and fetal growth)	100	NOAEL (0.3 mg/kg/day)		300	3	10	1	10	1	1		$4x10^{-6}$	1			https://www.dhs.wisconsin.gov/water/gws-cycle11.htm
	PFODA	0.4	Animals (rats)	Hirata-Koizumi., 2012	Body weight	100	NOAEL (40 mg/kg/day)		1000	10	10	1	10	1	1		0.04	1			https://www.dhs.wisconsin.gov/water/gws-cycle11.htm
	Gen X	0.3	Animals (mice)	Dupont, 2010b	Nephrotoxicity and hepatotoxicity	100	NOAEL (0.1 mg/kg/day)		3000	10	10	1	10	3	1		$3x10^{-5}$	1			https://www.dhs.wisconsin.gov/water/gws-cycle11.htm
	DONA	3	Animals (rats)	Gordon, 2011	Hemotoxicity and hepatotoxicity	100	NOAEL (1 mg/kg/day)		3000	10	10	1	10	3	1		0.0003	1			https://www.dhs.wisconsin.gov/water/gws-cycle11.htm

*= Advisory level is based on the total of more than one PFAS

Appendix C: State Surface Water PFAS Guideline Criteria

State	PFAS Analyte(s)	Guideline Level (ug/L)	Toxicity Data	Critical Effect Study	Endpoint	POD	UFs					RfD (mg/kg/day)	Drinking Water Intake Rate (L/day)	Resources & Notes
							Total	Interspecies	Intraspecies	LOAEL to NOAEL	Duration of Exposure (i.e., Subchronic to Chronic)			
CO	PFBS	400	Animals (mice)	EPA RSL	EPA RSL	EPA RSL	EPA RSL					EPA RSL	EPA RSL	
	PFHxS	0.7	Animals (mice)											
FL	PFOA	0.5										$2x10^{-5}$		Screening levels derived through a Probabilistic Risk Assessment https://floridadep.gov/sites/default/files/PFOA_PFOS_Human_Health_Surface_Water_Prob_Risk_Assessment.pdf
	PFOS	0.01										$2x10^{-5}$		Screening levels derived through a Probabilistic Risk Assessment https://floridadep.gov/sites/default/files/PFOA_PFOS_Human_Health_Surface_Water_Prob_Risk_Assessment.pdf
HI	PFOA-	0.04 (drinking water [DW] toxicity), 8.5											0.54 L/kg/day	Drinking water action levels applied if aquatic toxicity action levels not available; chronic aquatic toxicity action level also used as acute aquatic toxicity action level if latter not available. Refer to technical memorandum for additional detail: https://health.hawaii.gov/heer/guidance/ehe-and-eals/
	PFOS-	0.04 (DW), 1.1 (CA), 31 (AA)												
	PFNA-	0.004 (DW) 8.0 (CA) 8.0 (AA)												
	PFBS-	0.600 (DW), 130000 (CA), 130000 (AA)												
	PFHxS-	0.019 (DW), 10 (CA), 10 (AA)												
	PFHpS-	0.020 (DW) 0.020 (CA) 0.020 (AA)												
	PFDS-	0.020 (DW) 0.020 (CA) 0.020 (AA)												
	PFBA-	7.6 (DW) 830 (CA) 830 (AA)												
	PFPeA-	0.800 (DW) 0.800 (CA) 0.800 (AA)												

State	PFAS Analyte(s)	Guideline Level (ug/L)	Toxicity Data	Critical Effect Study	Endpoint	POD	UFs					RfD (mg/kg/day)	Drinking Water Intake Rate (L/day)	Resources & Notes
							Total	Interspecies	Intraspecies	LOAEL to NOAEL	Duration of Exposure (i.e., Subchronic to Chronic)			
HI	PFHxA-	4.0 (DW), 6300 (CA) 48000 (AA)												Drinking water action levels applied if aquatic toxicity action levels not available; chronic aquatic toxicity action level also used as acute aquatic toxicity action level if latter not available. Refer to technical memorandum for additional detail: https://health.hawaii.gov/heer/guidance/ehe-and-eals/
	PFHpA-	0.040 (DW) 0.040 (CA) 0.040 (AA)												
	PFDA-	0.004 (DW) 10 (CA) 10 (AA)												
	PFUnDA-	0.010 (DW) 0.010 (CA) 0.010 (AA)												
	PFDoDA-	0.013 (DW) 20 (CA) 20 (AA)												
	PFTrDA-	0.013 (DW) 0.013 (CA) 0.013 (AA)												
	PFTeDA-	0.130 (DW) 0.130 (CA) 0.130 (AA)												
	PFOSA-	0.024 (DW) 0.024 (CA) 0.024 (AA)												
	HFPO-DA-	0.160 (DW) 0.160 (CA) 0.160 (AA)												
MI	PFOA (drinking water source)	0.42	Animals (primates)	Butenhoff et al., 2002	Hepatotoxicity	LOAEL	3000	3	10	10	10	$2x10^{-5}$	2	https://www.michigan.gov/egle/0,9429,7-135-3313_3681_3686_3728-11383--,00.html
	PFOA	12	Animals (primates)	Butenhoff et al., 2002	Hepatotoxicity	LOAEL	3000	3	10	10	10	$2x10^{-5}$	0.01	
	PFOS (drinking water source)	0.011	Animals (primates)	Seacat et al., 2002	Decreased body weight, hepatotoxicity, thyroid toxicity	NOAEL	30	3	10			$1.3667x10^{-5}$	2	
	PFOS	0.012	Animals (primates)	Seacat et al., 2002	Decreased body weight, hepatotoxicity, thyroid toxicity	NOAEL	30	3	10			$1.3667x10^{-5}$ mg/kg/day	0.01	

State	PFAS Analyte(s)	Guideline Level (ug/L)	Toxicity Data	Critical Effect Study	Endpoint	POD	UFs					RfD (mg/kg/day)	Drinking Water Intake Rate (L/day)	Resources & Notes
							Total	Interspecies	Intraspecies	LOAEL to NOAEL	Duration of Exposure (i.e., Subchronic to Chronic)			
MN	PFOS (in fish tissue and surface water)	0.37 nanograms per gram (fish tissue), 0.00005 ug/L	Animals (mice)	Dong et al., 2011	Immunotoxicity, adrenal, developmental effects, liver effects, thyroid effects	2.36 mg/L serum concentration	100	3	10			$3.1x10^{-6}$	95th percentile	For this standard, MN used a relative source contribution of 0.2, a fish consumption rate of 66 grams/70 kilograms, and a bioaccumulation factor of 7210 liters/kilogram for the water based standard. For more info: MPCA Water Quality Standards/ site-specific Water Quality Criteria: https://www.pca.state.mn.us/water/site-specific-water-quality-criteria
	PFOA, PFHxS, PFBA, and PFBS (in development… see notes).													MN is updating its surface water criteria for PFOA; the existing value is outdated and should not be used. MN is also developing new criteria PFHxS, PFBA, and PFBS. These criteria are expected to be available in mid- to late 2021. Note that these are site-specific criteria for the protection of human health (fish consumption and recreation).
NM	PFOA, PFOS	0.07*												
	HFPO-DA, NEtFOSAA, NMeFOSAA, PFBS, PFDA, PFDoA, PFHpA, PFHxS, PFHxA, PFNA, PFTA, PFTrDA, PFUnA, 11 C1-PF3OUdS, 9C1-PF3ONS, ADONA													Coverage under EPA's 2021 MSGP in NM requires monitoring and analyzing for 18 PFAS compounds using modified EPA Method 537.1. Only PFOA + PFOS are used for screening.
OR	PFOA	24												Note: The Oregon wastewater initiation levels were adopted into rule (OAR 340-045-0100, Table A) in 2011. The PFAS are 5 chemicals on a list of 118 persistent priority pollutants for water that Oregon DEQ developed in response
	PFOS	300												
	PFNA	1												
	PFOSA	0.2												
	PFHpA	300												

*= Advisory level is based on the total of more than one PFAS

Appendix D: State Soil PFAS Guideline Criteria

State	PFAS Analyte(s)	Guideline Level (mg/kg, unless otherwise specified)	Toxicity Data	Critical Effect Study	Endpoint	RSC (%)	POD	UFs							RfD (mg/kg/day)	Drinking Water Intake Rate (L/day unless otherwise	Exposure assumptions	Target Populations	Resources & Notes
								Total	Interspecies	Intraspecies	LOAEL to NOAEL	Database Limitation	Duration of Exposure (i.e., Subchronic to Chronic)	Sensative Developmental Endpoints					
AK	PFOA	2.2 in Arctic Zone, 1.6 under 40" zone, 1.3 over 40" zone, 0.003 migration to groundwater	Animals (mice)	Lau et al., 2006	Decreassed ossification of pup proximal phalanges, accelerated preputial separation	100	EPA (2016)	EPA (2016)									Residential exposure for 6 yrs old child receptor	Child	http://dec.alaska.gov/media/7543/20180201_pccl.pdf
	PFOS	2.2 in Arctic Zone, 1.6 under 40" zone, 1.3 over 40" zone, 0.0017 migration to groundwater	Animals (mice)	Luebker et al., 2005	Reduced pup body weight	100	EPA (2016)	EPA (2016)									Residential exposure for 6 yrs old child receptor	Child	http://dec.alaska.gov/media/7543/20180201_pccl.pdf
CT	PFOA, PFOS, PFHxS, PFHpA, PFNA	1.35 (residential), 41 (industrial/ commercial), 1.4 ug/kg (GA leachability), 14 ug/kg (GB leachability)															Residential, industrial, and commercial are for direct exposure criteria		
FL	PFOA	1.3 (residential), 25 (industrial/ commercial), 0.002 (leachability) Soil Cleanup Target Levels	Animals (mice)	Lau et al., 2006	Decreassed ossification of pup proximal phalanges, accelerated preputial separation	20	5.3x10^-3 mg/kg/day	300	3		10			10	$2x10^{-5}$	0.054 L/kg/day	Children- 200 mg/day, worker- 50 mg/day, oral	Children ages 0-6	
	PFOS	1.3 (residential), 25 (industrial/ commercial), 0.007 (leachability) Soil Cleanup Target Levels	Animals (mice)	Luebker et al., 2005	decreased weight	20	5.1x10^-4 mg/kg/day	30	3					10	$2x10^{-5}$	0.054 L/kg/day	Risk target level of 10^-6 and hazard quotient of 1	Children ages 0-6	
HI	PFOA-	0.025 (residential), 1.1 (industrial/commercial), 0.001 (dw leaching to gw), 0.25 (non-dw leaching to gw)				20											Noncancer HQ =0 0.5, RSC = 20% and USEPA RSL default exposure parameter values. SESOIL leaching model.	Children ages 0-6	Applicable to soil where potentially impacted groundwater is a current or potential drinking water resource and where the surface water body is located within 150 meters of a release site. Refer to technical memorandum for additional detail: https://health.hawaii.gov/heer/files/2020/12/PFASs-Techncal-Memo-HDOH-Dec-2020.pdf
	PFOS-	0.025 (residential), 1.1 (industrial/commercial), 0.007 (dw leaching to gw), 0.20 (non-dw leaching to gw)				20											Noncancer HQ =0 0.5, RSC = 20% and USEPA RSL default exposure parameter values. SESOIL leaching model.		
	PFNA-	0.003 (residential), 0.12 (industrial/commercial), 0.0008 (dw leaching to gw), 1.4 (non-dw leaching to gw)				20											Noncancer HQ =0 0.5, RSC = 20% and USEPA RSL default exposure parameter values. SESOIL leaching model.		

State	PFAS Analyte(s)	Guideline Level (mg/kg, unless otherwise specified)	Toxicity Data	Critical Effect Study	Endpoint	RSC (%)	POD	UFs							RfD (mg/kg/day)	Drinking Water Intake Rate (L/day unless otherwise	Exposure assumptions	Target Populations	Resources & Notes
								Total	Interspecies	Intraspecies	LOAEL to NOAEL	Database Limitation	Duration of Exposure (i.e., Subchronic to Chronic)	Sensative Developmental Endpoints					
HI	$PFBS^-$	0.38 (residential), 17 (industrial/commercial), 0.003 (dw leaching to gw), 260 (non-dw leaching to gw)				20											Noncancer HQ =0 0.5, RSC = 20% and USEPA RSL default exposure parameter values. SESOIL leaching model.		Applicable to soil where potentially impacted groundwater is a current or potential drinking water resource and where the surface water body is located within 150 meters of a release site. Refer to technical memorandum for additional detail: https://health.hawaii.gov/heer/files/2020/12/PFASs-Technical-Memo-HDOH-Dec-2020.pdf
	$PFHxS^-$	0.012 (residential), 0.55 (industrial/commercial), 0.002 (dw leaching to gw), 0.93 (non-dw leaching to gw)				20											Noncancer HQ =0 0.5, RSC = 20% and USEPA RSL default exposure parameter values. SESOIL leaching model.		
	$PFHpS^-$	0.013 (residential), 0.56 (industrial/commercial), 0.004 (dw leaching to gw), 0.004 (non-dw leaching to gw)				20											Noncancer HQ =0 0.5, RSC = 20% and USEPA RSL default exposure parameter values. SESOIL leaching model.		
	$PFDS^-$	0.013 (residential), 0.56 (industrial/commercial), 0.013 (dw leaching to gw), 0.013 (non-dw leaching to gw)				20											Noncancer HQ =0 0.5, RSC = 20% and USEPA RSL default exposure parameter values. SESOIL leaching model.		
	$PFBA^-$	4.8 (residential), 210 (industrial/commercial), 0.099 (dw leaching to gw), 11 (non-dw leaching to gw)				20											Noncancer HQ =0 0.5, RSC = 20% and USEPA RSL default exposure parameter values. SESOIL leaching model.		
	$PFPeA^-$	0.51 (residential), 23 (industrial/commercial), 0.003 (dw leaching to gw), 0.003 (non-dw leaching to gw)				20											Noncancer HQ =0 0.5, RSC = 20% and USEPA RSL default exposure parameter values. SESOIL leaching model.		
	$PFHxA^-$	2.5 (residential), 110 (industrial/commercial), 0.013 (dw leaching to gw), 21 (non-dw leaching to gw)				20											Noncancer HQ =0 0.5, RSC = 20% and USEPA RSL default exposure parameter values. SESOIL leaching model.		
	$PFHpA^-$	0.025 (residential), 1.1 (industrial/commercial), 0.0003 (dw leaching to gw), 0.0003 (non-dw leaching to gw)				20											Noncancer HQ =0 0.5, RSC = 20% and USEPA RSL default exposure parameter values. SESOIL leaching model.		

State	PFAS Analyte(s)	Guideline Level (mg/kg, unless otherwise specified)	Toxicity Data	Critical Effect Study	Endpoint	RSC (%)	POD	UFs							RfD (mg/kg/day)	Drinking Water Intake Rate (L/day unless otherwise	Exposure assumptions	Target Populations	Resources & Notes
								Total	Interspecies	Intraspecies	LOAEL to NOAEL	Database Limitation	Duration of Exposure (i.e., Subchronic to Chronic)	Sensative Developmental Endpoints					
HI	PFDA	0.003 (residential), 0.11 (industrial/commercial), 0.0005 (dw leaching to gw), 1.2 (non-dw leaching to gw)				20											Noncancer HQ =0 0.5, RSC = 20% and USEPA RSL default exposure parameter values. SESOIL leaching model.		Applicable to soil where potentially impacted groundwater is a current or potential drinking water resource and where the surface water body is located within 150 meters of a release site. Refer to technical memorandum for additional detail: https://health.hawaii.gov/heer/files/2020/12/PFASs-Techncal-Memo-HDOH-Dec-2020.pdf
	PFUnDA	0.006 (residential), 0.28 (industrial/commercial), 0.004 (dw leaching to gw), 4.5 (non-dw leaching to gw)				20											Noncancer HQ =0 0.5, RSC = 20% and USEPA RSL default exposure parameter values. SESOIL leaching model.		
	PFDoDA	0.008 (residential), 0.38 (industrial/commercial), use lab test for leaching to gw				20											Noncancer HQ =0 0.5, RSC = 20% and USEPA RSL default exposure parameter values. SESOIL leaching model.		
	PFTrDA	0.008 (residential), 0.38 (industrial/commercial), use lab test for leaching to gw				20											Noncancer HQ =0 0.5, RSC = 20% and USEPA RSL default exposure parameter values. SESOIL leaching model.		
	PFTeDA	0.084 (residential), 3.8 (industrial/commercial), use lab test for leaching to gw				20											Noncancer HQ =0 0.5, RSC = 20% and USEPA RSL default exposure parameter values. SESOIL leaching model.		
	PFOSA	0.015 (residential), 0.68 (industrial/commercial), 50 (dw leaching to gw), 50 (non-dw leaching to gw)				20											Noncancer HQ =0 0.5, RSC = 20% and USEPA RSL default exposure parameter values. SESOIL leaching model.		
	HFPO-DA	0.1 (residential), 4.5 (industrial/commercial), 0.0003 (dw leaching to gw), 0.0003 (non-dw leaching to gw)															Noncancer HQ =0 0.5, RSC = 20% and USEPA RSL default exposure parameter values. SESOIL leaching model.		
IN	PFBS	1800 (residential), 16000 (commercial/ industrial), 34000 (evacuation worker)	Animals (mice)	EPA RSL Tables		100											Direct contact exposure duration of 250 days/year, or 100000 mg/kg (10% by weight)		

State	PFAS Analyte(s)	Guideline Level (mg/kg, unless otherwise specified)	Toxicity Data	Critical Effect Study	Endpoint	RSC (%)	POD	UFs							RfD (mg/kg/day)	Drinking Water Intake Rate (L/day unless otherwise	Exposure assumptions	Target Populations	Resources & Notes
								Total	Interspecies	Intraspecies	LOAEL to NOAEL	Database Limitation	Duration of Exposure (i.e., Subchronic to Chronic)	Sensative Developmental Endpoints					
MA	PFOA	0.720 ug/kg	Based on soil background data; 90th percentile.																Note: Method 1 standards. Based on 90th percentile value of soil background data set from Vermont soils.
	PFOS	2.000 ug/kg	Based on soil background data; 90th percentile.																
	PFNA	0.320 ug/kg	Based on soil background data; 90th percentile.																
	PFHxS	0.300 ug/kg	Based on soil background data; 90th percentile.																
	PFHpA	0.500 ug/kg	Based on soil background data; 90th percentile.																
	PFDA	0.30 ug/kg	Based on soil background data; 90th percentile.																
ME	PFOA	1.7 (residential), 22 (commercial worker), 4.9 (park user), 5.7 (recreator sediment), 5.1 (construction worker), 0.0095 (leaching to groundwater), 2.5 ng/g (beneficial use)																	
	PFOS	1.7 (residential), 22 (commercial worker), 4.9 (park user), 5.7 (recreator sediment), 5.1 (construction worker), 0.021 (leaching to groundwater), 5.2 ng/g (beneficial use)																	
	PFBS	1700 (residential), 22000 (commercial worker), 4900 (park user), 5700 (recreator sediment), 51000 (construction worker), 7.1 (leaching to groundwater), 1900 ng/g (beneficial use)																	

State	PFAS Analyte(s)	Guideline Level (mg/kg, unless otherwise specified)	Toxicity Data	Critical Effect Study	Endpoint	RSC (%)	POD	UFs							RfD (mg/kg/day)	Drinking Water Intake Rate (L/day unless otherwise	Exposure assumptions	Target Populations	Resources & Notes
								Total	Interspecies	Intraspecies	LOAEL to NOAEL	Database Limitation	Duration of Exposure (i.e., Subchronic to Chronic)	Sensative Developmental Endpoints					
MI	PFOA	10	Animals (primates)	Butenhoff et al., 2002	Hepatotoxicity		LOAEL (3 mg/kg/day)	3000	3	10	10		10		$2x10^{-5}$	0.01			https://www.michigan.gov/egle/0,9429,7-135-3311_4109-251790--,00.html
	PFOA (drinking water source)	0.35	Animals (primates)	Butenhoff et al., 2002	Hepatotoxicity		LOAEL (3 mg/kg/day)	3000	3	10	10		10		$2x10^{-5}$	2			https://www.michigan.gov/egle/0,9429,7-135-3311_4109-251790--,00.html
	PFOS	0.00024	Animals (primates)	Seacat et al., 2002	Decreased body weight, hepatotoxicity, thyroid toxicity		NOAEL (0.03 mg/kg/day)	30	3	10					$1.3667x10^{-5}$	0.01			https://www.michigan.gov/egle/0,9429,7-135-3311_4109-251790--,00.html
	PFOS (drinking water source)	0.00022	Animals (primates)	Seacat et al., 2002	Decreased body weight, hepatotoxicity, thyroid toxicity		NOAEL (0.03 mg/kg/day)	30	3	10					$1.3667x10^{-5}$	2			https://www.michigan.gov/egle/0,9429,7-135-3311_4109-251790--,00.html
MN	PFOA	0.24, 3.2 (ug/kg)	Animals (mice)	Numerous	Hepatotoxicity, Kidney Effects, Immunotoxicity, Developmental Effects	0.2 (combined HQ/RSC)	38 mg/L serum concentration	300	3	10	3	3			$1.8x10^{-5}$		Resident, Industrial	Children, adults	https://www.pca.state.mn.us/waste/risk-based-site-evaluation-guidance
	PFOS	0.041, 0.56 (ug/kg)	Animals (mice)	Numerous	Hepatotoxicity, Thyroid efects, Immunotoxicity, Developmental Effects	0.2 (combined HQ/RSC)	2.36 ug/L serum concentration	100	3	10		3			$3.1x10^{-6}$		Resident, Industrial	Children, adults	https://www.pca.state.mn.us/waste/risk-based-site-evaluation-guidance
	PFBA	38, 520 (ug/kg)	Animals (rats)	Numerous	Hepatotoxicity, Thyroid Effects	0.2 (combined HQ/RSC)	6.9 mg/kg/day	300	3	10		10			$2.9x10^{-3}$		Resident, Industrial	Children, adults	https://www.pca.state.mn.us/waste/risk-based-site-evaluation-guidance
	PFBS	5.7, 77 (ug/kg)	Animals (mice)	Numerous	Developmental effects, Thyroid effects, Reproduction	0.2 (combined HQ/RSC)	60 mg/kg/day	300	3	10		3	3		$1.4x10^{-3}$		Resident, Industrial	Children, adults	https://www.pca.state.mn.us/waste/risk-based-site-evaluation-guidance
	PFHxS	0.13, 1.7 (ug/kg)	Animals (rats)	Numerous	Hepatotoxicity, Thyroid Effects	0.2 (combined HQ/RSC)	32.4 ug/mL	300	3	10		10			$9.7x10^{-6}$		Resident, Industrial	Children, adults	https://www.pca.state.mn.us/waste/risk-based-site-evaluation-guidance

State	PFAS Analyte(s)	Guideline Level (mg/kg, unless otherwise specified)	Toxicity Data	Critical Effect Study	Endpoint	RSC (%)	POD	UFs							RfD (mg/kg/day)	Drinking Water Intake Rate (L/day unless otherwise	Exposure assumptions	Target Populations	Resources & Notes
								Total	Interspecies	Intraspecies	LOAEL to NOAEL	Database Limitation	Duration of Exposure (i.e., Subchronic to Chronic)	Sensative Developmental Endpoints					
NH	PFOA	0.2 (residential), 1.3 (maintenance worker)				0.2									$6.1x10^{-6}$		Residential (young child), Maintenance worker (outdoor)		https://www4.des.state.nh.us/nh-pfas-investigation/wp-content/uploads/PFAS-DCRB-value-121119.pdf
	PFOS	0.1 (residential), 0.6 (maintenance worker)				0.2									$3x10^{-6}$		Residential (young child), Maintenance worker (outdoor)		https://www4.des.state.nh.us/nh-pfas-investigation/wp-content/uploads/PFAS-DCRB-value-121119.pdf
	PFHxS	0.1 (residential), 0.9 (maintenance worker)				0.2									$4x10^{-6}$		Residential (young child), Maintenance worker (outdoor)		https://www4.des.state.nh.us/nh-pfas-investigation/wp-content/uploads/PFAS-DCRB-value-121119.pdf
	PFNA	0.1 (residential), 0.9 (maintenance worker)				0.2									$4.3x10^{-6}$		Residential (young child), Maintenance worker (outdoor)		https://www4.des.state.nh.us/nh-pfas-investigation/wp-content/uploads/PFAS-DCRB-value-121119.pdf
NM	PFOS	1.56 (residential) 26.0 (industrial) 7.08 (construction)																	20.6.2.4103.A of the New Mexico Administrative Code, implemented in conjunction with NMED's 2019 Risk Assessment Guidance
	PFOA	1.56 (residential) 26.0 (industrial) 7.08 (construction)																	
	PFHxS	1.56 (residential) 26.0 (industrial) 7.08 (construction)																	
NY	PFOA	0.66 ug/kg (unrestricted), 6.6 ug/kg (residential), 33 ug/kg (restricted residential), 500 ug/kg (commercial), 600 ug/kg (industrial), 1.1 ug/kg (protection of groundwater)																	
	PFOS	0.88 ug/kg (unrestricted), 8.8 ug/kg (residential), 44 ug/kg (restricted residential), 440 ug/kg (commercial), 440 ug/kg (industrial), 3.7 ug/kg (protection of groundwater)																	

State	PFAS Analyte(s)	Guideline Level (mg/kg, unless otherwise specified)	Toxicity Data	Critical Effect Study	Endpoint	RSC (%)	POD	UFs							RfD (mg/kg/day)	Drinking Water Intake Rate (L/day unless otherwise	Exposure assumptions	Target Populations	Resources & Notes
								Total	Interspecies	Intraspecies	LOAEL to NOAEL	Database Limitation	Duration of Exposure (i.e., Subchronic to Chronic)	Sensative Developmental Endpoints					
TX	PFBA	0.2	Animals (mice)	MDH	Hepatotoxicity		NOAEL (6.9 mg/kg/d)	2400	1	10		10	3		$2.9x10^{-3}$				Note: oral dose, 0.5 acre source area) (Res GWSoiling PCLs) https://www.tceq.texas.gov/assets/public/implementation/tox/evaluations/pfcs.pdf
	PFBuS	0.11	Animals (mice)	Leider et al., 2009, York et al., 2002	Systemic Toxicity		NOAEL (60 mg/kg/d)	42600	1	10		10	3		$1.4x10^{-3}$				
	PFPeA	0.00032	Animals (mice)	Surrogate: PFHxS	Hematotoxicity		NOAEL (0.3 mg/kg/d)	78900	1	10	3	10			$3.8x10^{-6}$				
	PFHxS	0.002	Animals (mice)	Hoberman and York, 2003	Hematotoxicity		NOAEL (0.3 mg/kg/d)	78900	1	10	3	10			$3.8x10^{-6}$				
	PFHxA	0.00048	Animals (mice)	Surrogate: PFHxS	Hematotoxicity		NOAEL (0.3 mg/kg/d)	78900	1	10	3	10			$3.8x10^{-6}$				
	PFHpA	0.0046	Animals (mice)	Surrogate: PFOS	Neurodevelopment		NOAEL (0.6 mg/kg/d)	26300	1	10	10	1			$2.3x10^{-5}$				
	PFOS	0.05	Animals (mice)	Zeng et al., 2011	Neurodevelopment		NOAEL (0.6 mg/kg/d)	26300	1	10	10	1			$2.3x10^{-5}$				
	PFOA	0.003	Animals (mice)	Macon et al., 2011	Mammary gland development		NOAEL (0.3 mg/kg/d)	24300	1	10	30	1			$1.2x10^{-5}$				
	PFOSA	0.92	Animals (mice)	Surrogate: PFOA	Mammary gland development		NOAEL (0.3 mg/kg/d)	24300	1	10	30	1			$1.2x10^{-5}$				
	PFNA	0.0031	Animals (mice)	Fang et al., 2010	Spleen Cell Death		NOAEL (1 mg/kg/d)	81000	1	10		10	10		$1.2x10^{-5}$				
	PFDeA	0.022	Animals (mice)	Kawashima et al., 1995	Hepatotoxicity		NOAEL (1.2 mg/kg/d)	81000	1	10		10	10		$1.5x10^{-5}$				
	PFDS	0.04	Animals (mice)	Surrogate: PFDoA	Reduced Body Weight		NOAEL (1 mg/kg/d)	81000	1	10		10	10		$1.2x10^{-5}$				
	PFUA	0.018	Animals (mice)	Surrogate: PFDoA	Reduced Body Weight		NOAEL (1 mg/kg/d)	81000	1	10		10	10		$1.2x10^{-5}$				
	PFDoA	0.034	Animals (mice)	Shi et al., 2007	Reduced Body Weight		NOAEL (1 mg/kg/d)	81000	1	10		10	10		$1.2x10^{-5}$				
	PFTrDA	0.061	Animals (mice)	Surrogate: PFDoA	Reduced Body Weight		NOAEL (1 mg/kg/d)	81000	1	10		10	10		$1.2x10^{-5}$				
	PFTeDA	0.11	Animals (mice)	Surrogate: PFDoA	Reduced Body Weight		NOAEL (1 mg/kg/d)	81000	1	10		10	10		$1.2x10^{-5}$				
VT	PFOA, PFOS, PFHxS, PFHpA, PFNA	1.22*	Animals (mice)	EPA (2016)	EPA (2016)	20	EPA (2016)	EPA (2016)								0.175 L/kg/day			

State	PFAS Analyte(s)	Guideline Level (mg/kg, unless otherwise specified)	Toxicity Data	Critical Effect Study	Endpoint	RSC (%)	POD	UFs							RfD (mg/kg/day)	Drinking Water Intake Rate (L/day unless otherwise	Exposure assumptions	Target Populations	Resources & Notes
								Total	Interspecies	Intraspecies	LOAEL to NOAEL	Database Limitation	Duration of Exposure (i.e., Subchronic to Chronic)	Sensative Developmental Endpoints					
WI	PFOA	1.26 (residential), 16.4 (composite [industrial] worker)		EPA RSL Tables									26 yrs, 350 days/yr, 24 hrs (residential), 25 yrs, 250 days/yr, 8 hrs (composite worker)		$2x10^{-5}$		Vary through life (residential), 80 kg wt, 100 mg/day intake (composite worker) THQ=1, cancer risk 1x10-6, other default assumptions	Residential, Composite Worker	EPA RSL calculator
	PFOS	1.26 (residential), 16.4 (composite [industrial] worker)		EPA RSL Tables									26 yrs, 350 days/yr, 24 hrs (residential), 25 yrs, 250 days/yr, 8 hrs (composite worker)		$2x10^{-5}$		Vary through life (residential), 80 kg wt, 100 mg/day intake (composite worker) THQ=1, cancer risk 1x10-6, other default assumptions	Residential, Composite Worker	EPA RSL calculator
	PFBS	1260 (residential), 16400 (composite [industrial] worker)		EPA RSL Tables									26 yrs, 350 days/yr, 24 hrs (residential), 25 yrs, 250 days/yr, 8 hrs (composite worker)		$2x10^{-2}$		Vary through life (residential), 80 kg wt, 100 mg/day intake (composite worker) THQ=1, cancer risk 1x10-6, other default assumptions	Residential, Composite Worker	EPA RSL calculator

*= Advisory level is based on the total of more than one PFAS

Appendix E: State Air PFAS Guideline Criteria

State	PFAS Analyte(s)	Guideline Level ($\mu g/m^3$)	Toxicity Data	Critical Effect Study	Endpoint	POD	HED (mg/kg/day)	UFs						RfD (mg/kg/day)	Route-to-Route Extrapolation	Exposure Parameters	Target Populations	Resources
								Total	Interspecies	Intraspecies	LOAEL to NOAEL	Database Limitation	Duration of Exposure (i.e., Subchronic to Chronic)					
MI	PFOA (initial threshold screening level; ITSL)	0.07	Animals (mice)	EPA, 2016; Butenhoff et al., 2004; Lau, 2006	Acute, Reproductive/ Developmental		0.0053; 0.0064	300	3	10	10		2 generations +developmental	$2x10^{-5}$	Air Value (ITSL) = RfD x $70kg/20m^3$	Continuous over time period= 24 hours	Sensitive indivuals	http://www.deq.state.mi.us/aps/downloads/ATSL/335-67-1/335-67-1_24hr_ITSL.pdf
	PFOS (initial threshold screening level; ITSL)	0.07	Animals (rats)	EPA, 2016; Luebker et al., 2005	Acute, Reproductive/ Developmental		0.00051	30	10	3			2 generations +developmental	$2x10^{-5}$	Air Value (ITSL) = RfD x $70kg/20m^3$	Continuous over time period= 24 hours	Sensitive indivuals	http://www.deq.state.mi.us/aps/downloads/ATSL/1763-23-1/1763-23-1_24hr_ITSL.pdf
	6:2 FTS	1	Animals (rats)	ECHA, 2020; Rat, subchronic, oral	Cardiac	NOAEL 5 mg/kg	1.18	3000	3	10		10	10	0.00039	Air Value (ITSL) = RfD x $70kg/20m^3$	Continuous over time period= annual (chronic)	Sensitive indivuals	http://www.deq.state.mi.us/aps/downloads/ATSL/27619-97-2/
NH	APFO (CAS #3825-26-1; 24-hr Ambient Air Limit)	Regulatory Level 0.05	Animals (rats)	ACGIH TLV	Acute, Reproductive/ Developmental													
	APFO (CAS #3825-26-1; Annual Ambient Air Limit)	Regulatory Level 0.024	Animals (rats)	ACGIH TLV	Acute, Reproductive/ Developmental													
TX	PFOA (ESL) (CAS #335-67-1; based on annual average)	0.005		Republic of Germany DFG Maximum Concentration at the Workplace				1000								Occupational Exposure Limit		
	PFOS (ESL) (CAS #1763-23-1; based on annual average)	0.01		Republic of Germany DFG Maximum Concentration at the Workplace				100								Occupational Exposure Limit		

*= Advisory level is based on the total of more than one PFAS

Appendix F: State Fish and Wildlife Consumption PFAS Guideline Criteria

State	Media	PFAS Analyte(s)	Guideline Level (unit specified)	Frequency	Target Populations	Resources & Notes
CT	Fish	PFOA, PFOS	<20 ppb	No consumption advice	General Population	
	Fish	PFOA, PFOS	20 to <40 ppb	1 meal per week	General Population	
	Fish	PFOA, PFOS	40 to <159 ppb	1 meal per month	General Population	
	Fish	PFOA, PFOS	≥159 ppb	Do Not Eat	General Population	
ME	Fish	PFOA	0.052 mg/kg			
	Fish	PFOS	0.052 mg/kg			
	Fish	PFBS	52 mg/kg			
	Milk	PFOS	210 ug/L			
	Beef	PFOS	3.4 ng/g			
MI	Fish	PFOS	≤9 ppb	16 meals per month	All Populations	
	Fish	PFOS	>9-13 ppb	12 meals per month	All Populations	
	Fish	PFOS	>13-19 ppb	8 meals per month	All Populations	
	Fish	PFOS	>19-38 ppb	4 meals per month	All Populations	
	Fish	PFOS	>38-75	2 meals per month	All Populations	
	Fish	PFOS	>75-150	1 meal per month	All Populations	
	Fish	PFOS	>150-300	6 meals per year	All Populations	
	Fish	PFOS	>300 ppb	Do Not Eat	All Populations	
	Deer	PFOS	>300 ppb	Do Not Eat	All Populations	
MN	Fish	PFOS	>10-20 ppb	2 meals per week	All Populations	
	Fish	PFOS	>20-50 ppb	1 meal per week	All Populations	
	Fish	PFOS	>50-200 ppb	1 meal per month	All Populations	
	Fish	PFOS	>200 ppb	Do Not Eat	All Populations	
NJ	Fish	PFOS	0.56 ng/g; ppb	Unlimited (based on daily)	General Population and High Risk Population	
	Fish	PFOS	3.9 ng/g; ppb	1 meal per week	General Population and High Risk Population	
	Fish	PFOS	17 ng/g; ppb	1 meal per month	General Population and High Risk Population	
	Fish	PFOS	>17 ng/g; ppb	Do Not Eat	High Risk Population	
	Fish	PFOS	51 ng/g; ppb	1 meal every 3 months	General Population	
	Fish	PFOS	204 ng/g; ppb	1 meal per year	General Population	
	Fish	PFOS	>204 ng/g; ppb	Do Not Eat	General Population	

State	Media	PFAS Analyte(s)	Guideline Level (unit specified)	Frequency	Target Populations	Resources & Notes
NJ	Fish	PFNA	0.23 ng/g; ppb	Unlimited (based on daily)	General Population and High Risk Population	
	Fish	PFNA	1.6 ng/g; ppb	1 meal per week	General Population and High Risk Population	
	Fish	PFNA	6.9 ng/g; ppb	1 meal per month	General Population and High Risk Population	
	Fish	PFNA	>6.9 ng/g; ppb	Do Not Eat	High Risk Population	
	Fish	PFNA	21 ng/g; ppb	1 meal every 3 months	General Population	
	Fish	PFNA	84 ng/g; ppb	1 meal per year	General Population	
	Fish	PFNA	>84 ng/g; ppb	Do Not Eat	General Population	
	Fish	PFOA	0.62 ng/g; ppb	Unlimited (based on daily)	General Population and High Risk Population	
	Fish	PFOA	4.3 ng/g; ppb	1 meal per week	General Population and High Risk Population	
	Fish	PFOA	19 ng/g; ppb	1 meal per month	General Population and High Risk Population	
	Fish	PFOA	>19 ng/g; ppb	Do Not Eat	High Risk Population	
	Fish	PFOA	57 ng/g; ppb	1 meal every 3 months	General Population	
	Fish	PFOA	226 ng/g; ppb	1 meal per year	General Population	
	Fish	PFOA	>226 ng/g; ppb	Do Not Eat	General Population	
NY	Fish	PFOS	<50 ppb	4 meals per month	General Population	
	Fish	PFOS	>50-200 ppb	1 meal per month	General Population	
	Fish	PFOS	>50 ppb	Do Not Eat	Sensitive Population	
	Fish	PFOS	>200 ppb	Do Not Eat	General Population	
WA	Fish	PFOS	23 ng/g		General Population	In process
	Fish	PFOS	8 ng/g		High consumers	In process
WI	Fish	PFOS	>20-50 ppb	1 meal per week	All Populations	
	Fish	PFOS	>50-200 ppb	1 meal per month	All Populations	
	Fish	PFOS	>200 ppb	Do Not Eat	All Populations	
	Deer	PFOS	>20-50 ppb	1 meal per week	All Populations	Under Review
	Deer	PFOS	>50-200 ppb	1 meal per month	All Populations	Under Review
	Deer	PFOS	>200 ppb	Do Not Eat	All Populations	Under Review

EXHIBIT D

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December 30, 2021

VIA ELECTRONIC MAIL
Suhair Shallal
EPA Designated Federal Officer (DFO)
shallal.suhair@epa.gov

Re: Comments of the PFAS Regulatory Coalition to the SAB PFAS Review Panel

Dear Ms. Shallal:

The PFAS Regulatory Coalition (Coalition) appreciates the opportunity to submit comments relating to the Scientific Advisory Board (SAB) PFAS Review Panel's committee charge and meeting materials related to EPA's development of National Primary Drinking Water Regulations (NPDWRs) for per- and polyfluoroalkyl substances (PFAS).

I. The Coalition's Interest

The Coalition is a group of industrial companies, municipal entities, agricultural parties, and trade associations that are directly affected by policies and regulations related to PFAS. Coalition membership includes entities in the airport, automobile, coke and coal chemicals, iron and steel, municipal, paper, petroleum, and other sectors. None of the Coalition members manufactures PFAS compounds.

II. The Coalition's Comments

EPA has made final determinations to regulate two contaminants, perfluorooctanesulfonic acid (PFOS) and perfluorooctanoic acid (PFOA), and is moving forward to implement the national primary drinking water regulation development process for PFAS. As part of that process, EPA has developed draft documents to support the National Primary Drinking Water Regulations (NPDWRs) for PFAS and has requested SAB review.

The Coalition supports EPA's development of federal Maximum Contaminant Level (MCL) standards for PFOA and PFOS—two of the most well-known and perhaps highest risk PFAS chemicals. A patchwork of 50 different state solutions would prove unworkable and contrary to how the United States has previously addressed similar

emerging-contaminant issues. While some limited variations in state regulation may be expected and appropriate, the highly variable regulatory health advisories, action levels and, in particular, drinking water standards currently being developed or under consideration across the country create unnecessary confusion and complexity for the public and the regulated community. Therefore, the Coalition supports EPA's efforts to develop and build a consensus around the science that will inform the NPDWR for PFAS. Nonetheless, the Coalition has concerns, summarized below, regarding some of the data and methodology underlying the proposed toxicity values for PFOS and PFOA.

- Additional data are needed to justify the toxicity values. Specifically, environmental epidemiological studies, absent supporting data from animal laboratory studies, are insufficient. For example, with use of epidemiological studies alone, there is uncertainty regarding exposure, confounding factors, and sample size. Accordingly, the Coalition recommends using the epidemiology to complement animal laboratory data and corroborate findings, but not as an independent basis for developing toxicity values.

- The data do not reflect the best available science for estimating the half-life of PFAS in humans, which range considerably and appear to show a gender difference for some PFAS. Moreover, the half-life estimates are overstated, as they do not appear to account for the higher elimination rates when concentrations of PFAS saturate human retention systems. EPA's review should consider the elimination of higher doses of PFAS.

- The data from environmental epidemiology studies regarding vaccine antibodies are not an appropriate basis for deriving MCL goals for PFOA and PFOS. The proposed MCL goals are based on reports of a reduction in vaccine antibodies in children of the Faroe Islands—a unique population with documented exposure to other environmental pollutants, such as methylmercury and PCBs. Beyond these confounding factors, any reduction in vaccine antibodies does not constitute an adverse health effect in itself.

- Different classes of PFAS should not be treated as additive. There are thousands of PFAS compounds, with unique chemical structures. The Coalition supports EPA's focus on PFOS and PFOA in the Agency's ongoing rulemaking effort. However, even when evaluating a single PFAS compound, additivity should not be assumed unless the mode of action and organ system being evaluated are the same.

- EPA has not justified deviating from the standard relative source contribution (RSC) of 20 percent. There are numerous other exposure pathways, including from food ingestion, inhalation, and dermal contact. Although PFAS may be pervasive in source water, the data do not show that PFAS is widely found in concentrations that justify deviating from the standard RSC value.

- EPA should not rely on the recent Shearer, et al. study as the key study for modeling results for cancer. The study failed to control for confounding factors, which results in modeling that does not reflect actual health risks. The concerns about this study include: 1) the advanced age of the study group (ranging from 55 to 70+ years), which fails to represent child and young receptors; 2) failure to recognize that renal cell carcinoma is a common occurrence in adults 60 to 70 years old but is rare in young subjects; and 3) a weak, inconsistent, and insignificant dose-response relationship. Other epidemiological studies exist that more accurately represent the general population. The Coalition urges EPA to reconsider its reliance on the flawed Shearer, et al. study.

- The RfDs proposed for PFOA and PFOS are as low or lower than some substances that are generally recognized as extremely toxic. If EPA believes that PFOA and PFOS are as toxic as those other substances, it must provide a clearer explanation for that assessment.

III. Conclusion

The Coalition appreciates the opportunity to comment concerning the SAB PFAS Review Panel's committee charge and meeting materials. We look forward to working closely with EPA to support an informed SAB review and throughout EPA's NPDWR rulemaking effort for PFAS. Please feel free to call or e-mail if you have any questions, or if you would like any additional information concerning the issues raised in these comments.

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EXHIBIT E

December 30, 2021

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Chair
PFAS Review Panel
Science Advisory Board
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Re: Proposed approaches to the derivation of draft maximum contaminant level goals for perfluorooctanoic acid and perfluorooctane sulfonic acid

Dr. Chiu:

The American Chemistry Council (ACC) provides the following comments on the draft documents provided to the PFAS Review Panel (the Panel) for review relating to derivation of maximum contaminant level (MCL) goals for perfluorooctanoic acid (PFOA) and perfluorooctane sulfonic acid (PFOS). In light of the abbreviated review period that has been provided, we have highlighted the significant issues we have identified in the drafts to be reviewed. These issues include the following –

- The epidemiology data do not provide clear evidence of an association between PFOA or PFOS exposure and reduced vaccine response in children;
- The evidence for an increase in infection rates among children exposed to PFOA and PFOS is conflicting;
- USEPA has mischaracterized the evidence for other non-cancer endpoints
- There is a lack of consistent response in the human and animal evidence for the carcinogenic potential of PFOA;
- USEPA has not made the details of the benchmark dose and pharmacokinetic modeling available for stakeholder review and comment; and
- The relative source contribution of PFOA and PFOS in drinking water is considerably higher than the default assumption of twenty percent.

Reduced Vaccine Response in Children

Budtz-Jorgensen and Grandjean (2018)[1] report two findings from the study of diphtheria and tetanus antibody concentrations associations among Faroe Islands children –

- An association between prenatal exposure to PFOA/PFOS and antibody concentrations at 5 years of age, and
- An association between PFOA/PFOS serum concentrations at age 5 and antibody concentrations at age 7.[2]

In an earlier publication by Grandjean et al. (2012),[3] however, this research group did not observe an association between maternal PFOA/PFOS serum concentrations and antibody concentrations at age 5 in a cohort of children born between 1997 and 2000. Although the researchers reported an association in a cohort of Faroe Islands children born from 2007 and 2009, serum concentrations were lower than in the earlier cohort (**see Table 1**).

Table 1. Comparison of Serum Concentrations at Birth and 60 months in the Studies of Faroe Islands Children

	Median Concentration (Interquartile Range)			
	1997-2000 Cohort[a]		2007-2009 Cohort[b]	
	At birth	At 60 months	At birth	At 60 months
PFOS (ng/ml)	27.3 (23.2,33.1)	16.7 (13.5,21.1)	n/a	4.7 (3.5,6.3)
PFOA	3.20 (2.6,4.0)	4.1 (3.3,4.9)	n/a	2.2 (1.8,2.8)
[a] Source: Table 2, Grandjean *et al.* 2012;				
[b] Source: Table 1, Grandjean *et al.* 2017a[4]				

[1] Budtz-Jorgensen E and Grandjean P. Application of benchmark analysis for mixed contaminant exposures: mutual adjustment of perfluoroalkyl substances associated with immunotoxicity. *PLoS ONE* 13:e0205388 (2018).

[2] The draft approaches select the benchmark dose modeling results for the serum levels at age 5 and antibody levels at age 7 from the cohort of children born between 1997-2000 to calculate the reference doses.

[3] Grandjean P *et al.* Serum vaccine antibody concentrations in children exposed to perfluorinated compounds. *J Amer Med Assn* 307(4):391-397 (2012).

[4] Grandjean P *et al.* Estimated exposures to perfluorinated compounds in infancy predict antibody concentrations at age 5 years. *J Immuno* 14(1):188-195 (2017a). Maternal serum concentrations are not provided

Among 7-year olds, the Faroe Islands researchers did not find an association between serum concentrations at 7 and antibody levels after excluding children suspected of receiving additional antibodies (*i.e.*, no booster, ER visit, or unexplained antibody increase).[5] Although the 2012 publication reports an association between serum levels of PFOA at age 5 and tetanus antibody concentrations at age 7,[6] the analysis does not control for children receiving additional antibodies between ages 5 and 7. Given the results of the prior analysis, this would appear to be a significant oversight that raises additional questions about the broad conclusion that exposure to PFOA or PFOS reduces vaccine response in children.

Infection Rates Among Children

In the draft documents for PFOA and PFOS, EPA suggests that a decrease in antibody concentrations may reduce the prevention of diphtheria and tetanus in children. Results of associations between PFOA exposure and childhood infection are mixed, however, with studies reporting both increased and decreased associations with reported infections.[7] As a result, the National Toxicology Program (NTP) concluded that there is low confidence that exposure to either substance is associated with an increased incidence of infectious disease or a lower ability to resist or respond to infectious disease.[8]

The epidemiological evidence for an association between PFOA and PFOS exposure and hypersensitivity and autoimmune disease is also mixed. Studies that observed significant associations with "ever" or "current" asthma were seen primarily in sex- or age-specific subgroups but were null or insignificant in whole study analyses. For allergy and eczema outcomes, results were inconsistent across studies. Studies of PFOS exposure and autoimmune condition in humans are limited, and the results from studies of PFOA exposure and human autoimmune disease are mixed. While Steenland *et al.* reported an association with ulcerative colitis,[9] the analysis did not adequately control for confounding factors such as gastrointestinal infection and family history.[10]

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5 Grandjean P *et al.* Serum vaccine antibody concentrations in adolescents exposed to perfluorinated compounds. *Environ Health Perspect* 125:077018 (2017b).

6 No association is observed between PFOS serum concentrations at age 5 and diphtheria antibody concentrations at age 7, after adjusting for the antibody concentration at age 5.

7 Steenland K *et al.* Review: Evolution of evidence on PFOA and health following the assessments of the C8 Science Panel. *Environ Int* 145: 106125 (2020).

8 NTP. Immunotoxicity Associated with Exposure to Perfluorooctanoic acid or Perfluorooctane Sulfonate. NTP Monograph. US Department of Health and Human Services. (September 2016)

9 Steenland K *et al.* Ulcerative colitis and perfluorooctanoic acid (PFOA) in a highly exposed population of community residents and workers in the mid-Ohio valley. *Environ Health Perspect* 121: 900-905 (2013).

10 http://www.c8sciencepanel.org/study.html.

Evidence for Other Non-Cancer Endpoints

In addition to vaccine antibody response, EPA calculates candidate reference doses (RfDs) for PFOA and PFOS based on recent epidemiological studies reporting an association between prenatal exposure to the two substances and decreased birth weight. Although EPA does not calculate a candidate RfD for cardiovascular disease (CVD), the Agency has developed a draft analysis of the potential for reducing CVD risks as the result of implementation of drinking water standards for PFOA and PFOS.

Reduced Birth Weight

As noted in the draft documents, several human studies have investigated PFOA and PFOS exposure and birth outcomes, including birth weight. Most of these studies did not find an association between maternal serum levels and birth weight.[11] Among the negative studies was an occupational exposure study in which female workers were exposed to high levels of PFOS.[12] In many of those studies reporting an inverse relationship, moreover, the effect was small and limited to a single sex or exposure group.

Among the five studies for which EPA conducted benchmark dose modeling to develop a candidate RfD based on reduced birth weight, two did not report a significant association with maternal serum concentrations of PFOA or PFOS – Govarts *et al.* 2016[13] and Sagiv *et al.* 2017.[14] Moreover, Starling et al. (2017)[15] did not observe a significant association with serum concentration of PFOS and reported an association only in the highest tertile of PFOA concentration. In the study by Chu *et al.* (2020), the association was not significant in the analysis by serum concentration quartiles for either substance or in the continuous serum

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[11] Agency for Toxic Substances and Disease Registry (ATDSR). Toxicological Profile for Perfluoroalkyls. US Department of Health and Human Services (May 2021).

[12] Grice MM *et al.* Self-reported medical conditions in perfluorooctanesulfonyl fluoride manufacturing workers. *J Occup Environ Med* 49(7):722-729 (2007).

[13] Govarts E *et al.* Combined effects of prenatal exposures to environmental chemicals on birth weight. *Int J Environ Res Public Health* 13:495 (2016).

[14] Sagiv SK *et al.* Early Pregnancy Perfluoroalkyl Substance Plasma Concentrations and Birth Outcomes in Project Viva: Confounded by Pregnancy Hemodynamics? *Am J Epidemiol* 187: 793-802 (2017). The association with PFOS was not significant after adjusting for potential confounders.

[15] Starling AP *et al.* Perfluoroalkyl substances during pregnancy and offspring weight and adiposity at birth: Examining mediation by maternal fasting glucose in the healthy start study. *Environ Health Perspect* 125: 067016 (2017).

concentration analysis for PFOA.[16] The final study by Wikstrom *et al.* (2019)[17] reported an association with PFOA and PFOS concentration in the highest quartile of girls; no association was observed in infant boys. Calculating an RfD from these epidemiology studies is inappropriate based on the higher degree of uncertainty in the findings.

Cardiovascular Disease

Most of the research on cardiovascular disease (CVD) associated with PFOA and PFOS has focused on blood pressure in the general adult population. These studies do not provide consistent evidence for an association between exposure to the two substances and blood pressure. Similarly, the evidence for an association between PFOA or PFOS and an increased risk of hypertension is inconsistent. Evidence for other CVD-related outcomes across all study populations is limited and inconsistent. Although there is some evidence for an association with a modest increase in cholesterol, the increase does not correlate with increased CVD. Accordingly, the C8 Science Panel found no evidence of a link with CVD, raising the distinct possibility that people with high cholesterol may retain PFOA, rather than PFOA being responsible for an increase in cholesterol.[18]

Human and Animal Evidence for the Carcinogenic Potential of PFOA

EPA has developed a cancer slope factor for PFOA based on elevated levels of kidney cancer (renal cell carcinoma, or RCC) reported by Shearer *et al. (2021).*[19] The Agency concluded that the available data do not support the development of a cancer estimate for PFOS.

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.[20] The subjects had baseline serum collected during 1993-2002, although the samples were not analyzed for PFOA and other PFAS until 2018. The cases were diagnosed with RCC subsequent to serum collection.

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[16] Chu C *et al.* Are perfluorooctane sulfonate alternatives safer? New insights from a birth cohort study. *Environ Intl* 135: 105365 (2020). While the OR for continuous serum concentration (per nanogram/milliliter) did not include 1, the confidence interval is quite wide (1.08, 5.47).

[17] Wikström, S *et al.* Maternal serum levels of perfluoroalkyl substances in early pregnancy and offspring birth weight. *Pediatric Res* 87: 1093-1099 (2019).

[18] Fletcher T *et al.* Probable Link Evaluation for heart disease (including high blood pressure, high cholesterol, coronary artery disease). C8 Science Panel (2012). http://www.c8sciencepanel.org/pdfs/Probable_Link_C8_Heart_Disease_29Oct2012.pdf

[19] Shearer JJ *et al.* Serum concentrations of per-and polyfluoroalkyl substances and risk of renal cell carcinoma. *J Natl Cancer Inst* 113:580-587 (2021).

[20] 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.

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

As shown in **Table 2** 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

Table 2. Odds ratios and 95% confidence intervals (CIs) evaluating PFOA serum concentration and risk of renal cell carcinoma (Shearer *et al.* 2021)[22]

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[23]			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.

[21] 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.

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

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

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.

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.

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[24] provided by the authors suggests 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 practice" 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.[25] 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 for 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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[24] https://academic.oup.com/jnci/article/113/5/580/5906528#supplementary-data

[25] 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[26] 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 data that could clear up the discordance between human and laboratory animal kidney disease attributed to PFOA.

Two other publications explore the incidence of kidney cancer among residents of the Mid-Ohio Valley exposed to PFOA in drinking water – Vieira *et al.* (2023)[27] and Barry *et al.* (2013).[28] The study by Barry *et al.* 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 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)[29] 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.[30] The researchers calculated hazard ratios (HRs) for an increase in kidney cancer among

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[26] 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

[27] Vieira VM *et al.* Perfluorooctanoic acid exposure and cancer outcomes in a contaminated community: a geographic analysis. *Environ Health Perspect* 121: 318-323 (2013).

[28] Barry V *et al.* Perfluorooctanoic acid (PFOA) exposures and incident cancers among adults living near a chemical plant. *Environ Health Perspect* 121: 1313-1318 (2013).

[29] Steenland K and Woskie S. Cohort mortality study of workers exposed to perfluorooctanoic acid. *Am J Epidemiol* 176: 909-917 (2012).

[30] 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.

residents, workers, and the combined group cohort for both continuous and quartiles of PFOA serum concentration.[31]

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)[32]

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

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.

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 was conducted by the National Toxicology Program (NTP).[33] In addition, no plausible biological basis for the development of tumors from PFOA exposure has been reported. Without it, there does not appear to be sufficient information to establish causation.

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[31] 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.*

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

[33] 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).

Review of Benchmark Dose and Pharmacokinetic Models

In calculating the RfDs for vaccine antibody response, EPA used the results of benchmark dose (BMD) model presented by Budtz-Jorgensen and Grandjean (2018). The details of the model are not available for review by stakeholders and the validity of the model is questionable. Significantly, the dose-response relationship reported is driven by statistical, rather than clinical, significance. There is a clinical cut-off level that exists for antibody concentrations that represent long-term protection. Instead of using dichotomous antibody concentrations in the model, based on the clinical cut-off, the authors used continuous antibody concentration in order to detect evaluate a dose-response relationship.

Moreover, the estimated BMD and lower limit of the BMD (BMDL) obtained from the model are unstable. The authors reported BMD and BMDL estimates for PFOA, PFOS, and three other PFAS. Estimates for PFOA are unaffected by the mutual adjustment for other substances. For the other 4 PFAS, however, mutual adjustment yields unstable estimates that included infinity values. In addition, PFOA and PFOS have been observed to be highly correlated, but the model shows no indication of the interactions between these two compounds.

For its analysis, EPA selects the lowest BMDL from the Budtz-Jorgensen and Grandjean analysis using three models (piecewise, linear, conservative) adjusted and unadjusted for other PFAS. The dose-response relationship is only available for the linear and piecewise models from an earlier publication. Estimated BMDs and BMDLs obtained from the conservative model are almost 10 times higher compared to those of the piecewise model. The conservative model assumes no effect below the lowest observed concentration and therefore yields the highest plausible benchmark results that agree with the data.

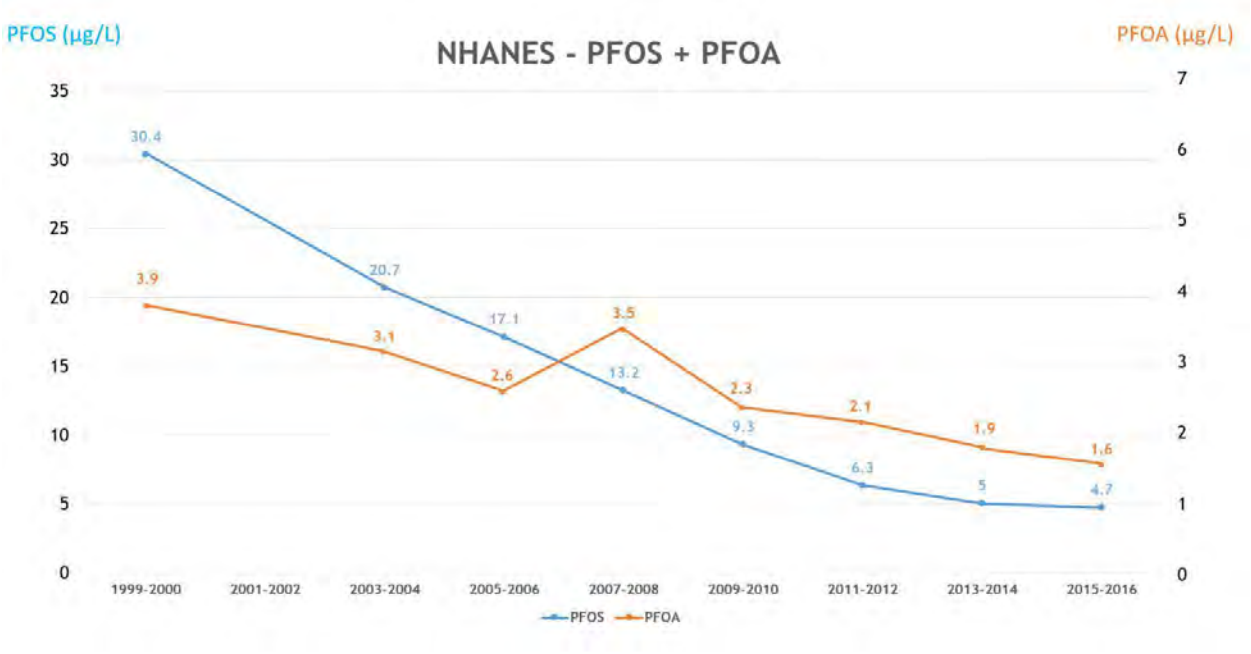
The authors suggested a BMDL of 1 nanograms per milliliter (ng/mL) serum for both PFOS and PFOA, and that an uncertainty factor of 10 (accounted for vulnerable population) be applied as serum-based target reference concentration of 0.1 ng/mL. The suggestion of 1 ng/mL of serum PFOA is arbitrary and has no statistical or clinical significance. The uncertainty adjustment seems excessive since the data is from a vulnerable population of children. A factor of 1 or 3 would be more consistent with standard risk assessment practices.

Using a no effect level of 0.1 ng/mL blood concentration in humans from the Budtz-Jorgensen publication, EPA applied a physiologically based pharmacokinetic (PBPK) model to determine what dose results in a blood concentration of 0.1 ng/ml. Despite the availability of several PBPK models in the peer reviewed literature, EPA chose to modify one of the existing model, including converting the model from one programming language to another, without submitting the new model for peer review or even making the model code publicly available.

Relative Source Contribution

After presenting a detailed review of the potential sources of exposure to PFOA and PFOS, EPA proposes to apply a default relative source contribution (RSC) of 20 percent in developing the MCL goals – meaning that 80 percent of exposure to these substances comes from sources other than drinking water – mainly from diet and dust. However, in a 2021 survey of nationally distributed processed foods, including several baby foods, conducted by the Food and Drug Administration PFOA was not detected and PFOS was detected in only 3 of the 167 foods sampled. Moreover, while PFOA and PFOS are often detected in dust samples, the concentrations as generally not correlated with serum concentrations.

Figure 1. Serum levels of PFOA and PFOS available from CDC.[34]



The available evidence suggests that other sources of potential exposure to PFOA and PFOS have declined drastically as a result of the phaseout of these substances. 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 since 1999.[35] According to CDC, mean serum levels of PFOA declined by 60 percent over the same time frame (see **Figure 1**). Given those

[34] Figure 1 does not include data available for 2017-18, which continues to show a decline in serum levels.

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

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.

ACC urges the Panel to consider the information provided above as part of its careful review of the draft approach documents provided by the Agency. Please fell free to contact me if you have questions about the issue raised in this letter.

Sincerely,

Steve Risotto

Stephen P. Risotto
Senior Director

EXHIBIT F

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

The 3M Company ("3M") appreciates the opportunity to provide written comments on the meeting materials published in advance of the Environmental Protection Agency ("EPA" or the "Agency") Science Advisory Board's ("SAB") public meetings to review data and analysis prepared by EPA as it considers setting Maximum Contaminant Level Goals ("MCLGs") and National Primary Drinking Water Regulations ("NPDWR") for Perfluorooctanoic Acid ("PFOA") and Perfluorooctanesulfonic Acid ("PFOS").

As an initial matter, the extremely abbreviated timeframe provided for public input on thousands of pages of highly technical reports is wholly inadequate. This rushed process is inconsistent with EPA's regular procedure and timeframe for obtaining input from the SAB. It is particularly problematic that the public was provided with only 50 days for review and comment during the November and December holiday period. The inadequate comment period, and SAB and EPA's refusal to extend the period, is a concerning indication that EPA views the SAB review process here as perfunctory and a procedural impediment rather than an opportunity for robust technical input to ensure the agency is using the best available science in reaching its conclusions.

Due to the inadequate comment period and the timing of the same, 3M is not able to provide the full scope of its technical comments here. This document includes certain of 3M's comments on some aspects of the meeting materials, specifically including EPA's Proposed Approaches to the Derivation of a Draft Maximum Contaminant Level Goal for Perfluorooctanoic Acid ("PFOA) in Drinking Water, and EPA's Proposed Approaches to the Derivation of a Draft Maximum Contaminant Level Goal for Perfluorooctanesulfonic Acid ("PFOS") in Drinking Water (collectively, the "Draft MCLG Documents").[1] 3M anticipates

[1] 86 Fed. Reg. 62526 (Nov. 10, 2021).

providing further technical input on these documents, as well as technical input on EPA's Analysis of Cardiovascular Disease Risk Reduction as a Result of Reduced PFOA and PFOS Exposure in Drinking Water, and EPA's Draft Framework for Estimating Noncancer Health Risks Associated with Mixtures of PFAS. 3M anticipates supplementing these comments in the coming weeks. 3M currently expects its supplemental comments will include additional technical input on at least the following topics:

- Further comment and analysis of the epidemiology and toxicology literature that report alternative endpoint considerations. Expanded discussion of the animal and human evidence for EPA's candidate Points of Departure ("PODs") and candidate Reference Doses ("RfDs") beyond those selected for the proposed RfDs (i.e., human tetanus and diphtheria vaccine response).
- Further assessment of epidemiology studies that were omitted from the Draft MCLG Documents.
- Additional assessment of single vaccine antibody response as a critical endpoint, e.g., consider the factors that must be taken into account to properly assign associations with PFOA and PFOS.
- Further considerations of norms and variability in responses to vaccines, and public health benefits of incremental changes in vaccine antibody responses.
- Attempt to replicate and further comment on EPA toxicokinetic and benchmark dose modeling.
- Further consideration of the implications for the remarkably low levels proposed in this draft document, including considerations of infectious disease rates compared with nationwide data on PFOA/PFOS serum levels, and the potential consequences for nationwide regulation based on EPA's analysis

3M encourages SAB to consider the information presented in the comments below as well as any supplemental comments when providing EPA with SAB's technical input on the meeting materials. EPA's approach is deeply scientifically flawed, substitutes non-scientific judgments for science, and employs unprecedented approaches to reach an illogical outcome. SAB should make these technical deficiencies clear to EPA in its response and should recommend that the Agency use scientifically sound approaches in considering these important regulatory levels.

EXECUTIVE SUMMARY

The technical comments below identify a series of compounding errors that raise serious concerns regarding the validity of EPA's approach in the Draft MCLG Documents. Perhaps the most significant error is EPA's failure to clearly and appropriately identify the critical endpoint it is trying to protect against. The Draft MCLG Documents indicate that immune effects may be the critical endpoint considered, but EPA does not explain what it means by this. There is no scientific basis to use antibody titers in response to a single vaccine as the critical endpoint. Indeed, we have found no evidence that EPA has ever taken this approach before for any substance and it is out of step with the larger scientific community. In at least one instance, the Draft MCLG Documents suggest that the critical endpoint is actually infectious disease resulting from decreased immune response. But then EPA fails to provide reliable evidence of *any*

relevant infectious disease outcomes, or evidence of overall immunological suppression. EPA's decision to focus on a single anti-vaccine antibody level – which has not been demonstrated to result in a suppressed immune response to infectious disease, and hence cannot appropriately be characterized as an "immunosuppression effect" – as a critical endpoint here is opaque and lacks a foundation in the science.

The human data relied on in the Draft MCLG Documents is a cherry-picked subset of data that focuses on the insular population of the Faroe Islands. These data are problematic for numerous reasons, including they are not applicable to the pediatric population of the United States, reflect a highly atypical antibody response, and are inconsistent with data from other cohorts. Moreover, EPA's use of the cited immunology data is simply wrong. EPA improperly relies only on a purported decrease in antibody titers. Antibody titers measure only one aspect of immune function and cannot be used as a predictor of immune failure or infection. EPA's treatment of a 0.1 IU/ml antibody titer level as a bright line differentiation between protected and unprotected is arbitrary and rests on a fundamental misunderstanding of how diphtheria and tetanus vaccines work. As discussed below, these vaccines are not intended to prevent infection, but rather are designed to neutralize toxoids generated by a diphtheria or tetanus infection. EPA relies on clinically meaningless differences to draw conclusions regarding protection levels for a single vaccine. The combination of unsound and arbitrary assumptions that form the basis of EPA's conclusions in the Draft MCLG Documents should be rejected by SAB in its responsive feedback to EPA.

As further explained in Section II below, the Draft MCLG Documents include a series of additional scientific errors. Those errors include the fact that the animal studies contradict the human immune response cited by EPA. Although not at all clear from the main text of the Draft MCLG Documents, it appears that EPA simply used BMD modeling results reported by Budtz-Jorgensen and Grandjean 2018 without independently evaluating those results. In addition, EPA's application of an uncertainty factor of 10 was either too high or insufficiently explained. Explanation of the cancer slope factor calculations for PFOA are unclear, lacking equations, and include multiple values for purportedly the same cancer slope factor.

These errors are not without consequence. The cumulative result of the errors and omissions in the Draft MCLG Documents could result in the recommendation of an RfD based on an endpoint never before used by EPA that has no clinical meaning and which would be a gross overstatement of the relative toxicity of PFOA and PFOS. The misdirection of resources that is likely to arise out of these erroneous proposed RfD values may have wide-ranging implications. SAB should identify these and other errors for EPA and provide guidance on how to use the best available science to establish meaningful and appropriate RfDs for PFOA and PFOS.

These and other concerns are addressed in more detail in the "Technical Comments" below. 3M strongly encourages SAB to use its independent review process to help EPA recognize and address these serious deficiencies in its technical analyses and help provide more sound alternative methodologies and frameworks for deriving these important regulatory limits.

TECHNICAL COMMENTS

Given the extremely limited comment period and the complex nature[2] of the meeting materials published by EPA, the comments below are focused on the Draft MCLG Documents. Although not specifically addressed, much of the information provided herein may also be applicable to the other two technical documents prepared by EPA in advance of the SAB meetings. As discussed above, 3M anticipates providing additional feedback in the coming weeks.

I. EPA'S SELECTION OF CRITICAL ENDPOINTS IS UNCLEAR AND NOT GROUNDED IN SCIENCE.

3M is particularly concerned by EPA's failure to clearly and appropriately identify the critical human health endpoint it is trying to protect against in developing the Draft MCLG Documents. The implication from the documents is that EPA viewed immune effects as the critical endpoint driving the analysis, but EPA has never used a specific antibody titer to a single vaccine, without increased risk to the infectious disease to which the titer is to protect in this manner before. A review of EPA's Risk assessment information system[3] indicates that, while human data has been used for the critical effect for a number of compounds, vaccine response has not been used before for reference dose ("RfD") development. This novelty alone demands close scrutiny and even a high level review, limited by the short timeframe provided, has revealed serious errors that the SAB should identify and help EPA address. Moreover, even if the critical endpoint EPA is using is actually infectious disease resulting from decreased immune response, which the Draft MCLG Documents vaguely imply, there is no reliable evidence given of *any* relevant infectious disease outcomes, nor is there evidence of overall immunological suppression. Such an approach also fundamentally misunderstands how the diphtheria and tetanus vaccines work. EPA erroneously states that "[t]hough decreases in anti-tetanus [anti-diphtheria] antibody concentrations are not in themselves an adverse effect, they do prevent against tetanus [diphtheria] infection . . . ."[4] Neither anti-tetanus nor anti-diphtheria antibodies protect against infection. They are antitoxin antibodies that protect against tetanus or diphtheria toxoids. EPA's opaque discussions of the critical endpoint it used, combined with misunderstandings and misapplications of immune response data that do not rely on best available science, should be emphasized by SAB in its feedback to EPA.

More broadly, the SAB should consider whether the novel use of vaccine antibody response, pertaining to only two specific endpoints, tetanus and diphtheria, as the 'critical endpoint' for regulatory purposes is appropriate. As discussed in detail below, antibody responses to administration of a vaccine are highly dependent on many factors that must be taken into consideration to equate a particular antibody titer to protection from the agents in particular and more broadly to immune status. These include:

[2] The complexity of the Draft MCLG Documents should not be confused for accuracy. Indeed, as discussed below, much of EPA's analysis is opaque and in many cases, simply does not add up upon closer inspection. 3M anticipates being able to provide further detail with adequate time to fully respond to the Agency's materials.
[3] https://rais.ornl.gov/cgi-bin/tools/TOX_search.
[4] PFOA draft p. 340, PFOS draft at p. 310.

- Measurement and testing protocols e.g., timing of measurement post administration, assay methods and validation/consistency.
- The human subject's individual factors, some known and some unknown, e.g., age, method of administration, diet, body mass, disease/immune status, household factors that influence immune factors, genetics, and others.
- Significance of the ranges of antibodies measured and identifiable levels that associate protection with measured levels - the FDA level of 0.1 is merely a guidance level without intention or support for being a bright line to define vaccine effectiveness; small and inconsistent variations are not meaningful.

EPA failed to account for these factors in developing the Draft MCLG Documents. The SAB should also recommend that EPA consider the lack of consistent evidence of responses to vaccines in general and the lack of confirmatory evidence to demonstrate immune system challenges or infectious disease consequence, which if confirmed would require evidence for designation of 'critical endpoint' for either rather than for the single, or limited, measurement of antibodies as a response to a vaccine.

A. EPA's Unprecedented Use of a 5% BMR for Vaccine Antitoxin Antibodies as the POD Is Scientifically Inappropriate.

EPA's novel choice of a 5% decrease in tetanus anti-toxin antibody for PFOA and diphtheria anti-toxin antibody for PFOS as the benchmark responses on which to base the respective MCLGs is not based on best available science and is inappropriate. EPA justifies this choice by contending that a 5% decrease may result in clinically significant effects as a sizable portion of the population may have antibody concentrations close to 0.1 IU/ml and excess PFOA or PFOS exposures may decrease these levels below 0.1 IU/ml – a level EPA cites as the protection threshold. As EPA states:

> For tetanus and diphtheria, a clinically significant decrease would be a decrease that brought a person's antibody concentration below a level thought to provide protection. If a person had a concentration of 0.1 IU/ml but a 5% decrease brought their concentration below 0.1 IU/ml, that would be clinically significant. Depending on the population, there might be a large number of persons (30-40%) with antibody concentrations close to 0.1 IU/ml.[5]

There are several profound problems with this reasoning. First, antibody titers measure only one aspect of immune function. Immunity also depends significantly on other physiological factors, including cellular-mediated immune response that are not captured by a simple titer measurement. Nor was cellular-mediated immune measured in the Faroese cohort studies. Thus, a 5% antibody titer decrease cannot be used *a priori* as a predictor of immune failure as EPA

[5] EPA. External Peer Review Draft – Proposed Approaches to the Derivation of a Draft Maximum Containment Level Goal for Perfluorooctanoic Acid (PFOA) CASRN 335-67-1) in Drinking Water ("Draft PFOA MCLG Approach"), at 340, December 2021; EPA. External Peer Review Draft – Proposed Approaches to the Derivation of a Draft Maximum Containment Level Goal for Perfluorooctane Sulfonic Acid (PFOA) CASRN 1763-23-1) in Drinking Water ("Draft PFOS MCLG Approach") at 310, December 2021. At one point (PFOA draft at p. 340), EPA also references 0.15 IU/ml as the protection level for tetanus but provides no reference for this.

purports to do. Second, there is no bright line antibody titer cut-off between protected and unprotected and the EPA's treatment of 0.1 IU/ml as such is immunologically flawed and leads to inappropriate conclusions.[6] Protection occurs along a gradient, one aspect of which is the antibody titer. A 5% change, particularly around the 0.1 IU/ml level, is *de minimus* and likely within the intra-assay variability of the antibody assay, *i.e.*, unmeasurable. Immunologically, having a 5% lower antibody level has no clinical or biological significance in terms of response to the toxins involved and, similarly, in terms of response to infection. EPA apparently deems a 5% decrease as biologically significant by positing that a significant portion of the population might have an antibody titer between 0.1 and 0.1053 IU/ml where a 5% decrease would lead to titers between 0.095 and 0.099 IU/ml, which then strictly fall below the EPA-presumed "protection" level. These small differences are clinically meaningless and cannot be used to predict immunity. Third, 0.1 IU/ml is not a universally recognized level of protection as EPA seems to presume. The World Health Organization ("WHO") uses 0.01 IU/ml as the protection level for diphtheria and also for tetanus, when using a modified ELISA or bead-based immunofluorescence assay to measure titers.[7] By deeming only persons above 0.1 IU/ml as protected, EPA and the Faroese studies on which it relies overstate the subjects who would fall below protective levels resulting from a 5% decrease. Moreover, a 5% change at the 0.01 IU/ml level is even smaller than a respective change around the 0.1 IU/ml level, which is already clinically and biologically meaningless. A 5% decrease in an antibody response cannot be used as a surrogate for a meaningful biologic effect and EPA should not use it as the benchmark response.

B. Faroe Islands Population Data Are Not Appropriate For Quantitative Use in Deriving Generally Applicable PFOA and PFOS MCLGs

EPA's unprecedented critical endpoint approach is predicated primarily upon several Faroe population studies. But these studies show highly atypical antibody responses, precluding the generalizability of the results. For example, notwithstanding receiving three inoculations within the first year after birth, at age five (pre-booster), over 37% of the Faroese cohort members had diphtheria antitoxin antibody levels below 0.1 IU/ml.[8] Similarly, after receiving the age-five booster, the antibody levels at age 13 were also abnormally low, with nearly 40% of the subjects having levels below 0.1 IU/mL for diphtheria anti-toxin antibodies.[9] This contrasts with U.S. population data for adolescents (not segregated by vaccine status), where only

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[6] WHO. The Immunological Basis for Immunization Series Module 2: Diphtheria. Update 2009 (noting that "there is no sharply defined level of antitoxin that gives complete protection from diphtheria" and "[o]ther factors may influence vulnerability to diphtheria including the infecting dose and virulence of the diphtheria bacilli, and the general immune status of the person infected. . . ."); WHO. The Immunological Basis for Immunization Series Module 3: Tetanus. Update 2017 (noting a "protective antibody concentration may not be considered a guarantee of immunity under all circumstances.").

[7] WHO. The Immunological Basis for Immunization Series Module 2: Diphtheria,. Update 2009; WHO The Immunological Basis for Immunization Series Module 3: Tetanus. Update 2017.

[8] Grandjean P, Andersen EW, Budtz-Jørgensen E, Nielsen F, Mølbak K, Weihe P, Heilmann C. Serum vaccine antibody concentrations in children exposed to perfluorinated compounds. JAMA. 2012 Jan 25;307(4):391-7.

[9] Grandjean P, Heilmann C, Weihe P, Nielsen F, Mogensen UB, Budtz-Jørgensen E. Serum Vaccine Antibody Concentrations in Adolescents Exposed to Perfluorinated Compounds. Environ Health Perspect. 2017 Jul 26;125(7):077018.

approximately 20% had diphtheria anti-toxin antibody levels less than 0.1 IU/ml, respectively.[10] The proportion of children aged 6 to 11 with titers below this limit was even lower. The atypical immune response seen among the Faroe population makes quantitative use of their antibody titers to derive a 5% benchmark response level applicable to a generalized United States pediatric population inappropriate.

There could be several reasons for the poor antibody response seen among the Faroese children, all of which argue against EPA's quantitative use of these cohorts. First, the Faroese cohorts utilized a four-vaccine administration schedule, starting with three doses spaced at 3, 5, and 12 months followed by a booster administered at age 5, which was not the standard in the United States at the time. Furthermore, the current routine schedule for administering DTaP to children in the United States calls for five shots: a 3-dose series at age 2, 4, and 6 months, followed by boosters at age 15–18 months and 4–6 years.[11] Accordingly, the immune response from the Faroe population has limited applicability to children in the United States either in the past or currently.

Second, vaccine response is highly dependent on administration technique, with optimum results achieved via intramuscular injections into the deltoid or the anterolateral aspects of the thigh. Injection into subcutaneous fat by going more medial in the thigh, using a shorter needle, or administering in the buttocks will lead to significantly lower seroconversion rates and poor overall antibody response.[12] The overall lower antibody levels in the Faroese cohort may be due to suboptimal vaccine administration technique. Furthermore, the administration of the vaccine in more outlying islands and rural areas where dietary differences are expected to lead to higher PFAS levels (discussed below) would have likely been given by different health care providers than those on the main island. Less optimal vaccination techniques by some rural health care providers could skew the results and account for the apparent inverse associations between some antibody and PFAS levels.

Third, the Faroese population is a unique, relatively insular society, with a high level of inbreeding, particularly in rural areas.[13] Dietary differences between rural and urban areas are also significant, with seafood being the main source of food in poorer, rural areas. The suboptimal antibody response seen in the population may well be the result of these unique population features and make generalizing the results to a United States pediatric population inappropriate.

Finally, the poor overall immune responses exhibited in the Faroese cohorts compared with the United States adolescent population cannot be explained by higher PFAS exposures

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[10] McQuillan GM, Kruszon-Moran D, Deforest A, Chu SY, Wharton M. Serologic immunity to diphtheria and tetanus in the United States. Ann Intern Med. 2002 May 7;136(9):660-6.

[11] Centers for Disease Control and Prevention, Recommended child and adolescent immunization schedules for ages 18 or younger, United States, 2021, *available at* https://www.cdc.gov/vaccines/schedules/hcp/imz/child-indications.html#note-dtap.

[12] Zuckerman JN. The importance of injecting vaccines into muscle. Different patients need different needle sizes. BMJ. 2000 Nov 18;321(7271):1237-8.

[13] Binzer S, Imrell K, Binzer M, Kyvik KO, Hillert J, Stenager E. High inbreeding in the Faroe Islands does not appear to constitute a risk factor for multiple sclerosis. Mult Scler. 2015 Jul;21(8):996-1002 (noting the average level of relatedness observed in the Faroe Islands is to the decree of second cousins).

among the Faroe population. The mean maternal, five-year-old, seven-year-old, and thirteen-year-old PFOA and PFOS serum concentrations in the Faroese cohorts are lower than mean background PFOS/PFOA exposures reported in the United States from the 1988-1994 timeframe, when the antibody data reported by McQuillan discussed above were collected, as well as the 1999-2000 timeframe as reported in the first NHANES general population PFOA/PFOS analysis.[14]

Genetic, geographic, and dietary differences within the Faroese population are also important confounders that were not thoroughly assessed by the authors in evaluating correlations between PFAS and the toxoid antibody responses, making quantitative use of the data inappropriate. Immune response is modified by innumerable individual factors that can never be completely controlled for in observational studies. When associations are observed between PFOA or PFOS and toxoid antibody responses among the many comparisons conducted in Faroe studies, the magnitude of those associations are at most modest, making it difficult to distinguish any true relationships from residual confounding "noise." Approximately 42% of the Faroe Island population lives in metropolitan areas, with Torshavn on the island of Streymoy being the largest.[15] The remaining population majority is rural, generally poorer, and less genetically diverse than the urban population. The rural population also consumes more seafood, including marine mammals, than the urban population, which can be a source of PFAS, making rural residence have a potential impact on of PFAS levels.[16] The urban population, with lower PFAS levels, is also expected to contain more recent emigrants, be more outbred, and thus have a different genetic makeup than the rural population. Genetics is a key component of the immune response due to highly variable immune response genes.[17] Rural residents are expected to have had a different network of routine health care providers who administered vaccines as noted above. If rural study participants, who have higher PFAS concentrations as a result of their predominant seafood diets, have less than optimal vaccine administration or if urban participants are on average better vaccine responders due to increased genetic diversity, it could lead to the observed inverse associations between PFOA or PFOS and toxoid antibody responses. The inability to completely control for the many potential confounding factors could explain the

[14] Olsen GW, Huang HY, Helzlsouer KJ, Hansen KJ, Butenhoff JL, Mandel JH. Historical comparison of perfluorooctanesulfonate, perfluorooctanoate, and other fluorochemicals in human blood. Environ Health Perspect. 2005 May;113(5):539-45 (reporting geometric mean PFOS and PFOA concentrations of 33.3 ppb and 5.5 ppb from general population samples taken in 1989 from the Washington County, Maryland area). See also Centers for Disease Control and Prevention. Fourth National Report on Human Exposure to Environmental Chemicals, Updated Tables, March 2021. Volume 1 NHANES 1999-2010 (reporting geometric mean PFOS and PFOA concentrations of 30.4 ppb and 5.12 ppb, respectively, in the U.S. general population and 29.1 ppb and 5.46 ppb, respectively, among adolescents 12-19 in 1999-2000 – the first year of general population analysis).

[15] World Bank, Urban Population (% of total population) – Faroe Islands, United Nations Population Division. World Urbanization Prospects: 2018 Revision, *available at* Urban population (% of total population) - Faroe Islands | Data (worldbank.org); United States Central Intelligence Agency, The World Factbook – Faroe Islands, last updated Dec. 14, 2021, *available at* Faroe Islands - The World Factbook (cia.gov).

[16] See Timmermann CAG, Pedersen HS, Budtz-Jørgensen E, Bjerregaard P, Oulhote Y, Weihe P, Nielsen F, Grandjean P. Environmental chemical exposures among Greenlandic children in relation to diet and residence. Int J Circumpolar Health. 2019 Dec;78(1):1642090 (noting in a similar north Atlantic location and population that area of residence and marine diet are significant predictors of PFAS concentrations).

[17] Mangino M, Roederer M, Beddall MH, Nestle FO, Spector TD. Innate and adaptive immune traits are differentially affected by genetic and environmental factors. Nat Commun. 2017 Jan 5;8:13850.

modest associations found in the Faroese studies in whole, or in part, and makes quantitative use of the Faroese cohorts wholly inappropriate for deriving MCLGs.

II. EPA'S ANALYSIS IN THE DRAFT MCLG DOCUMENTS IS FUNDAMENTALLY FLAWED

EPA's flawed approach using a novel critical endpoint is compounded by numerous additional analytical errors. Some of the obvious errors identified during 3M's high-level review are described in turn below. Additionally, many of the critical aspects in the Draft MCLG Documents lack adequate transparency in the methods and/or decision process used by EPA, including but not limited to benchmark dose modeling, use of pharmacokinetic model-derived internal dose-metrics when measured values are available, and cancer slope derivation and reporting. Additional analytical analysis is needed, as well as likely more disclosure from EPA, to truly understand and provide necessary input on the Agency's approach here.

A. EPA's Literature Review Omits Numerous Relevant Epidemiological Studies Addressing Immunotoxicity.

To understand the potential immunotoxicity of PFOA and PFOS, EPA should consider all of the available epidemiological studies of PFOA and PFOS in association with immune outcomes. EPA's literature review, however, omits a substantial proportion of the approximately 100 published epidemiological studies on this topic. Even for the more focused endpoints of antibody-mediated immunity and infection (grouped by EPA as "immunosuppression effects"),[18] EPA omits ten relevant epidemiological studies published in 2020 or earlier, as well as seven additional studies published in 2021. These omitted publications include six studies of antibody-mediated immunity (Granum et al. 2013, Looker et al. 2014, Kielsen et al. 2016, Stein et al. 2016b, Shih et al. 2021, Timmermann et al. 2022); nine studies of infectious disease outcomes other than COVID-19 (Leonard et al. 2008, Fei et al. 2010, Okada et al. 2012, Kishi et al. 2013, Huang et al. 2020, Bulka et al. 2021; including one update of a study considered by EPA (Dalsager et al. 2021) and two studies that also evaluated antibody levels (Granum et al. 2013, Looker et al. 2014)); and four studies of COVID-19 outcomes (Grandjean et al. 2020, Catelan et al. 2021, Ji et al. 2021, Nielsen and Jöud 2021). SAB should recommend that EPA broaden its literature review to include recent studies to ensure the Agency does not turn a blind eye to recent developments.

Among the 17 omitted studies, eight are prospective cohort studies (two from the same study population (Okada et al. 2012, Kishi et al. 2013)) with individual-level serum or plasma PFOA, PFOS, and other PFAS, highly complete follow-up for validated health outcomes, and statistical adjustment for multiple confounders (Fei et al. 2010, Okada et al. 2012, Granum et al. 2013, Kishi et al. 2013, Huang et al. 2020, Dalsager et al. 2021, Shih et al. 2021, Timmermann et al. 2022). Another is a retrospective cohort mortality study with no information on individual-level PFOA exposure and minimal adjustment for confounders, but with the advantage of taking place in an occupational setting with high average exposure levels (Leonard et al. 2008). Likewise, Olsen et al. 2001 retrospectively reviewed administrative employee health data to evaluate episodes of care among workers with occupational-level exposures to PFOS. Two of

[18] Draft PFOA MCLG Approach, p. 150; Draft PFOS MCLG Approach, p. 136.

these study populations were investigated in studies that were included in EPA's review (Granum et al. 2013, Dalsager et al. 2021); however, the included studies addressed somewhat different endpoints and age groups, making their results non-duplicative (Dalsager et al. 2016, Impinen et al. 2019). EPA's omission of these studies thus leaves important gaps in the Agency's presentation of the context of the epidemiological literature on potential "immunosuppression effects" of PFOA and PFOS. The exclusion of these studies also impairs EPA's ability to evaluate the consistency of findings on its selected critical effect (i.e., decreased serum anti-tetanus antibody levels in children) across studies, as well as the consistency of these data with results on other specific antibody levels and clinical infectious disease endpoints.[19]

B. EPA's Reliance on Decreased Serum Anti-Tetanus Antibody Levels in Children (PFOA), and Serum Anti-Diphtheria Levels in Children (PFOS), Ignores Inconsistent Results Across and Within Epidemiological Studies.

EPA's reliance on observed associations of PFOA with decreased serum anti-tetanus antibody levels and PFOS with decreased serum anti-diphtheria antibody levels among children in the Faroe Islands (Grandjean et al. 2012, Mogensen et al. 2015, Grandjean et al. 2017a, Grandjean et al. 2017b) ignores inconsistent results presented in other epidemiological studies. EPA should not be considering the Faroe Islands data in isolation. Instead, like all scientific results, they must be interpreted in the context of other, related findings within and among independent study populations. In particular, comparisons with other relevant results should be made to evaluate whether the overall data set is consistent and coherent, and thus supportive of the validity of the potential critical effect.

Combining the studies EPA identified and as well as those not identified by EPA in the Agency's Draft MCLG Documents, 16 publications from 14 independent study populations addressed the relationship between PFOA and/or PFOS and antibody levels (Grandjean et al. 2012, Granum et al. 2013, Looker et al. 2014, Mogensen et al. 2015, Kielsen et al. 2016, Stein et al. 2016a, Stein et al. 2016b, Grandjean et al. 2017a, Grandjean et al. 2017b, Pilkerton et al. 2018, Zeng et al. 2019, Abraham et al. 2020, Timmermann et al. 2020, Zeng et al. 2020, Shih et al. 2021, Timmermann et al. 2022). EPA refers to Grandjean et al. (2012, 2017a, 2017b) and Mogensen et al. (2015) as being "three studies,"[20] but in fact these represent *two* independent study populations, since three of these publications are based on the same cohort (Grandjean et al. 2012, Mogensen et al. 2015, Grandjean et al. 2017a), and one reports results for a non-overlapping cohort, as well as the two cohorts combined (Grandjean et al. 2017b).

A review of the design and results of the broader body of scientific literature, briefly summarized in 3M's Appendix A, Table 1 (below),[21] reveals several overarching points. First,

[19] While the remaining eight omitted studies have methodological weaknesses such as an ecological (Catelan et al. 2021, Nielsen and Jöud 2021), cross-sectional (Looker et al. 2014, Kielsen et al. 2016, Stein et al. 2016b, Grandjean et al. 2020, Bulka et al. 2021), or retrospective case-control study design (in this instance, prone to reverse causation) (Ji et al. 2021), EPA's failure to consider them at all demonstrates an inadequate literature review. EPA's literature review protocols require the Agency to review all relevant studies before evaluating the data. https://www3.epa.gov/pesticides/EPA-HQ-OPP-2008-0316-DRAFT-0075.pdf.

[20] Draft PFOA MCLG Approach, p. 151; Draft PFOS MCLG Approach, p. 137.

[21] Tables are intended to provide a broad overview of the design and results of epidemiological studies. Details on quantitative results and study methods are not described.

reported associations of PFOA and PFOS with specific antibody levels are diverse, including inverse, positive, and null associations, with no clear direction of association overall. Thus, any effect of PFOA or PFOS on antibody levels, if causal, is not global for all antibodies. Second, few studies reported results for any given antibody type. Several antibodies (e.g., anti-hepatitis A virus, anti-coxsackievirus A 16, anti-influenza A/H3N2) were measured in only one study each, and the most commonly studied antibodies (anti-diphtheria and anti-tetanus) were measured in eight and nine publications (six and seven separate study populations), respectively. Thus, the body of epidemiological literature on any given PFAS-antibody association is relatively sparse. Third, every study reported some apparent associations (inverse and/or positive) and some null results, sometimes for the same PFAS-antibody combination in different study subgroups. Thus, focusing only on inverse associations (i.e., between higher PFOA or PFOS levels and lower antibody levels) overlooks numerous other results that are relevant to the assessment of potential effects on antibody-mediated immunity.

Results for anti-tetanus antibody levels in particular are available from seven study populations (five of children and two of adults, although one of the adult studies measured PFAS exposure during childhood) (Grandjean et al. 2012, Granum et al. 2013, Mogensen et al. 2015, Kielsen et al. 2016, Grandjean et al. 2017a, Grandjean et al. 2017b, Abraham et al. 2020, Shih et al. 2021, Timmermann et al. 2022). This body of evidence enables an assessment of the consistency of findings for anti-tetanus antibodies across studies. As summarized briefly in Table 2, associations between PFOA and lower anti-tetanus antibody levels in at least some of the many comparisons were observed in 1) a prospective cohort study of children born in the Faroe Islands in 1997–2000 (Grandjean et al. 2012, Mogensen et al. 2015, Grandjean et al. 2017a); 2) a second prospective cohort study of Faroe Islands children born in 2007–2009 (Grandjean et al. 2017b); and 3) a cross-sectional study of one-year-old infants in Germany (Abraham et al. 2020). In contrast, no association between PFOA and anti-tetanus antibody levels was observed in 1) a prospective cohort study of children in Norway (Granum et al. 2013); 2) a prospective cohort study of children in Greenland (Timmermann et al. 2022); 3) a prospective cohort study of adults followed since birth in the Faroe Islands in 1986–1987 (Shih et al. 2021); and 4) an exploratory cross-sectional study of adults in Denmark (Kielsen et al. 2016).

For PFOS, an association with lower anti-tetanus antibody levels was observed only in the 2007–2009 Faroe Islands birth cohort (Grandjean et al. 2017b). In the 1997–2000 Faroe Islands birth cohort, prospective analyses showed either no association between PFOS and anti-tetanus antibodies or an association with *higher* anti-tetanus antibody titers (Grandjean et al. 2012, Mogensen et al. 2015, Grandjean et al. 2017a). Otherwise, besides the 1) 1997–2000 Faroe Islands birth cohort, no association between PFOS and anti-tetanus antibody level was found in the 2) German (Abraham et al. 2020), 3) Norwegian (Granum et al. 2013), 4) Greenland (Timmermann et al. 2022), 5) 1986–1987 Faroe Islands (Shih et al. 2021), and 6) Danish studies (Kielsen et al. 2016).

Results for anti-diphtheria antibody levels in association with PFOA and PFOS are available from all but one of the study populations that evaluated anti-tetanus antibody levels, again allowing for an evaluation of consistency across studies (Grandjean et al. 2012, Mogensen et al. 2015, Kielsen et al. 2016, Grandjean et al. 2017a, Grandjean et al. 2017b, Abraham et al. 2020, Shih et al. 2021, Timmermann et al. 2022). As broadly summarized in 3M's Appendix A,

Table 2, associations between PFOS and lower anti-tetanus antibody levels were reported in two prospective cohort studies of children born in the Faroe Islands in 1997–2000 (Grandjean et al. 2012, Mogensen et al. 2015, Grandjean et al. 2017a) and 2007–2009 (Grandjean et al. 2017b); and 3) the small cross-sectional study of adults in Denmark (Kielsen et al. 2016). In contrast, no association between PFOS and anti-diphtheria antibody levels was found in 1) the prospective cohort study of Faroe Islands adults followed from birth in 1986–1987 to age 28 years (Shih et al. 2021); or 2) the cross-sectional study of one-year-old infants in Germany (Abraham et al. 2020). In addition, 3) the prospective cohort study of children in Greenland found no association of maternal or child PFOS with continuous anti-diphtheria antibody levels, but a positive association of child PFOS with a greater risk of having an anti-diphtheria antibody concentration < 0.1 IU/mL (Timmermann et al. 2022)

For PFOA and anti-diphtheria antibody levels, some inverse associations (although not all associations tested) were reported in 1) the 1997–2000 Faroe Islands prospective birth cohort (Grandjean et al. 2012, Mogensen et al. 2015, Grandjean et al. 2017a); 2) the 2007–2009 Faroe Islands prospective birth cohort (Grandjean et al. 2017b); and 3) the cross-sectional study of German infants (Abraham et al. 2020). However, no association between PFOA and anti-diphtheria antibody levels was found in 1) the prospective cohort study of children in Greenland (Timmermann et al. 2022); 2) the 1986–1987 Faroe Islands prospective birth cohort (Shih et al. 2021); and 3) the small cross-sectional study of Danish adults (Kielsen et al. 2016).

Even within the combined Faroe Islands birth cohorts that EPA ultimately selected as the critical study for PFOA and PFOS, results were inconsistent (Grandjean et al. 2012, Grandjean et al. 2017a, Grandjean et al. 2017b). With respect to anti-tetanus antibody levels, for instance, in the 1997–2000 birth cohort, maternal prenatal serum levels of PFOA and PFOS were not associated with lower titers in their children at ages 5 and 7 years (on the contrary, maternal PFOS was associated with higher anti-tetanus antibodies in 7-year-olds) (Grandjean et al. 2012). Prospectively collected child serum PFOA in this cohort was associated with lower anti-tetanus antibody levels at 7 years, but not 13 years (Grandjean et al. 2012), and associations with anti-tetanus antibody levels at 5 years varied depending on whether PFOA was measured at birth, 3 months, or 18 months (no association) or 6 or 12 months (inverse association) (Grandjean et al. 2017b).

Internally inconsistent results were also observed for anti-diphtheria antibody levels in the Faroe Islands birth cohorts (Grandjean et al. 2012, Grandjean et al. 2017a, Grandjean et al. 2017b). For example, in the 1997–2000 birth cohort, maternal prenatal serum levels of PFOS were associated with lower anti-diphtheria antibodies at age 5 years, but not 7 years, whereas the opposite age-specific pattern was observed for PFOA (Grandjean et al. 2012). In the 2007–2009 cohort, PFOS measured at birth and 3, 6, 12, 18, and 60 months was not associated with anti-diphtheria antibody titers at 5 years; instead, where associations with PFOS were detected (with PFOS measured at birth and 3 months, but not later), they were only in the 1997–2000 cohort or the combined cohorts (Grandjean et al. 2017b). In contrast, the only observed associations between PFOA and anti-diphtheria antibodies (with PFOA measured at birth, but not at 3, 6, 12, 18, or 60 months) were seen in the 2007–2009 cohort or the combined cohorts.

In summary, although a superficial review may suggest some "consistent" associations of PFOA or PFOS with poorer antibody-mediated immunity based on selected results,[22] closer inspection reveals considerable within- and between-study heterogeneity in observed associations by vaccine type, PFAS type, timing and dose of PFAS exposure, age group, and other factors. Data on any specific association, such as between PFOA or PFOS and anti-tetanus antibody levels, as evaluated in seven study populations, are currently insufficient to determine whether the heterogeneity is due to chance, bias, confounding, or real differences in antigen-specific immune responses, PFOA or PFOS dose, participant characteristics, or study setting. Thus, besides selecting critical effects that are not established as causal, EPA ignores substantial unexplained inconsistency and variability in the observed association. Before relying on isolated results from a singular study for its risk assessment, EPA should seek a better understanding and explanation of why results differ among studies, including across the three Faroe Islands birth cohorts, as well as within studies.

C. EPA's Reliance on Decreased Serum Anti-Tetanus and Anti-Diphtheria Antibody Levels in Children as the Critical Effects for PFOA and PFOS, Respectively, Ignores Mostly Null Findings for Clinical Infectious Disease Outcomes.

Although serum diphtheria and tetanus antitoxin levels of at least 0.1 international units (IU) are sometimes referenced as "protective," levels as far as 10 times lower—that is, 0.01 IU/mL—still confer some degree of protection (Food and Drug Administration 1985) and are cited by WHO as protective levels. . Given that incremental changes in specific antibody levels may or may not translate to overt differences in antibody-mediated immunity to infectious agents, a full interpretation of the epidemiological database on EPA's selected critical effects also requires consideration of related findings on the association between PFOA and/or PFOS and clinical infectious disease endpoints. From a clinical perspective, susceptibility to infection is a leading indicator of immune function; indeed, nearly all of the 10 cardinal warning signs of primary immunodeficiency relate to the frequency and severity of recent infections (Jeffrey Modell Foundation 2016). If such clinically recognizable abnormalities are not observed, then immunodeficiency cannot be presumed to exist. Thus, from a clinical immunologist's point of view, proper interpretation of laboratory test results, such as specific antibody levels, requires a consideration of whether such results predict disease in the form of infection. If not, then "at best time and money are wasted, and at worst a patient is informed erroneously that he or she is sick or will get sick when this is not true, thereby breaking the rule of '*primum non nocere*' – above all do no harm" (Chang et al. 2016).

Combining the studies identified and not identified by EPA in the Agency's literature search, 21 publications from 16 independent study populations[23] addressed the relationships of PFOA and PFOS with various infectious disease outcomes (Leonard et al. 2008, Fei et al. 2010, Okada et al. 2012, Granum et al. 2013, Kishi et al. 2013, Looker et al. 2014, Dalsager et al. 2016, Goudarzi et al. 2017, Impinen et al. 2018, Impinen et al. 2019, Manzano-Salgado et al. 2019,

[22] See e.g., Draft PFOA MCLG Approach, pp. 166–167; Draft PFOS MCLG Approach, pp. 156–157.

[23] Five pairs of studies originated from the same underlying cohort: (Okada et al. 2012, Kishi et al. 2013), (Granum et al. 2013, Impinen et al. 2019), (Dalsager et al. 2016, Dalsager et al. 2021), (Goudarzi et al. 2017, Ait Bamai et al. 2020), (Impinen et al. 2018, Kvalem et al. 2020).

Abraham et al. 2020, Ait Bamai et al. 2020, Grandjean et al. 2020, Huang et al. 2020, Kvalem et al. 2020, Bulka et al. 2021, Catelan et al. 2021, Dalsager et al. 2021, Ji et al. 2021, Nielsen and Jöud 2021). *See* 3M's Appendix A, Table 3.

As summarized broadly in Table 3, these studies showed no apparent pattern of association between PFOA or PFOS and risk of overt infectious diseases, with scattered positive, inverse, and null associations. Focusing on the higher-quality prospective cohort studies, omitting one study with duplicative results (Okada et al. 2012) and retaining studies with non-duplicative results from the same cohort, reported findings remained inconsistent across 12 studies from eight separate study populations (Fei et al. 2010, Granum et al. 2013, Kishi et al. 2013, Dalsager et al. 2016, Goudarzi et al. 2017, Impinen et al. 2018, Impinen et al. 2019, Manzano-Salgado et al. 2019, Ait Bamai et al. 2020, Huang et al. 2020, Kvalem et al. 2020, Dalsager et al. 2021). The majority of associations tested were weak in magnitude and statistically null, and associations detected between PFOA and/or PFOS and specific types or groups of infection (e.g., upper or lower respiratory tract infections, gastroenteritis, or otitis media/ear infection) were not consistently detected within or across studies. Only one prospective cohort study tested associations with a vaccine-preventable infection, namely, chicken pox, which exhibited no association with PFOA or PFOS among 7-year-olds in Hokkaido, Japan (Ait Bamai et al. 2020).

If PFOA or PFOS exposures were having clinically meaningful effects on immune function as argued by EPA based on the hypothesis generating work of Grandjean et al. and others, one would predict the occurrence of primary and secondary immune effects, at a minimum, among the most highly exposed populations. For example, individuals with true immune deficiency exhibit clear increased risks to chronic respiratory diseases, such as COPD, brought on by immune system dysfunction.[24] Yet, the available studies show no indication of this in cohorts more highly exposed to PFAS.

Steenland et al. studied the incidence of disease among DuPont workers exposed to PFOA.[25] As of 2005, they had a median serum concentration of 115 ppb, compared with general population levels of 4 ppb at that time. Steenland et al. report no significant associations with COPD, which might be expected if workers had immune system dysfunction conferring susceptibility to respiratory infections. Likewise, Leonard et al. 2008 did not find any excess mortality due to infectious disease among DuPont workers.

In 2001, 3M conducted a study of its Decatur, Alabama workforce, who was more highly exposed to POSF-derived chemistries, including PFOS, by evaluating episodes of care[26] obtained

[24] Berger M, Geng B, Cameron DW, Murphy LM, Schulman ES. Primary immune deficiency diseases as unrecognized causes of chronic respiratory disease. Respir Med. 2017 Nov;132:181-188; Bhat TA, Panzica L, Kalathil SG, Thanavala Y. Immune Dysfunction in Patients with Chronic Obstructive Pulmonary Disease. *Ann Am Thorac Soc*. 2015;12 Suppl 2(Suppl 2):S169-S175.

[25] Steenland K, Zhao L, Winquist A. A cohort incidence study of workers exposed to perfluorooctanoic acid (PFOA). Occup Environ Med. 2015 May;72(5):373-80.

[26] An episode of care is a unique metric that is not directly comparable to other standard epidemiologic endpoints as it may include incident cases, prevalent cases, and tentatively diagnosed cases that are the routine consequence of the differential diagnoses that individuals may undergo in the course of disease diagnosis, treatment and management. The episode of care concept can be a useful screening method for the potential risk of diseases and/or

from administrative health data from 3M workers extending from 1993 to 1998.[27] Evaluating episodes of care is a particularly useful screening method for the potential risk of diseases and/or conditions when there are two study populations from the same company, covered by the same medical plan, who live within the same community undergoing comparable local/regional medical care, and who differ primarily only in their workplace exposure. This scenario existed with the employees at the 3M Decatur manufacturing site which had two separate neighboring manufacturing plants: fluorochemical and film production.

PFOS exposures in the fluorochemical cohort were significantly higher than the general population background-level PFOS exposures that were at issue in the Faroe Islands cohorts. For example, mean serum PFOS levels for Decatur fluorochemical production employees participating in a 1995 medical surveillance assessment were 2,400 ppb with levels extending up to and in excess of 12,000 ppb.[28] This contrasts with the Faroe Islands cohorts, whose highest mean PFOS levels were 27 ppb in maternal serum at birth and were as low as 6.7 ppb in children by age 13. In the adjacent 3M film plant, where fluorochemicals were not significantly used, PFOS exposures were shown to be substantially less based on a random sample of employees at these two adjacent plants at the Decatur site.[29]

The primary analysis in the study generated risk ratio episodes of care by dividing the observed to expected[30] episodes of care experienced among 652 fluorochemical production plant employees by the observed to expected episodes of care experienced among 659 film plant employees. Further, subgroup analyses included comparing only fluorochemical production plant employees who never worked in the film plant to film plant employees who never worked in the fluorochemical production plant as well as comparing the highest-exposed (those working in high-exposure jobs) and longest-exposed (those having at least 10 years employment in the fluorochemical plant prior to the study period) fluorochemical plant workers to the

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conditions where such an assessment would be impractical to conduct through formal investigations involving comprehensive medical record reviews.

[27] Olsen GW, Berlew MS, Hocking BB, Skratt JC, Burris JM, Mandel JH. An epidemiologic analysis of episodes of care of 3M Decatur chemical and film plant employees, 1993-1998. Final Report. May 18, 2001. EPA Doc. No. AR-226-1030a021. US Environmental Protection Agency, Washington DC.

[28] Olsen GW, Burris JM, Mandel JH, Zobel LR. An epidemiologic investigation of clinical chemistries, hematology and hormones in relation to serum levels of perfluorooctane sulfonate in male fluorochemical production employees. April 22, 1998. EPA Docket No. AR-226-0030. US Environmental Protection Agency, Washington DC.

[29] Final Report. Fluorochemical exposure assessment of Decatur chemical and film plant employees. August 11, 1999. EPA Docket No. AR-226-0950. US Environmental Protection Agency, Washington DC. See also Olsen GW, Logan PW, Hansen KJ, Simpson CA, Burris JM, Burlew MM, Vorarath PP, Venkateswarlu P, Schumpert JC, Mandel JH. An occupational exposure assessment of a perfluorooctanesulfonyl fluoride production site: biomonitoring. AIHA J (Fairfax, Va). 2003 Sep-Oct;64(5):651-9. Overall, mean PFOS serum levels for fluorochemical plant employees were approximately an order of magnitude higher than film plant employees. Exposure contrasts would be even larger for comparisons between highly exposed fluorochemical plant workers and the lowest exposed film plant workers.

[30] The expected number of episodes of care for the fluorochemical and film plant populations was calculated from the health claims experience of the larger 3M U.S. manufacturing population. In this way, the observed to expected ratios for the fluorochemical and film plants were each standardized for proper comparison to each other. Details on the methods and statistical analyses can be found in Olsen GW, Burlew MM, Hocking BB, Skratt JC, Burris JM, Mandel JH. An epidemiologic analysis of episodes of care of 3M Decatur chemical and film plant employees, 1993-1998. Final report. May 18, 2001. EPA Docket No. AR-226-1030a021. US Environmental Protection Agency, Washington DC. Portions of this report were published as Olsen et al. 2004 J Occup Environ Med 46 837-846.

corresponding lowest-exposed workers from the film plant. None of these comparative analyses showed a significant difference in the risk ratios of episodes of care for either infectious disease or respiratory infections between chemical plant and film plant workers.[31] If PFOS led to clinical immune deficiency, one would expect to see evidence of increased infections among the more highly exposed 3M fluorochemical production workers when compared to the film plant workers.

Moreover, EPA's analysis in the Draft MCLG Documents is inconsistent with three studies (two of which were omitted from the Agency's evaluation of "immunosuppression effects") that evaluated both specific antibody levels and infections simultaneously in the same population (Granum et al. 2013, Looker et al. 2014, Abraham et al. 2020). These studies generally indicated that even in the presence of some associations with lower antibody levels, no impact on actual infectious outcomes may be observed. Specifically, a cross-sectional study of one-year-old infants in Germany detected inverse associations between PFOA and anti-*Haemophilus influenza* type B, anti-tetanus, and anti-diphtheria antibody levels, but no associations between PFOA and any infections or surrogates of infection evaluated, including month of first infection, total number of infections, number of infections with fever, three-day fever, number of antibiotic treatments, ever use of antibiotics, otitis media (ever or number of episodes), pneumonia (ever or number of episodes), diarrhea (ever or number of episodes), varicella, napkin candidiasis, and oral candidiasis (Abraham et al. 2020). PFOS was not associated with any specific antibody levels or infections in this study. Another cross-sectional study conducted among adults in the Mid-Ohio River Valley found inverse associations between PFOA and post-vaccination anti-influenza A/H3N2 antibody levels (but not post-vaccination anti-influenza type B or A/H1N1 antibody levels), yet in the same study population, PFOA was not associated with self-reported "flu" infection, common cold, or number of colds in the past year, and PFOS was not associated with any of these outcomes (Looker et al. 2014). The third study, a small prospective cohort of up to 93 young children in Denmark, yielded a mixed pattern of findings, with inverse associations of PFOA and PFOS with antibody levels against rubella, but not measles, *Haemophilus influenzae* type B, or tetanus; and positive associations of PFOA with a greater number of episodes of common cold and gastroenteritis, but not ever having common cold or gastroenteritis, and no association of PFOS with any of these infectious outcomes (Granum et al. 2013).

Besides the generally null findings from epidemiological studies of PFOA and PFOS in association with clinical infectious diseases, population-level data show that despite substantial declines, approaching an 80 percent decline for PFOA and a 90 percent decline for PFOS in the U.S. general population over the past two decades (CDC 2021), incidence rates of tetanus and diphtheria in the U.S. appear not to have changed (World Health Organization 2020). Thus, these ecological data also fail to show any impact of PFOA or PFOS on the occurrence of tetanus and diphtheria.

In summary, most reported associations of PFOA and PFOS with infectious outcomes are null, and the remainder are an inconsistent assortment of positive and inverse associations with no clear pattern by type, timing, or dose of PFAS, type of infection, age or sex, or other study population characteristics. The general lack of associations between PFOA or PFOS and

[31] See Tables 7, 8, 9, and 10 in Olsen et al. 2001.

infectious outcomes suggests that any effect of PFOA or PFOS on antibody-mediated immunity to certain vaccine antigens (i.e., tetanus toxoid or diphtheria toxoid), if it exists at all, may not impact the immune response to other specific pathogens, or that any effect does not lead to a clinically apparent change in susceptibility to infections in general. At bottom, EPA's Draft MCLG Documents use antibody levels for diphtheria or tetanus toxoids as a critical effect in the face of, at best, extremely limited and contradictory evidence that PFOA or PFOS actually cause clinical adverse immunological outcomes. SAB should recommend that EPA reconsider its analytical approach.

D. The Reference Doses Proposed by EPA's Office of Water for the SAB's Consideration Are Far Lower Than Those It Previously Derived in 2016 and Are Not Supported by the Body of Scientific Literature.

The reference doses proposed by EPA present a stark contrast to its earlier values and those of other federal agencies and states regulatory authorities. As detailed in Tables 1 and 2 below for PFOA and PFOS respectively, EPA's proposed reference doses ("RfDs") are orders of magnitude smaller than those derived by EPA in 2016, ASTDR in 2021 and several states.

Table 1 PFOA Derivations of Reference Levels

			USEPA	MNDOH	MADEP	ATSDR	MDHHS	MSAW	NJDWQI	NHDES	CA OEHHA	**USEPA 2021**
	Parameter	Units	2016	2018	2019	2021	2019	2019	2016	2019	2019	**2021**
	Species	-	Mouse	Mouse	Mouse	Mouse	Mouse	Mouse	Mouse	Mouse	Mouse	**Human**
	Selected critical endpoint	-	Developmental (reduced ossification, accelerated puberty)	Delayed ossification, accelerated PPS in male offspring, trend for decreased pup body weight, and increased	Developmental (reduced ossification, accelerated puberty)	Skeletal alterations in mice (Koskela et al. 2016)	Neurobehavioral effects (decreased number of inactive periods, altered novelty induced activity), and skeletal alteration such as bone morphology and bone cell differentiation in the femurs and tibias.		Increase in relative liver weight		Hepatic mitochondrial membrane potential changes, increased biomarkers of apoptosis, increased	**Decreased serum anti-tetanus antibody concentration in children**
Dose-Response	Dose-response POD Modeling Method	-	LOAEL	LOAEL	LOAEL	LOAEL	LOAEL	LOAEL	BMDL	BMDL	LOAEL	**BMDL5**
	POD Serum	ng/mL	38,000	38,000	38,000	8,290	8,290	8,290	4,350	4,351	970	**0.17**
	POD Human Equivalent Dose	ng/kg/day	5,300	5,300	5,300	821	*1,368*	1,163	*610*	*610*	*136*	**0.015**
Uncertainty Extrapolation	Total Composite (UF_T)	unitless	300	300	1000	300	300	300	300	100	300	**10**
Reference Value - RfD, MRL, or 'toxicity value'	Serum	ng/mL	*130*	130.0	*38*	*28*	28	28	14.5	43.5	3.2	***0.017***
	Human Equivalent Dose (RfD)	ng/kg/day	20	18	5.3	3	5	3.9	2.0	6.1	0.45	**0.0015**
Drinking Water guidance level (DWGL)		ng/L	70	35	20	*10.5**	9	8	14	12	2	***0.0053*****

Notes:
Note for clarity the doses in the above are expressed in units of ng/kg/day rather than the customary mg/kg/day.
Italicized values are not presented in the orignal documents and have been calculated.
*ATSDR does not calculate DW levels, the value shown is calculated using the ratio of ATSDR's MRL to EPA's 2016 RfD on the EPA 2016 DWLG (70ppt).
** Value is the 2016 HA level of 70 ppt scaled by ratio of the 2016 to proposed 2021 RfD (13,333x lower) = 0.0053 ngL = 5.3 pg/L, parts per quadrillion

Table 2 PFOS Derivations of Reference Levels

			USEPA 2016	MNDOH	MADEP	ATSDR	MDHHS	MSAW	NJDWQI	NHDES	CA OEHHA	**USEPA 2021**
	Parameter	Units	2016	2019	2019	2021	2019	2019	2018	2019	2019	**2021**
	Species	-	Rat	Mouse	Rat	Rat	Rat	Mouse	Mouse	Mouse	Mouse	**Human**
	Selected critical endpoint	-	decreased pup body weight	Increased IL-4 and decreased SRBC specific IgM levels	Pup body weight and developmental delays	Delayed eye opening and decreased pup body weight in rats	Delayed eye opening and decreased mean pup body weight	Increase in liver mass and suppression of plaque-forming cell response in mice	Decreased plaque forming cell response	Suppressed immunoglobulin M (IgM) production in male mice	Decreased plaque forming cell response	**Decreased serum anti-diphtheria antibody concentration in children.**
Dose-Response	Dose-response POD Modeling Method	-	NOAEL	NOAEL	NOAEL	NOAEL	NOAEL	NOAEL	NOAEL	NOAEL	NOAEL	**BMDL5**
	POD Serum	ng/mL	6,260	2,360	6,260	7,430	7,430	674	674	2,360	674	**0.54**
	POD Human Equivalent Dose	ng/kg/day	510	307	510	515	*515*	86.6	*55*	*303*	*55*	**0.079**
Uncertainty Extrapolation	Total Composite (UF_T)	unitless	30	100	100	300	300	30	30	100	30	**10**
Reference Value - RfD, MRL, or 'toxicity value'	Serum	ng/mL	*209*	24	*63*	*25*	24.8	22	23	23.6	22	***0.054***
	Human Equivalent Dose (RfD)	ng/kg/day	20	3.1	5.1	2	2	2.89	1.8	3.0	1.8	**0.0079**
DW guidance level		ng/L	70	15	20	7*	*8*	16	13	15	7	***0.028****

Notes:

Note for clarity the doses in the above are expressed in units of ng/kg/day rather than the customary mg/kg/day.
Italicized values are not presented in the orignal documents and have been calculated.
*ATSDR does not calculate DW levels, the value shown is calculated using the ratio of ATSDR's MRL to EPA's 2016 RfD on the EPA 2016 DWLG (70 ppt).
** Value is the 2016 HA level of 70 ppt scaled by ratio of the 2016 to proposed 2021 RfD (2,532x lower) = 0.028 ngL = 28 pg/L, parts per quadrillion

Indeed, EPA's 2021 proposed RfD[32] for PFOA is over 13,300 times lower than the Agency's previous value derived in 2016. For PFOS the proposed RfD[33] is 2,532 times lower than the 2016 value. In addition, the reference doses proposed are far lower than those derived by ATSDR and state regulatory authorities.[34] Figures 1 and 2 demonstrate these differences.

Figure 1 PFOA RfD HED Values

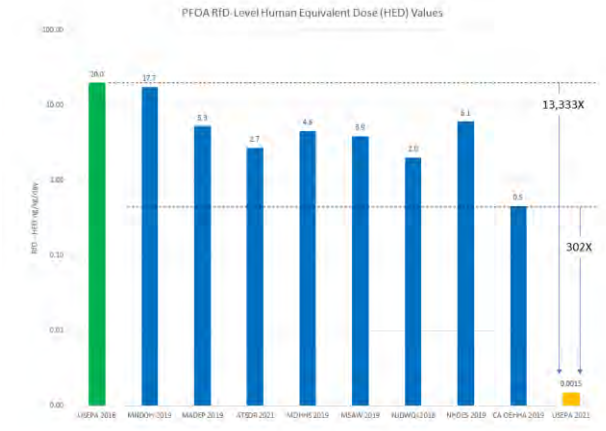
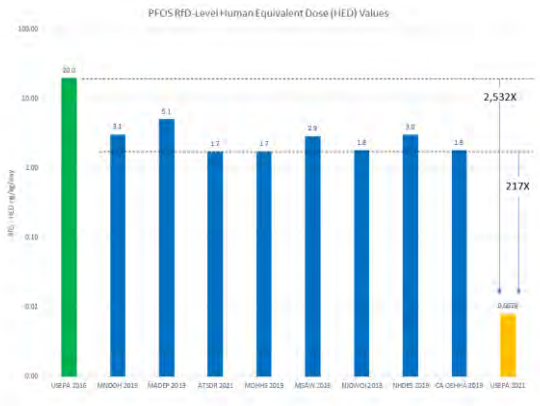


Figure 2 PFOS RfD HED Values



[32] Draft PFOA MCLG Approach, p. 340.
[33] Draft PFOS MCLG Approach, p.310.
[34] See references at the end for ATSDR and State values presented in these tables.

As part of its review, the SAB should consider PFOA and PFOS's relative toxicity and whether the proposed RfDs are supportable considering there is no reliable evidence of adverse effects in humans or animals at those levels.

E. The blood serum concentrations that correspond to the reference doses are significantly lower than background levels for the US population and lower than European guidance values for serum.

EPA's proposed PODs and RfDs, and analogous "reference" values from ATSDR (MRLs) and states, are human equivalent doses that correspond to internal dose blood serum levels. The blood serum levels that correspond to PODs and RfDs (or RfD-equivalent levels) are shown in Tables 1 and 2 (above) and on Figures 3 and 4 (PODs) and 5 and 6 (RfDs).

Figure 3 PFOA POD Serum Levels

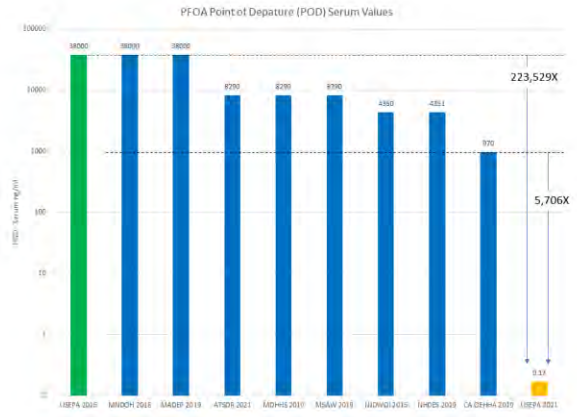


Figure 4 PFOS POD Serum Levels

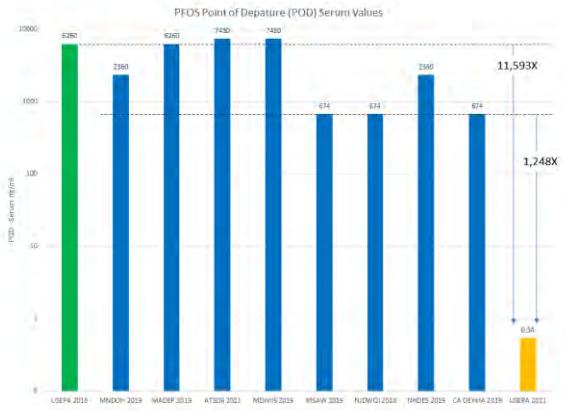


Figure 51 PFOA RfD Serum Levels

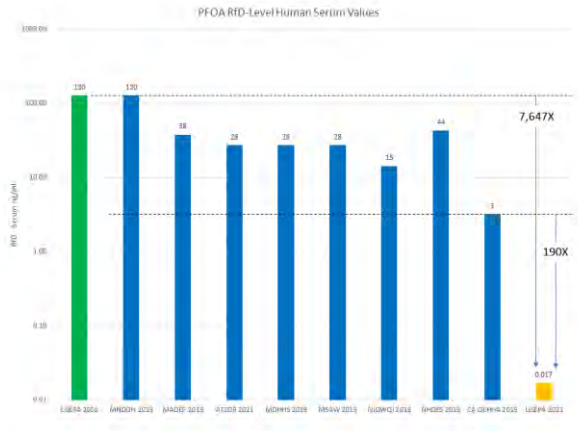
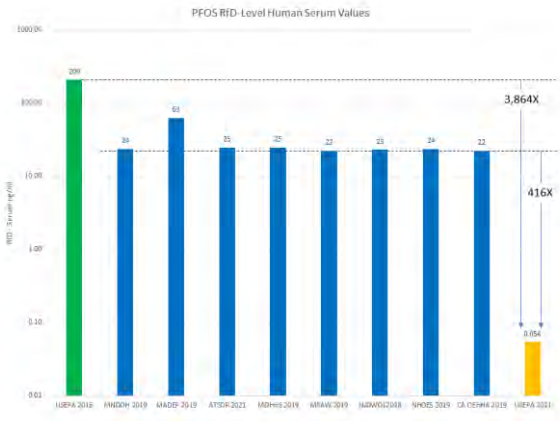
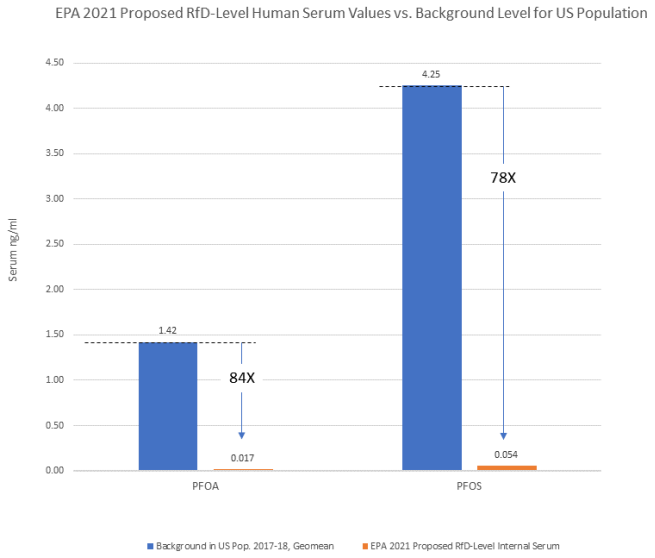


Figure 6 PFOS RfD Serum Levels



The EPA's 2021 proposed RfD-level serum values, 0.017 ng/ml for PFOA[35] and 0.054 ng/ml for PFOS[36], are well below background levels present in the US. The latest mean serum concentrations for the US population are 1.42 ng/ml (95% confidence interval 1.33-1.52) for PFOA and 4.25 (3.90-4.62) for PFOS. In both cases the proposed reference serum values are about 80 times lower than the mean background levels in the US population. *See* Figure 7.

Figure 7 Proposed Reference Serum Levels Compared to US Pop. Background

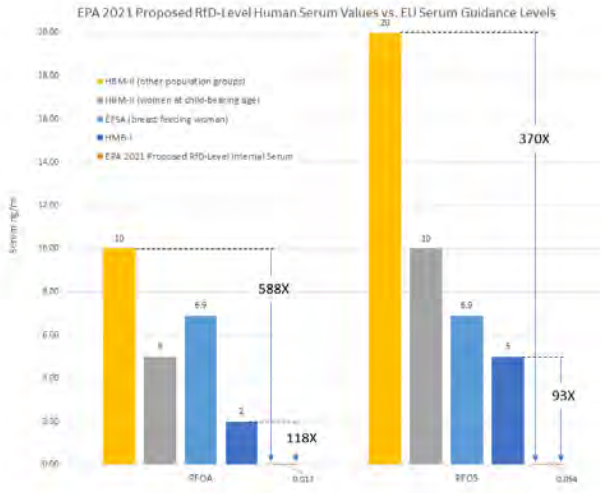


In Europe, the European Food Safety Authority (EFSA) and the Human Biomonitoring Commission of the German Environment Agency (HBM Commission) have derived guidance levels based on serum levels similarly based wholly or in part on human vaccine studies.[37] EFSA has derived its tolerable weekly intake ("TWI") value for food using vaccine studies – specifically the TWI is based on limiting the serum level in humans to 6.9 ng/ml for the sum of four PFAS (PFOA, PFOS, PFHxS and PFNA).[38] The HBM Commission has published HBM-I and HBM-II values for PFOA and PFOS. HBM-I values that are deemed safe "concentration of a substance in human biological material below which, according to the current status of assessment, no adverse health effects are to be expected" and HBM-II values that are "concentration[s] of a substance in human biological material which, when exceeded, may lead

[35] Draft PFOA MCLG Approach, 1.7 x 10-4 mg/L internal POD for tetanus (Table 21) divided by UF of 10 (Table 22) = 1.7 10-5 mg/L = 0.017 µg/L = 0.017 ng/ml.
[36] Draft PFOS MCLG Approach; 5.4 x 10-4 mg/L internal POD for diphtheria (Table 21) divided by UF of 10 (Table 22) = 5.4 10-5 mg/L = 0.054 µg/L = 0.054 ng/ml.
[37] Even EFSA's TWI values were extremely conservative. 3M provided extensive comments to EFSA on its guidance and will provide such comments to SAB and EPA upon request.
[38] EFSA. 2020. Risk to human health related to the presence of perfluoroalkyl substances in food. EFSA Panel on Contaminants in the Food Chain (CONTAM). doi: 10.2903/j.efsa.2020.6223. Adopted: 9 July 2020.

to health impairment which is considered as relevant to affected individuals."[39,40,41] These values are at least about 100x higher than those proposed by EPA. *See* Figure 8.

Figure 8 Proposed Reference Serum Levels vs EU Serum Guidance



F. EPA's benchmark dose analysis is flawed.

EPA used the benchmark dose levels ("BMDLs") as the basis of the points of departure ("PODs") in the Draft MCLG Documents The BMDLs were then fed into the pharmacokinetic ("PK") model, which was developed by EPA. The BMDLs underlying the PK model were flawed. For both PFOA and PFOS, EPA states a 5% benchmark response ("BMR") was used for the immune effects in children for reduced antibody concentrations for diphtheria and tetanus, and that a BMR of one standard deviation was used for the immune effects of decreased plaque forming cell response to SRBC (PFOS)[42] and reduced IgM response (PFOA).[43] While the BMR of one standard deviation is consistent with EPA BMD technical guidance, a BMR of 10% is generally recommended by EPA for dichotomous data.[44] The PFOA draft document specifically

[39] HBM I values for Perfluorooctanoic acid (PFOA) and Perfluorooctanesulfonic acid (PFOS) in blood plasma. Statement of the German Human Biomonitoring Commission (HBM Commission). Bundesgesundheitsbl 2016 · 59:1364. DOI 10.1007/s00103-016-2437-1. Translation of HBM-I-Werte für Perfluoroctansäure (PFOA) und Perfluoroctansulfonsäure (PFOS) in Blutplasma. Stellungnahme der Kommission Human-Biomonitoring des Umweltbundesamtes. (DOI 10.1007/s00103-016-2434-4).

[40] HBM-II values for perfluorooctanoic acid (PFOA) and perfluorooctane- sulfonic acid (PFOS) in blood plasma. Statement by the Human Biomonitoring Commission of the German Environment Agency. Translation of the German version in Bundesgesundheitsbl 2020 · 63:356–360 https:// doi.org/ 10.1007/ s00103- 020- 03101-2.

[41] The authors of HBM II have acknowledged various limitations in the analysis. "The HBM-II values were chosen from the range of POD values by expert assessment, considering the uncertainties and the specifics of certain target groups. However, this value cannot be used to quantify, with sufficient certainty, an individual's risk of suffering health impairment as a result of her/his internal exposure to PFOA or PFOS." Schumann et al. 2021 Regul Toxicol Pharmacol 121 104868.

[42] Draft PFOS MCLG Approach, p. 293 and Table 16.

[43] Draft PFOA MCLG Approach, p. 321 and Table 16.

[44] Benchmark Dose Technical Guidance. EPA/100/R-12/001 June 2012.

states: "When severe or frank effects are modeled, a lower BMR can be adopted. For example, developmental effects are frequently serious effects and BMDs for these effects could employ a 5% BMR…."[45] In addition, in Table 16 of both draft documents, the Agency states (regarding the 1SD BMR): "No information is readily available that allows for determining a minimally biologically significant response. The BMD Technical Guidance…recommends a BMR based on 1 SD…when biological information is not sufficient to identify the BMR."

The vaccine studies EPA ultimately selected for derivation of the RfD demonstrated only inconsistent reduced antibody concentrations; they did not demonstrate an increased incidence of infectious disease or fatalities from contracting these diseases. Thus, there is "no information readily available that allows for determining a minimally biologically significant response", according to Agency guidance. The Agency should reconsider using a BMR of 10% and following their own guidance since the antibody levels EPA considered are not biologically significant. There also seems to be no scientific discussion of what antibody levels would be considered "minimally adverse."

In the main text of the Draft MCLG Documents, EPA does not clearly state how its BMD results for the immune endpoints were calculated. In reading Appendix B of both documents, it becomes apparent that EPA simply used the BMD modeling results reported by Budtz-Jorgensen and Grandjean 2018.[46,47,48] Also, it is not stated if or how EPA independently evaluated these results. In fact, Budtz-Jorgensen and Grandjean 2018 did not even use the US EPA's BMD modeling software for their analyses (they used SAS). EPA should independently evaluate Budtz-Jorgensen's results, as well as perform BMD analysis using its own guidance and judgment.

G. The Toxicokinetic Modeling Lacks Necessary Detail to Allow Public Comment.

EPA's toxicokinetic model approach lacks the necessary detail to allow the public to provide adequate input. EPA states in both Draft MCLG Documents that the "large majority of [physiological based pharmacokinetic modeling] PBPK models for PFOA/PFOS are based on the original publications of Loccisano et al…and it was noted during a review of this model's code that the implementation of protein binding appears to 'double-count' the parameter that corresponds to the free fraction of PFOA/PFOS in plasma." [49,50] The Agency then summarily dismisses PBPK models and does not give further justification as to why they did not use these models or specifically what they found wrong with these models or any PBPK models that they discuss beyond stating that "due to the previous issues in implementing PBPK models for PFAS, the known issues with the Loccisano model and the models based upon it, we decided that a one-compartment model was the best approach…[as] a one-compartment model is sufficient to predict blood (or serum/plasma concentrations….[t]his makes serum/plasma a good biomarker

[45] Draft PFOA MCLG Approach, p. 320.
[46] *Id.*, B-1.
[47] Draft PFOS MCLG Approach, B-1.
[48] Budtz-Jorgensen E; Grandjean P. 2018. Application of benchmark analysis for mixed contaminant exposures: Mutual adjustment of perfluoroalkylate substances associated with immunotoxicity. PLoS ONE 13: e0205388.
[49] Draft PFOA MCLG Approach, p. 332-333.
[50] Draft PFOS MCLG Approach, p. 303.

for exposure." EPA should provide detail as to why it believes the Loccisano models and other models developed from them 'double-count' and further explain its rational for not using PBPK models.

For modeling animal PK, EPA chose the compartment model (consisting of 3 compartments) developed by Wambaugh et al. 2013,[51] which appears to be validated using literature data for rats, mice, and monkeys. EPA has not explained, however, why it did not develop or modify an existing physiologically-based model of its own if EPA did not find published models acceptable. EPA's methods of predicting parameter distributions using a compartmental model are confusing and there is no explanation for why the added complexity is necessary. The Wambaugh model did not originally account for various life stages, so EPA modified it for gestation, lactation, and post-weaning phases. For PFOA, EPA tested this life stage model with one rat study and one mouse study (gestation/lactation).[52] For PFOS, EPA tested this life stage model with one rat study (gestation/lactation).[53] This validation is quite limited and EPA states that "the Wambaugh model was not parameterized for a post-partum infant…", which implies uncertainty in model predictions yet the model accounts for post-weaning.[54] There is no analysis detailing whether EPA made any attempt to extend their animal model to humans or why EPA's animal model was not parameterized for post-partum infants, considering that the selected RfD was based on 5-year-olds. This lack of transparency prevents the public from providing fulsome comments to assist SAB in ensuring EPA is relying on the best available science.

Similarly, for human PK modeling, EPA used the Verner et al. 2016 model, which is a one-compartment model for humans.[55] EPA made several adjustments to the model, including how the body weight during pregnancy was calculated and updated parameters for some of the partition coefficients (specifically, those for the chemical cord blood: maternal serum and the chemical breastmilk: maternal serum).[56] This updated model was then used to simulate the HEDs from the animal PODs that were obtained from BMD modeling and to simulate selected human studies. There is no indication that EPA tested this modified model before using it to estimate internal PODs and subsequently HEDs. Considering that this human model was used for derivation of the RfD selected by the EPA, SAB should recommend that EPA validate the model or explain why EPA did not believe the model needed to be validated.

EPA also states that one of the advantages in its choice of a PK model is that a single model structure could be used for all species of interest.[57] Yet EPA did not do so. SAB should recommend that EPA should provide its rationale for choosing a different model structure for humans than was used for simulating the animal studies. This analytical choice has consequences on EPA's conclusions. Indeed, the internal dose metrics and the POD_{HED} values

[51] Wambaugh et al. 2013. Dosimetric anchoring of in vivo and in vitro studies for perfluorooctanoate and perfluoroctanesulfonate. Toxicol Sci 136: 308-327.
[52] Draft PFOA MCLG Approach, p. 329.
[53] Draft PFOS MCLG Approach, p. 300.
[54] Draft PFOA MCLG Approach, p. 328; Draft PFOS MCLG Approach, p. 299.
[55] Verner et al. 2016. A simple pharmacokinetic model of prenatal and postnatal exposure to perfluoroalkyl substances (PFAS). Environ Sci Technol 50: 978-986.
[56] Draft PFOA MCLG Approach, p. 331-332; Draft PFOS MCLG Approach, p. 301-302.
[57] Draft PFOA MCLG Approach, p. 323; Draft PFOS MCLG Approach, p. 295.

are much greater when derived from the animal studies than from the human studies.[58] EPA should explain why these values differ by orders of magnitude and what drove EPA's choices.

Limitations of the human modeling approach are discussed which include uncertainty in the parameters V_d, half-life, and clearance in the human population and how these parameters could be different in children and adults (i.e., even more uncertainty).[59] EPA states that in the Verner et al. 2016 model, these parameters (V_d, half-life, and thus clearance) were assumed to be constant across ages and sexes; EPA did not state that it did anything differently. Although there is uncertainty about these parameters (also, EPA previously stated in both documents that "the Wambaugh model was not parameterized for a post-partum infant…"), especially in kids, the Agency used this model in order to derive RfDs based on measurements in children (i.e., the Grandjean vaccine studies). This obviously could introduce uncertainty in the internal dose metrics and thus the estimated HEDs. The Agency should explain this rationale.

H. The Application of Uncertainty Factors is Unjustified.

For both PFOA and PFOS, EPA applied a total uncertainty factor ("UF") of ten times ("10X") for both immune and developmental endpoints.[60] This 10X factor (UF_H) was applied to account for variability in responses within the human population, including life stage. EPA states that "the Wambaugh model was not parameterized for a post-partum infant…" and that there is uncertainty around key PK parameters in children. These concerns do not support using the default 10X factor. If EPA believes its models have good predictive ability it should justify its use of the default 10X UF. Alternatively, EPA should explain why it chose to use models that lack the requisite predictive accuracy.

I. The Cancer Slope Factor for PFOA is Unclear.

For the revised (from EPA's 2016 assessment) PFOA cancer slop factor ("CSF"), EPA used both animal studies and a human study, Shearer et al. 2021 (discussing renal cell carcinoma in humans).[61,62] EPA states that it used the same methods as the draft CalEPA 2021 document to estimate the human CSF.[63] However, the methods as presented in the main text are confusing and unclear. EPA should present equations for each step. In addition, EPA discusses that the CSF is calculated as "CSF_{serum}" and presents two values in Table 25 (0.01483 per ng/kg/day and 0.0352 per ng/kg/day). Then EPA's Appendix B states that the estimated CSF_{serum} value is per 0.00178 per ng/kg/day. EPA needs to clarify why there are multiple CSF values and how, or whether, those values were used. EPA should also state its derived CSF in the main document text. EPA should also address why the CSFs derived from the human data are much lower than the CSFs derived from the animal studies.

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[58] Draft PFOA MCLG Approach, Table 21; Draft PFOS MCLG Approach, Table 21.
[59] Draft PFOS MCLG Approach, p. 304; Draft PFOA MCLG Approach , p. 333.
[60] Draft PFOA MCLG Approach, Table 23; Draft PFOS MCLG Approach, Table 23.
[61] Draft PFOA MCLG Approach, p. 343-345.
[62] Shearer et al. 2021. Serum concentrations of per- and polyfluoroalkyl substances and risk of renal cell carcinoma. J Natl Cancer Inst 113: 580-587.
[63] CalEPA 2021. Public Health Goals: Perfluorooctanoic Acid and Perfluorooctane Sulfonic Acid in Drinking Water (First Public Review Draft ed). California Environmental Protection Agency, Office of Environmental Health Hazard Assessment, Pesticide and Environmental Toxicology Branch.

J. The Animal Immune Response Data Selected for POD Modelling for PFOA and PFOS Differ From, and in Some Cases Contradict the Human Vaccine Response Data.

The immune system provides complex and varied mechanisms of responding to exogenous and endogenous triggers. Different immunoglobin classes have different functions and roles. The primary antibody response is characterized by the abundant generation of IgM antibodies that are not T cell dependent and do not show immunologic memory. In contrast, IgG antibodies predominate as part of the secondary antibody response (Janeway and Travers, 1996). The more mature IgG secondary antibodies, which have far greater affinity for the antigen than do primary response antibodies, are an important indicator of immunological memory. Grandjean et al. (2017) specifically measured secondary antibody responses to vaccination against both tetanus and diphtheria in a cohort of children from the Faroe Islands. These children were vaccinated at 3, 5 and 12 months and a booster was administered at 5 years. Blood sampling was conducted at 13 years of age and serum concentrations of IgG antibodies were again measured.

The animal studies cited by EPA and included for POD derivation focused instead on IgM antibodies and/or evaluated both IgM and IgG antibody responses, but with results that differed from the human studies included for POD derivation. [64] IgM antibody responses are not indicators of immune memory, the T cell component of the immune response, or the robustness of the immune response in humans. Thus, IgM responses, while employed in the mouse studies, are not evaluated in terms of protection from infection; their primary use is as an indication of early infection prior to the production of IgG antibodies.

For PFOA, DeWitt et al. (2008) evaluated both IgM and IgG antibody responses to injected sheep red blood cells (SRBC) in mice, while Loveless et al. (2008) only measured IgM levels in response to SRBC immunization in both rats and mice. While Grandjean et al. (2017) reported reduced IgG antibody levels in association with increased PFOA serum concentrations, DeWitt et al. (2008) actually found that, in mice, IgG antibody levels were either increased with PFOA exposure or not significantly different from control. Thus, the secondary antibody response in mice did was not found to be adversely affected by PFOA exposure. The inconsistency of these data across species calls into question their relevance to PFOA exposure.

For PFOS, Zhong et al. (2016) reported a decrease in SRBC-specific IgM antibody produced in 4-week-old offspring of mice treated with 1 mg/kg/day (males only) and 5 mg/kg/day (males and females) PFOS (but not 0.1 mg/kg/day) from gestation day (GD) 1 through GD 17. However, this decrease was transient; levels were not decreased at 8 weeks of age for either males or females at any dose. Unlike the secondary antibody IgG antibody levels measured by Grandjean et al. (2012, 2017a,b) in the human studies, Zhong et al. (2016) did not measure IgG levels, nor did the supporting animal studies cited in the EPA PFOS report (Peden-Adams et al. 2008; Keil et al. 2008).[65]

[64] Draft PFOA MCLG Approach, p. 335; Draft PFOS MCLG Approach, p. 305.
[65] Draft PFOS MCLG Approach , p. 154.

Thus, the animal toxicology studies do not provide supporting evidence for the human vaccine response studies. The endpoints measured in most animal studies were not equivalent. Further, the reported IgM-related immune effects are generally confined to one particular species of mice, but no effects were observed in rats and no effects in other types of mice. In short, even putting aside that the animal data are not themselves internally consistent, when the same aspects of immune response as measured in the human vaccine studies were assessed, the animal studies provide contradictory results from those reported by Grandjean et al. (2012, 2017a,b).

K. Effects on IgM Levels in Animals Appear to be a Stress-Related Response.

Although both DeWitt et al. (2008) and Loveless et al. (2008) reported significant effects of PFOA exposure on anti-SRBC IgM levels in mice, this response appears to be due to substantial stress in the animals. For example, Loveless et al. (2008) found 14% and 22% body weight reductions in mice with 29 days of gavage dosing at 10 and 30 mg/kg/day, respectively. Thymic and/or splenic atrophy were observed, and these organs substantially decreased in weight at these same doses. No effects on body weight, the spleen or thymus were seen at the next lower dose of 1 mg/kg/day.

DeWitt et al. (2008) similarly showed significant (6-15%) body weight loss after only 8 days of drinking water exposure at 30 mg/kg/day and a 6% body weight loss after only 15 days of treatment with 15 mg/kg/day. Again, spleen and thymus weights were affected (histopathologic examination was not conducted). Although body weights were not reduced after 15 days of exposure at the next lower doses of 7.5 and 3.75 mg/kg/day, spleen weights were significantly reduced at these doses in the second dose-response study (Study II). Thus, these data are generally consistent with those of Loveless et al. (2008).
Importantly, Loveless et al. (2008) showed substantial increases in serum corticosterone levels in mice at the same doses at which IgM levels were reduced. Further, serum corticosterone levels were not affected by PFOA in the rat; nor were IgM levels. Loveless et al. (2008) went on to note that a reduced IgM response in conjunction with increased serum corticosterone levels was consistent with other data reported in the literature by Dracott and Smith (1979) and Pruett et al. (1999).

Similar to the studies with PFOA, Zhong et al. (2016) reported substantially lower body weight (although not statistically significant) at doses associated with alterations in IgM in 4-week-old mice born to dams treated with PFOS during gestation: approximately 9% and 11% decreases for males treated with 1 and 5 mg/kg/day PFOS, respectively. Consistent with the reduced IgM response for females, the overall impact on body weight was also lower for females: approximately 5% and 7% decreases in mice at 1 and 5 mg/kg/day dose levels, respectively. As with the transient nature of the IgG response, body weight differences between groups lessened or disappeared by 8 weeks of age. Zhong et al. did not measure stress hormones in this study, but they noted that their previous research demonstrated increased corticosterone levels in adult mice treated PFOS.

Thus, based on the available data, it cannot be concluded that the reduced IgM responses in mice reported by DeWitt et al. (2008) and Loveless et al. (2008) for PFOA and by Zhong et al. (2016) for PFOS are specifically due to the chemical treatment and not secondary to a

generalized stress response. The inconsistency between rats and mice in the results reported by Loveless et al. (2008) further supports the contention that this is a secondary stress response. In light of this likelihood, a reduced IgM response should not be considered as a potential POD for PFOA.

L. EPA Provides No Justification For Using Pharmacokinetic Modeling to Determine the PFOA Internal Doses From Dewitt et al. (2008) and the PFOS Internal Doses From NTP (2009)

In Table B-16 in Appendix B, internal doses of PFOA in mg/L are shown for each of the doses administered in dose-response Study I from DeWitt et al (2008).[66] However, these concentrations do not agree with the serum concentrations of PFOA reported by DeWitt et al. (2008) (see table below). Incongruencies also exist regarding the internal doses of PFOA reported for dose response Study II (data not shown herein). [67] Consequently, it is assumed that EPA used pharmacokinetic modelling to derive the values reported in Appendix B. EPA should either use the internal dose data as reported in the actual study or provide a clear rationale for why pharmacokinetic modelling was used to determine the internal doses.

Table 3

Administered dose (mg/kg/day)	Internal dose (mg/L)		
		From Table 1 of DeWitt et al. (2008)	
	From EPA Table B-16	Day 1 post-dosing	Day 15 post-dosing
0	0	0.05	0.16
3.75	113.4	75	35
7.5	180.9	87	43
15	209.6	128	50
30	242.8	163	53

It is further noted that, in Table B-18 for dose-response Study II, the administered PFOA doses are reported as 0, 3.75, 7.5, 15, and 30 mg/kg/day. [68] However, the actual doses used in Study II were 0, 0.94, 1.88, 3.75, and 7.5 mg/kg/day. It is unclear if this is merely a typo on EPA's part or if the incorrect external doses were used in the pharmacokinetic modelling. However, because the internal doses calculated in Tables B-16 and B-18 do not match (see below), it is most likely a typo. EPA should further clarify the issue.

[66] Draft PFOA MCLG Approach, p. B-26.
[67] *Id.*, p. B-27.
[68] *Id.*, p. B-27.

Table 4

Administered Dose (mg/kg/day) EPA PFOA Tables B-16 & B-18	Study 1 Internal Dose (mg/L) EPA PFOA Table B-16	Study 2 Internal Dose (mg/L) EPA PFOA Table B-18
0	0	0
3.75	113.4	29.8
7.5	180.9	58.9
15	209.6	113.4
30	242.8	180.9

Similarly, for PFOS, the internal plasma concentrations of PFOS were measured and reported in the NTP (2019) study (see table below), but these do not match the internal doses used by EPA in its benchmark dose modelling. As noted for DeWitt et al. (2008) above, it is assumed that EPA used pharmacokinetic modelling to derive the values reported in the Draft MCLG Document, Appendix B.[69] EPA should either use the internal dose data as reported in the actual study (as these are a more accurate reflection of the actual internal doses achieved) or provide a clear rationale for why pharmacokinetic modelling was used to determine the internal doses.

Table 5

Administered dose (mg/kg/day)	Internal dose (mg/L)		
		Plasma concentration from NTP (2019)[70]	
	From EPA Table B-47	Males	Females
0	0	0	0.05
0.312	10.0	23.7	30.5
0.625	20.1	51.6	67.0
1.25	40.1	94.2	135.1
2.5	80.2	173.7	237.5
5	160.4	318.2	413.6

M. The Biological Relevance of the Measured IgM Response From Dose-Response Study II of Dewitt et al. (2008) is Questionable.

The extremely shallow slope of the dose-response curve shown in Figure 9 (an excerpt of Figure B-7 of Appendix B of the Draft MCLG Document for PFOA (copied below) calls into question whether the IgM data from dose-response study II of DeWitt et al. (2008) are appropriate for benchmark dose modelling.[71]

[69] Draft PFOS MCLG Approach, p. B-45.
[70] From Table PA48 – Summary of Tissue Concentration from the 28-day evaluation of the toxicity (C20617) of perfluorooctane sulfate (PFOS) (1763-23-1) on Harlan Sprague-Dawley rats exposed via gavage, available at: https://cebs.niehs.nih.gov/cebs/study/002-02656-0003-0000-4.
[71] Draft PFOA MCLG Approach, p. B-29.

Figure 9: Excerpt of Figure B-7 of Appendix B of the Draft MCLG Document for PFOA

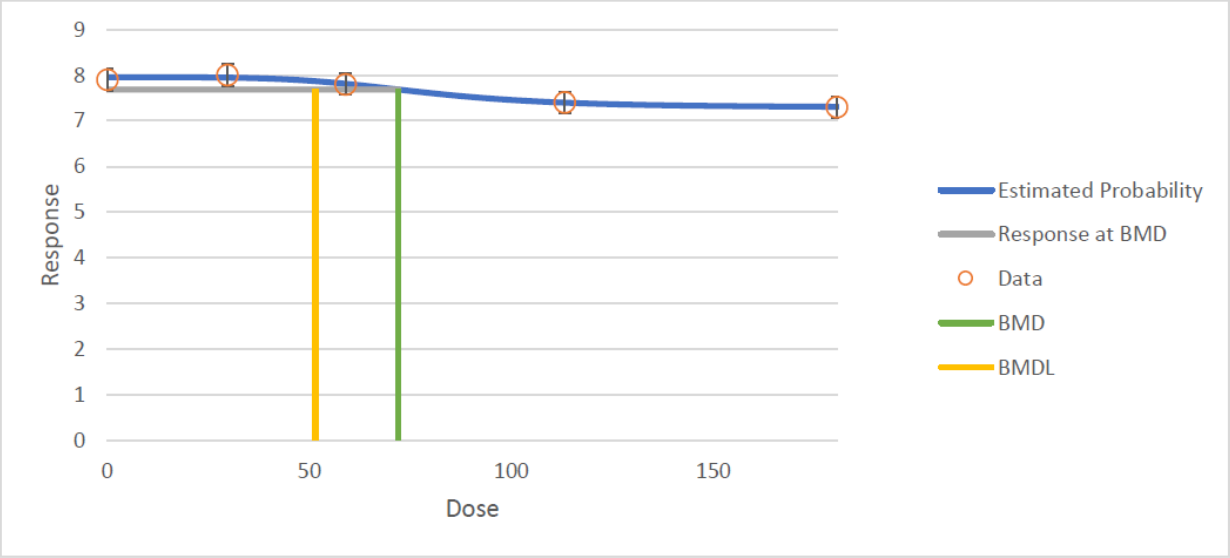

Figure B-7. Plot of Mean Response by Dose with Fitted Curve for the Selected Hill Model for Serum Sheep Red Blood Cells-specific IgM Antibody Titers in Female C57BL/6N Mice (Study II) Following Exposure to PFOA

The control IgM titer response was 7.9±0.3. The response at 7.5 mg/kg/day[72] (the highest dose tested) was 7.3±0.3 (-8% of control). [73] Based on the flatness of the dose-response curve and the minimal change measured, it is unclear whether or not the IgM response measured with PFOA treatment in this study is outside the normal range of biological variability.

Table 6

Administered Dose (mg/kg/day)	Study 1 Internal Dose (mg/L) EPA PFOA Table B-16	Study 2 Internal Dose (mg/L) EPA PFOA Table B-18
0		0
3.75	113.4	29.8
7.5	180.9	58.9
15	209.6	113.4
30	242.8	180.9

[72] Although Table B-18 indicates that the dose was 30 mg/kg/day, the actual top dose in Dose-reponse Study II from DeWitt et al. (2008) was actually 7.5 mg/kg/day.
[73] Although Table B-18 indicates that the dose was 30 mg/kg/day (Draft PFOA MCLG Approach, p. B-27), the actual top dose in dose-response Study II from DeWitt et al. (2008) was 7.5 mg/kg/day.

N. EPA May Have Made an Error in Benchmark Dose Modelling of the Data from Loveless et al. (2008).

In Table B-42 in Appendix B, the lowest dose administered to mice in Loveless et al. (2008) is shown as 0.1 mg/kg/day.[74] This is incorrect. The lowest dose in this study was 0.3 mg/kg/day. Based on the available information, it is unclear whether this is simply a typographic error or if EPA may have used an incorrect input in the internal dose pharmacokinetic modelling and/or benchmark dose modelling.

* * *

3M appreciates the opportunity to provide these technical comments on the meeting materials and encourages SAB to consider the above materials as it provides input to EPA. Thank you for your consideration.

Regards,

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[74] Draft PFOA MCLG Approach, p. B-52.

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APPENDIX A – IMMUNOTOXICITY TABLES

Table 1. Overview of studies of PFOA, PFOS, and antibody-mediated immunity

In EPA?	Reference	Study Design	Country	Age Group	Subjects (Max)	Associations	Null Results
Yes	Abraham 2020	Cross-sectional	Germany	Children	101	PFOA and lower anti-*Haemophilus influenza* type B IgG level at 1 y; NOAEL at 12.2 µg/L plasma PFOA PFOA and lower anti-tetanus IgG and IgG1 level at 1 y; NOAEL at 16.9 µg/L plasma PFOA PFOA and lower anti-diphtheria IgG level at 1 y; NOAEL at 16.2 µg/L plasma PFOA	PFOS and anti-*Haemophilus influenza* type B IgG level, anti-tetanus IgG or IgG1 level, or anti-diphtheria IgG level at 1 y
No	Catelan 2021	Ecological	Italy	Adults	563	ΣPFAS and greater risk of COVID-19 mortality	None
Yes	Grandjean 2012	Prospective cohort and cross-sectional	Faroe Islands	Children	587	Maternal PFOA and lower anti-diphtheria antibody level at 7 y (not adj. for 5 y) PFOA at 5 y and lower anti-tetanus antibody level at 7 y (adj./not adj. for 5 y) PFOA at 5 y and lower anti-diphtheria antibody level at 7 y (adj./not adj. for 5 y) Maternal PFOS and greater anti-tetanus antibody level at 7 y (adj. for 5 y) Maternal PFOS and lower anti-diphtheria antibody level at 5 y PFOS at 5 y and lower anti-tetanus antibody level at 5 y PFOS at 5 y and lower anti-diphtheria antibody level at 7 y (not adj. for 5 y)	Maternal PFOA and anti-tetanus antibody level at 5 or 7 y Maternal PFOA and anti-diphtheria antibody level at 5 y PFOA at 5 y and anti-tetanus antibody level at 5 y PFOA at 5 y and anti-diphtheria antibody level at 5 y Maternal PFOS and anti-tetanus antibody level at 5 y Maternal PFOS and anti-diphtheria antibody level at 7 y PFOS at 5 y and anti-tetanus antibody level at 7 y PFOS at 5 y and anti-diphtheria antibody level at 5 y

In EPA?	Reference	Study Design	Country	Age Group	Subjects (Max)	Associations	Null Results
Yes	Grandjean 2017a	Prospective cohort and cross-sectional	Faroe Islands	Children, adolescents	505	PFOA at 13 y and lower anti-diphtheria antibody level at 13 y (no ER visit/booster) PFOA at 7 y and lower anti-diphtheria antibody level at 7 and 13 y (total, no ER visit/booster, indirect effect (via 7-year antibody)) PFOS at 7 y and greater anti-tetanus antibody level at 13 y (no ER visit/booster) PFOS at 7 y and lower anti-diphtheria antibody level at 7 and 13 y (total, no ER visit/booster, total and indirect effects)	PFOA at 7 y and anti-diphtheria antibody level at 13 y PFOA at 13 y and anti-diphtheria antibody level at 13 y (total, no ER visit/booster and no antibody increase) PFOA at 7 or 13 y and anti-tetanus antibody level at 13 y PFOA at 7 y and anti-diphtheria antibody level at 7 and 13 y (no ER visit/booster and no antibody increase) PFOA at 7 y and anti-tetanus antibody level at 7 and 13 y PFOS at 7 or 13 y and anti-diphtheria antibody level at 13 y PFOS at 7 y and anti-tetanus antibody level at 13 y (total, no ER visit/booster and no antibody increase) PFOS at 13 y and anti-tetanus antibody level at 13 y PFOS at 7 y and anti-diphtheria antibody level at 7 and 13 y (no ER visit/booster and no antibody increase) PFOS at 7 y and anti-tetanus antibody level at 7 and 13 y

In EPA?	Reference	Study Design	Country	Age Group	Subjects (Max)	Associations	Null Results
Yes	Grandjean 2017b	Prospective cohort	Faroe Islands	Children	349	PFOA at birth, 18 m, and 60 m and lower anti-tetanus antibody level at 5 y (2007-2009 cohort, joint cohorts) PFOA at 3 m, 6 m, and 12 m and lower-anti-tetanus antibody level at 5 y, adj. for breastfeeding (2007-2009 cohort, 1997-2000 cohort, joint cohorts, except at 3 m in 1997-2000 cohort) PFOA at birth and lower anti-diphtheria antibody level at 5 y (2007-2009 cohort, joint cohorts) PFOS at 3 m and lower anti-tetanus antibody level at 5 y, adj. for breastfeeding (joint cohorts) PFOS at 6 m and lower anti-tetanus antibody level at 5 y, adj. for breastfeeding (1997-2000 cohort, joint cohorts) PFOS at birth and lower anti-diphtheria antibody level at 5 y (1997-2000 cohort, joint cohorts) PFOS at 3 m and lower anti-diphtheria antibody level at 5 y, adj. for breastfeeding (1997-2000 cohort)	PFOA at birth, 18 m, and 60 m and anti-tetanus antibody level at 5 y (1997-2000 cohort) PFOA at 3 m and anti-tetanus antibody level at 5 y, adj. for breastfeeding (1997-2000 cohort) PFOA at birth and anti-diphtheria antibody level at 5 y (1997-2000 cohort) PFOA at 18 m and 60 m and anti-diphtheria antibody level at 5 y (2007-2009 cohort, 1997-2000 cohort, joint cohorts) PFOA at 3 m, 6 m, and 12 m and anti-diphtheria antibody level at 5 y, adj. for breastfeeding (2007-2009 cohort, 1997-2000 cohort, joint cohorts) PFOS at birth, 18 m, and 60 m and anti-tetanus antibody level at 5 y (2007-2009 cohort, 1997-2000 cohort, joint cohorts) PFOS at 3 m, 6 m, and 12 m and anti-tetanus antibody level at 5 y, adj. for breastfeeding (2007-2009 cohort, at 3 and 12 m in 1997-2000 cohort, at 12 m in joint cohorts) PFOS at birth and anti-diphtheria antibody level at 5 y (2007-2009 cohort) PFOS at 18 m and 60 m and anti-diphtheria antibody level at 5 y (2007-2009 cohort, 1997-2000 cohort, joint cohorts) PFOS at 3 m, 6 m, and 12 m and anti-diphtheria antibody level at 5 y, adj. for breastfeeding (2007-2009 cohort, 1997-2000 cohort except at 3 m, joint cohorts)
Yes	Grandjean 2020	Cross-sectional	Denmark	Adults	323	None	PFOA and COVID-19 severity PFOS and COVID-19 severity

In EPA?	Reference	Study Design	Country	Age Group	Subjects (Max)	Associations	Null Results
No	Granum 2013	Prospective cohort	Norway	Children	93	PFOA and lower anti-rubella antibody level at 0-3 y PFOS and lower anti-rubella antibody level at 0-3 y	PFOA and anti-measles antibody level, anti-*Haemophilus influenzae* type B antibody level, anti-tetanus antibody level at 0-3 y PFOS and anti-measles antibody level, anti-*Haemophilus influenzae* type B antibody level, anti-tetanus antibody level at 0-3 y
No	Ji 2021	Case-control	China	Adults	160	PFOA and greater risk of COVID-19 PFOS and greater risk of COVID-19	None
No	Kielsen 2016	Cross-sectional	Denmark	Adults	12	PFOS and lower post-vaccination anti-diphtheria antibody increase	PFOA and post-vaccination anti-diphtheria antibody level PFOA and post-vaccination anti-tetanus antibody level PFOS and post-vaccination anti-tetanus antibody level
No	Looker 2014	Cross-sectional	United States	Adults	411	PFOA and lower post-vaccination anti-influenza A/H3N2 antibody increase PFOA and lower odds post-vaccination anti-influenza A/H3N2 seroprotection (titer ≥ 1:40)	PFOA and post-vaccination anti-influenza type B antibody level, seroconversion (4-fold titer increase), or seroprotection (titer ≥ 1:40) PFOA and post-vaccination anti-influenza A/H1N1 antibody level, seroconversion, or seroprotection PFOA and post-vaccination anti-influenza A/H3N2 seroconversion PFOS and post-vaccination anti-influenza type B antibody level, seroconversion, or seroprotection PFOS and post-vaccination anti-influenza A/H1N1 antibody level, seroconversion, or seroprotection PFOS and post-vaccination anti-influenza A/H3N2 antibody level, seroconversion, or seroprotection

In EPA?	Reference	Study Design	Country	Age Group	Subjects (Max)	Associations	Null Results
Yes	Mogensen 2015	Prospective cohort	Faroe Islands	Children	459	PFOA at 7 y or 5 and 7 y and lower anti-diphtheria antibody level at 7 y PFOA at 5 and 7 y and lower anti-tetanus antibody level at 7 y PFOS at 7 y or 5 and 7 y and lower anti-diphtheria antibody level at 7 y	PFOA at 7 y and anti-tetanus antibody level at 7 y PFOS at 7 y or 5 and 7 y and anti-tetanus antibody level at 7 y
No	Nielsen 2021	Ecological	Sweden	Adults	898	ΣPFAS and greater risk of COVID-19	None
Yes	Pilkerton 2018	Cross-sectional	United States	Children, adults	1,196 children 1,193 adults	PFOA and lower anti-rubella antibody level (19-60 y total, 19-60 y men) PFOA × sex and anti-rubella antibody level (19-60 y) PFOS and lower anti-rubella antibody level (19-60 y total)	PFOA and anti-rubella antibody level (12-18 y, 19-60 y women) PFOA × sex interaction and anti-rubella antibody level (12-18 y) PFOA × ethnicity interaction and anti-rubella antibody level (12-18 y, 19-60 y) PFOS and anti-rubella antibody level (12-18y, 19-60 y women, 19-60 y men)) PFOS × sex interaction and anti-rubella antibody level (12-18 y, 19-60 y) PFOS × ethnicity interaction and anti-rubella antibody level (12-18 y, 19-60 y)

In EPA?	Reference	Study Design	Country	Age Group	Subjects (Max)	Associations	Null Results
No	Shih 2021	Prospective cohort	Faroe Islands	Adults	399	PFOA at birth and lower anti-hepatitis A virus antibody level at 28 y (women) PFOA at birth and greater anti-hepatitis A virus antibody level at 28 y (men) PFOA at 14 y and lower anti-hepatitis A virus antibody level at 28 y (men) PFOS and birth and lower anti-hepatitis A virus antibody level at 28 y (women) PFOS at birth and greater anti-hepatitis A virus antibody level at 28 y (men) PFOS at 7 y and greater anti-hepatitis A virus antibody level at 28 y (women) PFOS at 7 y and greater anti-hepatitis B surface antibody level at 28 y (women)	PFOA at birth (all), 7 y (all, women, men), 14 y (all, women), 22 y (all, women, men), or 28 y (all, women, men) and anti-hepatitis A virus antibody level at 28 y PFOA at birth, 7 y, 14 y, 22 y, or 28 y (all, women, men) and anti-hepatitis A virus antibody level at 28 y PFOA at birth, 7 y, 14 y, 22 y, or 28 y (all, women, men) and anti-diphtheria antibody level at 28 y PFOA at birth, 7 y, 14 y, 22 y, or 28 y (all, women, men) and anti-tetanus antibody level at 28 y PFOS at birth (all), 7 y (all, men), 14 y (all, women, men), 22 y (all, women, men), or 28 y (all, women, men) and anti-hepatitis A virus antibody level at 28 y (all, women, men) PFOS at birth (all, women, men), 7 y (all, men), 14 y (all, women, men), 22 y (all, women, men), or 28 y (all, women, men) and anti-hepatitis A virus antibody level at 28 y PFOS at birth, 7 y, 14 y, 22 y, or 28 y (all, women, men) and anti-diphtheria antibody level at 28 y PFOS at birth, 7 y, 14 y, 22 y, or 28 y (all, women, men) and anti-tetanus antibody level at 28 y
Yes	Stein 2016a	Cross-sectional	United States	Adults	78	PFOS and greater odds of seroconversion to FluMist vaccine (anti-influenza A/H1N1) measured by hemagglutinin inhibition (low baseline antibodies; tertile 2, not 3)	PFOA and seroconversion to FluMist vaccine (anti-influenza A/H1N1) measured by hemagglutinin inhibition or by immunohistochemisty PFOS and seroconversion to FluMist vaccine (anti-influenza A/H1N1) measured by hemagglutinin inhibition (total population) or by immunohistochemisty

In EPA?	Reference	Study Design	Country	Age Group	Subjects (Max)	Associations	Null Results
Yes	Timmermann 2020	Randomized controlled trial (prospective cohort)	Guinea-Bissau	Children	237	PFOA and lower measles antibody titer at 4-7 m, no vaccination (excl. outliers) PFOA and lower measles antibody titer at 2 y, 1 vaccination (excl. outliers) PFOS and lower measles antibody titer at 4-7 m, no vaccination (excl. outliers) PFOS and lower measles antibody titer at 9 m, no vaccination (full dataset, excl. outliers) PFOS and lower measles antibody titer at 9 m, 1 vaccination (full dataset, excl. outliers) PFOS and lower measles antibody titer at 2 y, 1 vaccination (excl. outliers) PFOS × sex and measles antibody titer at 2 y, 1 vaccination (inverse for girls, null for boys)	PFOA and measles antibody titer at 4-7 m, no vaccination (full dataset) PFOA and measles antibody titer at 9 m, no vaccination (full dataset, excl. outliers) PFOA and measles antibody titer at 9 m, 1 vaccination (full dataset, excl. outliers) PFOA and measles antibody titer at 2 y, 1 vaccination (full dataset) PFOA and measles antibody titer at 2 y, 2 vaccinations (full dataset, excl. outliers) PFOS and measles antibody titer at 4-7 m, no vaccination (full dataset) PFOS and measles antibody titer at 2 y, 1 vaccination (full dataset) PFOS and measles antibody titer at 2 y, 2 vaccinations (full dataset, excl. outliers)
No	Timmermann 2022	Prospective cohort and cross-sectional	Greenland	Children	314	PFOS and greater risk of anti-diphtheria antibody level < 0.1 IU/mL at 7-12 y	PFOA (maternal or child) and anti-tetanus antibody level at 7-12 y PFOA (maternal or child) and anti-diphtheria antibody level or < 0.1 IU/mL at 7-12 y PFOS (maternal or child) and anti-tetanus antibody level at 7-12 y PFOS (maternal or child) and anti-diphtheria antibody level at 7-12 y
Yes	Zeng 2019	Prospective cohort and cross-sectional	China	Children	201	ΣPFOA and lower anti-coxsackievirus A 16 level at birth ΣPFOA and greater risk of anti-coxsackievirus A 16 below protective level at birth and at 3 m ΣPFOA and lower anti-enterovirus 71 levels at birth and at 3 m ΣPFOA and greater risk of anti-enterovirus 71 below protective level at birth and at 3 m	ΣPFOA and anti-coxsackievirus A 16 level at 3 m n-PFOA and anti-coxsackievirus A 16 level at 3 m ΣPFOS and anti-coxsackievirus A 16 level at 3 m n-PFOS and anti-coxsackievirus A 16 level at 3 m Br-PFOS and anti-coxsackievirus A 16 level at 3 m

In EPA?	Reference	Study Design	Country	Age Group	Subjects (Max)	Associations	Null Results
						n-PFOA and lower anti-coxsackievirus A 16 level at birth n-PFOA and greater risk of anti-coxsackievirus A 16 below protective level at birth and at 3 m n-PFOA and lower anti-enterovirus 71 levels at birth and at 3 m n-PFOA and greater risk of anti-enterovirus 71 below protective level at birth and at 3 m ΣPFOS and lower anti-coxsackievirus A 16 level at birth ΣPFOS and greater risk of anti-coxsackievirus A 16 below protective level at birth and at 3 m ΣPFOS and lower anti-enterovirus 71 levels at birth and at 3 m ΣPFOS and greater risk of anti-enterovirus 71 below protective level at birth and at 3 m n-PFOS and lower anti-coxsackievirus A 16 level at birth n-PFOS and greater risk of anti-coxsackievirus A 16 below protective level at birth and at 3 m n-PFOS and lower anti-enterovirus 71 levels at birth and at 3 m n-PFOS and greater risk of anti-enterovirus 71 below protective level at birth and at 3 m Br-PFOS and lower anti-coxsackievirus A 16 level at birth Br-PFOS and greater risk of anti-coxsackievirus A 16 below protective level at birth and at 3 m Br-PFOS and lower anti-enterovirus 71 levels at birth and at 3 m Br-PFOS and greater risk of anti-enterovirus 71 below protective level at 3 m	Br-PFOS and anti-enterovirus 71 below protective level at birth 1m-PFOS and anti-coxsackievirus A 16 levels at birth and at 3 m 1m-PFOS and anti-coxsackievirus A 16 below protective level at birth and at 3 m 1m-PFOS and anti-enterovirus 71 below protective level at birth Σ3m-, 4m-, 5m-PFOS and anti-coxsackievirus A 16 level at 3 m Σ3m-, 4m-, 5m-PFOS and anti-coxsackievirus A 16 below protective level at birth Σ3m-, 4m-, 5m-PFOS and anti-enterovirus 71 below protective level at birth iso-PFOS and anti-coxsackievirus A 16 level at 3 m iso-PFOS and anti-enterovirus 71 below protective level at birth (girls)

In EPA?	Reference	Study Design	Country	Age Group	Subjects (Max)	Associations	Null Results
						1m-PFOS and greater risk of anti-enterovirus 71 below protective level at 3 m 1m-PFOS and lower anti-enterovirus 71 levels at birth and at 3 m Σ3m-, 4m-, 5m-PFOS and lower anti-coxsackievirus A 16 level at birth Σ3m-, 4m-, 5m-PFOS and greater risk of anti-coxsackievirus A 16 below protective level at 3 m Σ3m-, 4m-, 5m-PFOS and lower anti-enterovirus 71 levels at birth and at 3 m Σ3m-, 4m-, 5m-PFOS and greater risk of anti-enterovirus 71 below protective level at 3 m iso-PFOS and lower anti-coxsackievirus A 16 level at birth iso-PFOS and greater risk of anti-coxsackievirus A 16 below protective level at birth and at 3 m iso-PFOS and lower anti-enterovirus 71 levels at birth and at 3 m iso-PFOS and greater risk of anti-enterovirus 71 below protective level at birth (all, boys) and at 3 m (Sex-stratified results shown only where PFAS × sex interaction $p < 0.10$)	

In EPA?	Reference	Study Design	Country	Age Group	Subjects (Max)	Associations	Null Results
Yes	Zeng 2020	Cross-sectional	China	Adults	605	PFOA and greater risk of hepatitis B surface antibody seronegativity n-PFOS and lower serum hepatitis B surface antibody titer n-PFOS and greater risk of hepatitis B surface antibody seronegativity Br-PFOS and greater risk of hepatitis B surface antibody seronegativity	PFOA and serum hepatitis B surface antibody titer Br-PFOS and serum hepatitis B surface antibody titer

Table 2. Overview of studies of PFOA, PFOS, and anti-tetanus or anti-diphtheria antibody levels

In EPA?	Reference	Design	Country	Age Group	Subjects (Max)	Associations	Null Results	
Yes	Abraham 2020	Cross-sectional	Germany	Children	101	PFOA and lower anti-tetanus IgG and IgG1 level at 1 y; NOAEL at 16.9 µg/L plasma PFOA PFOA and lower anti-diphtheria IgG level at 1 y; NOAEL at 16.2 µg/L plasma PFOA	PFOS and anti-tetanus IgG or IgG1 level or anti-diphtheria IgG level at 1 y	
Yes	Grandjean 2012	Prospective cohort and cross-sectional	Faroe Islands	Children	587	Maternal PFOA and lower anti-diphtheria antibody level at 7 y (not adj. for 5 y) PFOA at 5 y and lower anti-tetanus antibody level at 7 y (adj./not adj. for 5 y) PFOA at 5 y and lower anti-diphtheria antibody level at 7 y (adj./not adj. for 5 y) Maternal PFOS and greater anti-tetanus antibody level at 7 y (adj. for 5 y) Maternal PFOS and lower anti-diphtheria antibody level at 5 y PFOS at 5 y and lower anti-tetanus antibody level at 5 y PFOS at 5 y and lower anti-diphtheria antibody level at 7 y (not adj. for 5 y)	Maternal PFOA and anti-tetanus antibody level at 5 or 7 y Maternal PFOA and anti-diphtheria antibody level at 5 y PFOA at 5 y and anti-tetanus antibody level at 5 y PFOA at 5 y and anti-diphtheria antibody level at 5 y Maternal PFOS and anti-tetanus antibody level at 5 y Maternal PFOS and anti-diphtheria antibody level at 7 y PFOS at 5 y and anti-tetanus antibody level at 7 y PFOS at 5 y and anti-diphtheria antibody level at 5 y	

In EPA?	Reference	Design	Country	Age Group	Subjects (Max)	Associations	Null Results	
Yes	Grandjean 2017a	Prospective cohort and cross-sectional	Faroe Islands	Children	505	PFOA at 13 y and lower anti-diphtheria antibody level at 13 y (no ER visit/booster) PFOA at 7 y and lower anti-diphtheria antibody level at 7 and 13 y (total, no ER visit/booster, indirect effect (via 7-year antibody)) PFOS at 7 y and greater anti-tetanus antibody level at 13 y (no ER visit/booster) PFOS at 7 y and lower anti-diphtheria antibody level at 7 and 13 y (total, no ER visit/booster, total and indirect effects)	PFOA at 7 y and anti-diphtheria antibody level at 13 y PFOA at 13 y and anti-diphtheria antibody level at 13 y (total, no ER visit/booster and no antibody increase) PFOA at 7 or 13 y and anti-tetanus antibody level at 13 y PFOA at 7 y and anti-diphtheria antibody level at 7 and 13 y (no ER visit/booster and no antibody increase) PFOA at 7 y and anti-tetanus antibody level at 7 and 13 y PFOS at 7 or 13 y and anti-diphtheria antibody level at 13 y PFOS at 7 y and anti-tetanus antibody level at 13 y (total, no ER visit/booster and no antibody increase) PFOS at 13 y and anti-tetanus antibody level at 13 y PFOS at 7 y and anti-diphtheria antibody level at 7 and 13 y (no ER visit/booster and no antibody increase) PFOS at 7 y and anti-tetanus antibody level at 7 and 13 y	

In EPA?	Reference	Design	Country	Age Group	Subjects (Max)	Associations	Null Results	
Yes	Grandjean 2017b	Prospective cohort	Faroe Islands	Children	349	PFOA at birth, 18 m, and 60 m and lower anti-tetanus antibody level at 5 y (2007-2009 cohort, joint cohorts) PFOA at 3 m, 6 m, and 12 m and lower-anti-tetanus antibody level at 5 y, adj. for breastfeeding (2007-2009 cohort, 1997-2000 cohort, joint cohorts, except at 3 m in 1997-2000 cohort) PFOA at birth and lower anti-diphtheria antibody level at 5 y (2007-2009 cohort, joint cohorts) PFOS at 3 m and lower anti-tetanus antibody level at 5 y, adj. for breastfeeding (joint cohorts) PFOS at 6 m and lower anti-tetanus antibody level at 5 y, adj. for breastfeeding (1997-2000 cohort, joint cohorts) PFOS at birth and lower anti-diphtheria antibody level at 5 y (1997-2000 cohort, joint cohorts) PFOS at 3 m and lower anti-diphtheria antibody level at 5 y, adj. for breastfeeding (1997-2000 cohort)	PFOA at birth, 18 m, and 60 m and anti-tetanus antibody level at 5 y (1997-2000 cohort) PFOA at 3 m and anti-tetanus antibody level at 5 y, adj. for breastfeeding (1997-2000 cohort) PFOA at birth and anti-diphtheria antibody level at 5 y (1997-2000 cohort) PFOA at 18 m and 60 m and anti-diphtheria antibody level at 5 y (2007-2009 cohort, 1997-2000 cohort, joint cohorts) PFOA at 3 m, 6 m, and 12 m and anti-diphtheria antibody level at 5 y, adj. for breastfeeding (2007-2009 cohort, 1997-2000 cohort, joint cohorts) PFOS at birth, 18 m, and 60 m and anti-tetanus antibody level at 5 y (2007-2009 cohort, 1997-2000 cohort, joint cohorts) PFOS at 3 m, 6 m, and 12 m and anti-tetanus antibody level at 5 y, adj. for breastfeeding (2007-2009 cohort, at 3 and 12 m in 1997-2000 cohort, at 12 m in joint cohorts) PFOS at birth and anti-diphtheria antibody level at 5 y (2007-2009 cohort) PFOS at 18 m and 60 m and anti-diphtheria antibody level at 5 y (2007-2009 cohort, 1997-2000 cohort, joint cohorts) PFOS at 3 m, 6 m, and 12 m and anti-diphtheria antibody level at 5 y, adj. for breastfeeding (2007-2009 cohort, 1997-2000 cohort except at 3 m, joint cohorts)	
No	Granum 2013	Prospective cohort	Norway	Children	93	None	PFOA and anti-tetanus antibody level at 0-3 y PFOS and anti-tetanus antibody level at 0-3 y	

In EPA?	Reference	Design	Country	Age Group	Subjects (Max)	Associations	Null Results	
No	Kielsen 2016	Cross-sectional	Denmark	Adults	12	PFOS and lower post-vaccination anti-diphtheria antibody increase	PFOA and post-vaccination anti-diphtheria antibody level PFOA and post-vaccination anti-tetanus antibody level PFOS and post-vaccination anti-tetanus antibody level	
Yes	Mogensen 2015	Prospective cohort	Faroe Islands	Children	459	PFOA at 7 y or 5 and 7 y and lower anti-diphtheria antibody level at 7 y PFOA at 5 and 7 y and lower anti-tetanus antibody level at 7 y PFOS at 7 y or 5 and 7 y and lower anti-diphtheria antibody level at 7 y	PFOA at 7 y and anti-tetanus antibody level at 7 y PFOS at 7 y or 5 and 7 y and anti-tetanus antibody level at 7 y	
No	Shih 2021	Prospective cohort	Faroe Islands	Adults	281	None	PFOA at birth, 7 y, 14 y, 22 y, or 28 y (all, women, men) and anti-diphtheria antibody level at 28 y PFOA at birth, 7 y, 14 y, 22 y, or 28 y (all, women, men) and anti-tetanus antibody level at 28 y PFOS at birth, 7 y, 14 y, 22 y, or 28 y (all, women, men) and anti-diphtheria antibody level at 28 y PFOS at birth, 7 y, 14 y, 22 y, or 28 y (all, women, men) and anti-tetanus antibody level at 28 y	
No	Timmermann 2022	Prospective cohort and cross-sectional	Greenland	Children	314	PFOS and greater risk of anti-diphtheria antibody level < 0.1 IU/mL at 7-12 y	PFOA (maternal or child) and anti-tetanus antibody level at 7-12 y PFOA (maternal or child) and anti-diphtheria antibody level or < 0.1 IU/mL at 7-12 y PFOS (maternal or child) and anti-tetanus antibody level at 7-12 y PFOS (maternal or child) and anti-diphtheria antibody level at 7-12 y	None

Table 3. Overview of epidemiological studies of PFOA, PFOS, and infections

In EPA?	Reference	Study Design	Country	Age Group	Subjects (Max)	Associations	Null Results
Yes	Abraham 2020	Cross-sectional	Germany	Children	101	None	PFOA and month of first infection in first year, total infections in first year, number of infections with fever, number of antibiotic treatments, antibiotic treatment ever, number of otitis media episodes, otitis media infections ever, 3-day fever ever, number of pneumonia episodes, number of diarrhea episodes, diarrhea ever, varicella ever, napkin candidiasis ever, oral candidiasis ever at 1 year PFOS and month of first infection in first year, total infections in first year, number of infections with fever, number of antibiotic treatments, antibiotic treatment ever, number of otitis media episodes, otitis media infections ever, 3-day fever ever, number of pneumonia episodes, number of diarrhea episodes, diarrhea ever, varicella ever, napkin candidiasis ever, oral candidiasis ever at 1 year
Yes	Ait Bamai 2020	Prospective cohort	Japan	Children	2,689	PFOA and greater risk of pneumonia at 7 y (total, with siblings) PFOA and greater risk of respiratory syncytial virus at 7 y (without siblings) PFOS and lower risk of respiratory syncytial virus at 7 y (total, with siblings)	PFOA and rhino-conjunctivitis, chicken pox (total, without siblings, with siblings), otitis media (total, without siblings, with siblings), pneumonia (without siblings), respiratory syncytial virus (total, with siblings) at 7 y PFOS and rhino-conjunctivitis, chicken pox (total, without siblings, with siblings), otitis media (total, without siblings, with siblings), pneumonia (total, without siblings, with siblings), respiratory syncytial virus (without siblings) at 7 y

In EPA?	Reference	Study Design	Country	Age Group	Subjects (Max)	Associations	Null Results
No	Bulka 2021	Cross-sectional	United States	Children, adults	8,778	PFOA and greater total pathogen burden (adolescents, adults) PFOA and greater risk of persistent herpes simplex virus 1 infection (adults) PFOA and greater risk of persistent herpes simplex virus 2 infection (adults) PFOS and greater total pathogen burden (adolescents, adults) PFOS and greater risk of persistent herpes simplex virus 1 infection (adults) PFOS and greater risk of persistent Toxocara spp infection (adults)	PFOA and persistent infection with cytomegalovirus, Epstein-Barr virus, herpes simplex 1 virus, Toxoplasma gondii, or Toxocara spp. (adolescents) PFOA and persistent infection with cytomegalovirus, hepatitis C virus, hepatitis E virus, *Toxoplasma gondii*, or *Toxocara* spp. (adults) PFOS and persistent infection with cytomegalovirus, Epstein-Barr virus, herpes simplex 1 virus, *Toxoplasma gondii*, or *Toxocara* spp. (adolescents) PFOS and persistent infection with cytomegalovirus, hepatitis C virus, hepatitis E virus, herpes simplex 2 virus, or *Toxoplasma gondii* (adults)
Yes	Dalsager 2016	Prospective cohort	Denmark	Children	346	PFOA and greater proportion of days with fever at 1-4 y PFOA and greater number of episodes of co-occurrence of fever and nasal discharge at 1-4 y (medium, not high PFOA) PFOS and greater number and proportion of days with fever at 1-4 y	PFOA and number of days with fever at 1-4 y PFOA and proportion or number of days with cough, nasal discharge, diarrhea, or vomiting at 1-4 y PFOA and number of episodes of co-occurrence of fever and coughing at 1-4 y PFOS and proportion or number of days with cough, nasal discharge, diarrhea, or vomiting at 1-4 y PFOS and number of episodes of co-occurrence of fever and coughing or fever and nasal discharge at 1-4 y

In EPA?	Reference	Study Design	Country	Age Group	Subjects (Max)	Associations	Null Results
No	Dalsager 2021	Prospective cohort	Denmark	Children	1,503	PFOA and greater risk of hospitalization for lower respiratory tract infection at 0-4 y PFOS and greater risk of hospitalization for any infection at 0-4 y PFOS and greater risk of hospitalization for lower respiratory tract infection at 0-4 y	PFOA and hospitalization for any infection at 0-4 y PFOA and hospitalization for upper respiratory tract infection at 0-4 y PFOA and hospitalization for gastrointestinal infection at 0-4 y PFOA and hospitalization for other infection at 0-4 y PFOS and hospitalization for upper respiratory tract infection at 0-4 y PFOS and hospitalization for gastrointestinal infection at 0-4 y PFOS and hospitalization for other infection at 0-4 y
No	Fei 2010	Prospective cohort	Denmark	Children	1,400	PFOA and lower risk of hospitalization for infectious diseases (0–10 y (quartile 2 only), 0–<1 y (quartile 2 only), 1–<2 y (quartile 2 only), and 2–<4 y (quartile 3 only); boys; multiparous mothers) PFOA and greater risk of hospitalization for infectious diseases (girls) PFOS and lower risk of hospitalization for infectious diseases (0-<1 y; boys (quartile 3 only)) PFOS and greater risk of hospitalization for infectious diseases (≥4 y (quartile 2 only); girls)	PFOA and hospitalization for infectious diseases (≥4 y; primiparous mothers) PFOS and hospitalization for infectious diseases (0–10 y, 1–<2 y, 2–<4 y; primiparous and multiparous mothers)

In EPA?	Reference	Study Design	Country	Age Group	Subjects (Max)	Associations	Null Results
Yes	Goudarzi 2017	Prospective cohort	Japan	Children	1,558	PFOS and greater risk of total infectious diseases (otitis media, pneumonia, respiratory syncytial virus, and/or varicella) at 4 y (total, boys quartile 4 no trend, girls)	PFOA and total infectious diseases (otitis media, pneumonia, respiratory syncytial virus, and/or varicella) at 4 y
No	Granum 2013	Prospective cohort	Norway	Children	93	PFOA and greater number of episodes of common cold at 0-3 and 3 y PFOA and greater number of episodes of gastroenteritis at 0-3 y	PFOA and ever common cold or ever gastroenteritis at 0-3 y and 3 y PFOS and number of episodes of common cold, ever common cold, number of episodes of gastroenteritis, ever gastroenteritis at 0-3 y and 3 y
No	Huang 2020	Prospective cohort	China	Children	344	None	PFOA and recurrent respiratory tract infections up to 5 years PFOA and number of respiratory tract infections up to 5 y (or in any year up to 5) PFOS and recurrent respiratory tract infections up to 5 years PFOS and number of respiratory tract infections up to 5 y (or in any year up to 5)
Yes	Impinen 2018	Prospective cohort	Norway	Children	641	PFOA and greater number of lower respiratory tract infection episodes from 0-10 y PFOS and greater number of lower respiratory tract infection episodes from 0-10 y	PFOA and number of common cold episodes from 0-2 y PFOA and rhinitis current or ever at 10 y, rhinoconjunctivitis ever at 10 y, rhinitis ever and sIgE > 0.35 at 10 y PFOS and number of common cold episodes from 0-2 y PFOS and rhinitis current or ever at 10 y, rhinoconjunctivitis ever at 10 y, rhinitis ever and sIgE > 0.35 at 10 y

In EPA?	Reference	Study Design	Country	Age Group	Subjects (Max)	Associations	Null Results
Yes	Impinen 2019	Prospective cohort	Norway	Children	1,207 at 3 y 921 at 7 y	PFOA and lower risk of common cold at 0-3 y (all, girls) PFOA and greater risk of bronchitis/pneumonia at 0-3 y (all, girls) PFOA and greater risk of throat infection with streptococcus at 0-3 y (boys) PFOA and greater risk of pseudocroup at 0-3 y (all) PFOA and lower risk of ear infection at 0-3 y (girls) PFOA and greater risk of diarrhea/gastric flu at 6-7 y (all, girls, boys) PFOA and lower risk of urinary tract infection at 0-3 y (all, girls) PFOS and lower risk of common cold at 0-3 y (all, girls) PFOS and greater risk of bronchitis/pneumonia at 0-3 y (all) PFOS and lower risk of ear infection at 0-3 y (all, girls) PFOS and greater risk of diarrhea/gastric flu at 6-7 y (boys) PFOS and lower risk of urinary tract infection at 0-3 y (all, girls)	PFOA (boys) and common cold at 0-3 y PFOA (boys) and bronchitis/pneumonia at 0-3 y PFOA and bronchitis/pneumonia at 6-7 y PFOA (all, girls) and throat infection with streptococcus at 0-3 y PFOA and other throat infections at 0-3 y PFOA (girls, boys) and pseudocroup at 0-3 y PFOA (all, boys) and ear infection at 0-3 y PFOA and ear infection at 6-7 y PFOA and diarrhea/gastric flu at 0-3 y PFOA (boys) and urinary tract infection at 0-3 y PFOA and urinary tract infection at 6-7 y PFOS (boys) and common cold at 0-3 y PFOS (girls, boys) and bronchitis/pneumonia at 0-3 y PFOS and bronchitis/pneumonia at 6-7 y PFOS and throat infection with streptococcus at 0-3 y PFOS and other throat infections at 0-3 y PFOS and pseudocroup at 0-3 y PFOS (boys) and ear infection at 0-3 y PFOS and ear infection at 6-7 y PFOS and diarrhea/gastric flu at 0-3 y PFOS (all, girls) and diarrhea/gastric flu at 6-7 y PFOS (boys) and urinary tract infection at 0-3 y PFOS and urinary tract infection at 6-7 y
No	Kishi 2013	Prospective cohort	Japan	Children	514	None	PFOA and otitis media at 18 months PFOS and otitis media at 18 months

In EPA?	Reference	Study Design	Country	Age Group	Subjects (Max)	Associations	Null Results
Yes	Kvalem 2020	Prospective cohort and cross-sectional	Norway	Children	378	PFOA and greater risk of rhinitis in last 12 m at 16 y (total) PFOA and lower risk of ≥ 3 common colds in last 12 m at 16 y (total) PFOA and greater risk of lower respiratory tract infection at 10-16 y (total, girls) PFOS and lower risk of 1-2 or ≥ 3 common colds in last 12 m at 16 y (total, boys) PFOS and greater risk of lower respiratory tract infection at 10-16 y (total, girls, boys)	PFOA and rhinitis in last 12 m at 10 y (total, girls, boys) or 16 y (girls, boys) PFOA and common colds at 10-16 y (total, girls, boys) or in last 12 m at 16 y (girls, boys) PFOA and lower respiratory tract infection at 10-16 y (boys) or in last 12 m at 16 y (total, girls, boys) PFOS and rhinitis in last 12 m at 10 y (total, girls, boys) or 16 y (total, girls, boys) PFOS and common colds at 10-16 y (total, girls, boys) or in last 12 m at 16 y (girls) PFOS and lower respiratory tract infection in last 12 m at 16 y (total, girls, boys)
No	Leonard 2008	Retrospective cohort	United States	Adults	6,027	PFOA and lower risk of mortality from infectious and parasitic diseases (vs. US)	PFOA and mortality from infectious and parasitic diseases (vs. West Virginia or DuPont Region 1)
No	Looker 2014	Cross-sectional	United States	Adults	411	None	PFOA and self-reported "flu" infection in last 12 months PFOA and self-reported cold in last 12 months PFOA and self-reported cold or "flu" in last 12 months PFOA and number of colds reported in last 12 months PFOS and self-reported "flu" infection in last 12 months PFOS and self-reported cold in last 12 months PFOS and self-reported cold or "flu" in last 12 months PFOS and number of colds reported in last 12 months

In EPA?	Reference	Study Design	Country	Age Group	Subjects (Max)	Associations	Null Results
Yes	Manzano-Salgado 2019	Prospective cohort	Spain	Children	1,188	PFOS × study site and risk of lower respiratory tract infection at 1.5-7 y (inverse in Valencia only)	PFOA and lower respiratory tract infection at 1.5-7 y (total, girls, boys), 1.5 y, 4 y, and 7 y PFOS and lower respiratory tract infection at 1.5-7 y (total, girls, boys), 1.5 y, 4 y, and 7 y
No	Okada 2012	Prospective cohort	Japan	Children	343	None	PFOA and otitis media at 18 months PFOS and otitis media at 18 months

EXHIBIT G

3M Company
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January 14, 2022

Dr. Suhair Shallal, Designated Federal Officer (DFO)
Science Advisory Board
Environmental Protection Agency
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Mail Code: 1400R

Submitted via email: shallal.suhair@epa.gov

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

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

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

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

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Corporate Medical Director

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November 8, 2021

VIA ELECTRONIC SUBMISSION

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

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

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

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

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

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

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

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

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

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

Regards,

Oyebode A. Taiwo, MD, MP

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Epidemiology Comments

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

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

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

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

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

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

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

Toxicology Comments

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

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

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

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

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

[4] Butenhoff et al. 2012 Toxicology 293 1-15

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

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

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

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

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

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

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

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

[7] Bjork et al. 2011 Toxicology 288 8-17
[8] Bjork and Wallace 2009 Toxicol Sci 111 89-99
[9] Elcombe et al. 2012 Toxicology 293 16-29
[10] Elcombe et al. 2012 Toxicology 293 30-40
[11] Vanden Heuvel et al. 2006 Toxicol Sci 92 476-489
[12] Proposed Public Health Goals for Perfluorooctanoic Acid and Perfluorooctane Sulfonic Acid in Drinking Water, Office of Environmental Health Hazard Assessment at 153 (July 2021).
[13] Proposed Public Health Goals for Perfluorooctanoic Acid and Perfluorooctane Sulfonic Acid in Drinking Water, Office of Environmental Health Hazard Assessment at 159 (July 2021).
[14] Corton et al. 2014 Crit Rev Toxicol 44 1-49
[15] Elcombe et al. 2014 Crit Rev Toxicol 44 64-82
[16] Gonzales and Shah 2008 Toxicology 246 2-8
[17] Klaunig et al. 2012 Reprod Toxicol 33 410-418
[18] Lake 2009 Xenobiotica 39 582-596
[19] Ross et al. 2010 Toxicol Sci 116 452-466

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

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

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

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

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

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

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

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

[22] Butenhoff et al. 2012 Toxicology 293 1-15

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

In the 2-year cancer bioassay study for PFOS where food was given *ad libitum*, Butenhoff et al. 2012[25] reported that the control and K^+PFOS-treated male rats had generally similar food consumption rates. However, there were intermittent lower body weights observed in the 20 ppm-treated group animals. While the actual metabolic caloric balance was not evaluated in that study, it is possible that the subtle difference in food consumption per body weight may have, in part, contributed to the observation of intermittent lower body weights.

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

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

USEPA, 2016[29]

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

Health Canada, 2018[30]

[23] Suzuki et al. 1979 J Cancer Res Clin Oncol 95 187-196
[24] Dillberger 1994 Toxicol Path 22 48-55
[25] Butenhoff et al. 2012 Toxicology 293 1-15
[26] Butenhoff et al. 2012 Toxicology 298 1-13
[27] Biegel et al. 2001 Toxicol Sci 60 44-55
[28] Myer et al. 2014 Toxicol Pathol 42 260-274.
[29] https://www.epa.gov/sites/production/files/2016-05/documents/pfos_hesd_final_508.pdf, accessed 22 October 2021
[30] https://www.canada.ca/en/health-canada/services/publications/healthy-living/guidelines-canadian-drinking-water-quality-guideline-technical-document-perfluorooctane-sulfonate/document.html, accessed 23 October 2021

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

EFSA, 2020[31]

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

Inclusion of "Transformation and Degradation Precursors" in the Listing

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

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

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

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

[31] Schrenk et al. 2020 EFSA J 18 e06223

EXHIBIT A

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May 10, 2021

Tyler Saechao
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Submitted electronically via https://oehha.ca.gov/comments

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

Dear Mr. Saechao:

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

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

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

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Epidemiology Comments

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

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

Hurley et al. (2018)[8]

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Ghisari et al. (2014) [10]

The Ghisari et al. (2014) published study was not included among the epidemiology studies cited in OEHHA's Prioritization Document. Ghisari et al. is a follow-up study to Bonefeld-Jørgensen et al. (2011), which examined breast cancer risk in Inuit women in a hospital-based case-control study of 31 cases and 115 controls. (Note: Wilsøe et al. was the additional case-control study that included those subjects from Bonefeld-Jørgensen et al. (2011)). Ghisari et al. conducted phenotyping for CYP1A1, CYP1B1, COMT, CYP17A1, and CYP19A1 genes and the Greenlandic founder mutation BRCA1. Ghisari et al. reported an increased breast cancer risk with women who had high PFOS and PFOA and carriers of at least one CYP1A1 variant allele (OR = 2.63, 95% CI 1.46, 4.75) one variant COMT Met allele (OR = 2.65, 95% CI 1.44, 4.89) or the common CYP17A1 A1A2+A2A2 allele (OR = 2..21, 95% CI 1.19, 4.12). See Supplemental Table 2 in Ghisari et al (2014). No combined effects were seen between PFOS/PFOA exposure and CYP1B1 and CYP19 polymorphisms. As would be expected, the frequency of the BRCA1 mutation was higher in the cases than controls. As noted by the OEHHA screening process, in a subsequent study by Ghisari et al. (2017) in a much larger studied population of 178 breast cancer cases and 233 controls from the Danish National Birth Cohort, they found no significant association between the same investigated polymorphisms and the risk of breast cancer with PFOS (or PFOA). Ghisari et al. (2017) did find an association with PFOSA (perfluorooctane sulfonamide); however, these blood samples were taken between 1996-2002. According to CDC NHANES, the last time PFOSA was detected at the 95th percentile in the United States population was in the 2005-2006 time period. Because of this lack of detection, NHANES even ceased analyzing for PFOSA starting in the 2013-2014 time period. The conclusion from both Ghisari et al. studies (2014; 2017) should be that the reported association with breast cancer risk and PFOS

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

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

Omoike et al. (2020)[11]

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

Toxicology Comments

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

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

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

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

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

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[11] Ogbebor Omoike et al., *A Cross-Sectional Study of the Association Between Perfluorinated Chemical Exposure and Cancers Related to Deregulation of Estrogen Receptors*, *Env't Rsch.* 110329 (2020), https://pubmed.ncbi.nlm.nih.gov/33068574/.
[12] John Butenhoff et al., *Chronic Dietary Toxicity and Carcinogenicity Study with Potassium Perfluorooctanesulfonate in Sprague Dawley Rats*, 293 *Toxicology* 1 (2012), https://pubmed.ncbi.nlm.nih.gov/22266392/.
[13] Riker, *Two-Year Oral (Diet) Toxicity/carcinogenicity Study of Fluorochemical FM-3924 in Rats,* Riker Laboratories, Inc., Experiment No. 0281CR0012 (May 1983), USPEA AR-226-0257 through AR-226-0262.
[14] Covance Study No. 6329-212, 2001, USEPA AR226-1051a

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

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

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

While the OEHHA cited several short-term studies as evidence of "induced chronic inflammation," they were not representative of chronic exposure by study design. Studies by Qazi et al. (2009a;[24] 2009b[25]) were only 10 days in exposure duration and the other three studies (Sørli

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

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

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

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

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

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

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

[22] Luebker et al., *supra* note 15.

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

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

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

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et al. 2020;[26] Giménez-Bastida et al. 2015;[27] and Brieger et al. 2011[28]) were based on tissue culture (*in vitro*).

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

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

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

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

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

[26] J. Sørli et al., *Per- and Polyfluoroalkyl Substances (PFASs) Modify Lung Surfactant Function and Pro-Inflammatory Responses in Human Bronchial Epithelial Cells*, 62, Toxicology in Vitro, 104656 (February 2020).
[27] J. Giménez-Bastida et al., *In Vitro Evaluation of the Cytotoxicity and Modulation of Mechanisms Associated with Inflammation Induced by Perfluorooctanesulfonate and Perfluorooctanoic Act in Human Colon Myofibroblasts CCD-18Co*, 29 Toxicology in Vitro, Issue 7, 1683-1691 (October 2015).
[28] A. Brieger et al., *Impact of Perfluorooctanesulfonate and Perfluorooctanoic Acid on Human Peripheral Leukocytes*, 25 Toxicology in Vitro Issue 4, 960-968 (June 2011).
[29] Ibid, page 1.
[30] M. Peden-Adams et al., *Developmental Toxicity in White Leghorn Chickens Following in ovo Exposure to Perfluorooctane Sulfonate (PFOS)*, 27 Reproductive Toxicology, Issues 3-4, 307-318 (June 2009).
[31] MR Qazi et al., *28-Day Dietary Exposure of Mice to a Low Total Dose (7mg/kg) of Perfluorooctanesulfonate (PFOS) Alters Neither the Cellular Compositions of the Thymus and Spleen nor Humoral Immune Responses: Does the Route of Administration Play a Pivitol Role in PFOS-Induced Immunotoxicity?,* 267 Toxicology Issues 1-3, 132-139 (January 2010).
[32] L. Zheng et al., *Type 1 and Type 2 Cytokines Imbalance in Adult Male C57BL/6 Mice Following a 7-Day Oral Exposure to Perfluorooctanesulfonate (PFOS),* 8 Journal of Immunotoxicology Issue 1, 30-38 (February 2011).
[33] Guang-Hui Dong et al., *Sub-Chronic Effect of Perfluorooctanesulfonate (PFOS) on the Balance of Type 1 and Type 2 Cytokine in Adult C57BL6 Mice*, 85 *Archives of Toxicology* 1235 (2011), https://www.researchgate.net/publication/49842219_Sub-chronic_effect_of_perfluorooctanesulfonate_PFOS_on_the_balance_of_type_1_and_type_2_cytokine_in_adult_C57BL6_mice.

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to human relevance[34] as well as carcinogen listing criteria. For example, the following narrative is from NTP:[35]

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

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

[34] U.S. EPA, Proposed OPPTS Science Policy: PPARa-Mediated Hepatocarcinogenesis in Rodents and Relevance to Human Health Risk Assessments (2003).
[35] National Toxicology Program, Report on Carcinogens Process & Listing Criteria (2019), https://ntp.niehs.nih.gov/whatwestudy/assessments/cancer/criteria/index.html.
[36] James Bjork et al., *Multiplicity of nuclear receptor activation by PFOA and PFOS in primary human and rodent hepatocytes*, 288 *Toxicology* 8 (2011), https://www.researchgate.net/publication/51461697_Multiplicity_of_nuclear_receptor_activation_by_PFOA_and_PFOS_in_primary_human_and_rodent_hepatocytes.
[37] James Bjork and Kendall Wallace, *Structure-Activity Relationships and Human Relevance for Perfluoroalkyl Acid-Induced Transcriptional Activation of Peroxisome Proliferation in Liver Cell Cultures*, 111 *Toxicological Sciences* 89 (2009), https://pubmed.ncbi.nlm.nih.gov/19407336/.
[38] Clifford Elcombe et al., *Hepatocellular hypertrophy and cell proliferation in Sprague-Dawley rats from dietary exposure to potassium perfluorooctanesulfonate results from increased expression of xenosensor nuclear receptors PPARα and CAR/PXR*, 293 *Toxicology* 16 (2012), https://pubmed.ncbi.nlm.nih.gov/22245121/.
[39] Clifford Elcombe et al., *Evaluation of Hepatic and Thyroid Responses in Male Sprague Dawley Rats for up to Eighty-Four Days Following Seven Days of Dietary Exposure to Potassium Perfluorooctanesulfonate*,293 *Toxicology* 30 (2012),https://www.sciencedirect.com/science/article/abs/pii/S0300483X11005506.
[40] John Vanden Heuvel et al., *Differential Activation of Nuclear Receptors by Perfluorinated Fatty Acid Analogs and Natural Fatty Acids: A Comparison of Human, Mouse, and Rat Peroxisome Proliferator-Activated Receptor-Alpha, -Beta, and -Gamma, Liver X Receptor-Beta, and Retinoid X Receptor-Alpha*, 92 *Toxicology* 476 (2006), https://pubmed.ncbi.nlm.nih.gov/16731579/.

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

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

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

Regards,

[redacted]

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[41] JC Corton et al., *Mode of Action Framework Analysis for Receptor-Mediated Toxicity: The Peroxisome Proliferator-Activated Receptor Alpha (PPARα) as a Case Study*, 44 Critical Reviews in Toxicology Issue 1, 1-49 (2014).
[42] C. Elcombe et al., *Mode of Action and Human Relevance Analysis for Nuclear Receptor-Mediated Liver Toxicity: A Case Study with Phenobarbital as a Model Constitutive Androstane Receptor (CAR) Activator*, 44 Critical Reviews in Toxicology, Issue 1, 64-82 (2014).
[43] Frank Gonzales and Yatrik Shah, *PPARalpha: Mechanism of Species Differences and Hepatocarcinogenesis of Peroxisome Proliferators*, 246 *Toxicology* 2 (2008), https://pubmed.ncbi.nlm.nih.gov/18006136/.
[44] J. Klaunig et al., *Mode of Action Analysis of Perfluorooctanoic Act (PFOA) Tumorigenicity and Human Relevance,* 33Reproductive Toxicology Issue 4, 410-418 (July 2012).
[45] B. Lake, *Species Differences in the Hepatic Effects of Inducers of CYP2B and CYP4A Subfamily Forms: Relationship to Rodent Liver Tumour Formation*, 39 *Xenobiotica* 582 (2009), https://pubmed.ncbi.nlm.nih.gov/19622001/.

[46] J. Ross et al., *Human Constitutive Androstane Receptor (CAR) and Pregnane X Receptor (PXR) Support the Hypertrophic but not the Hyperplastic Response to the Murine Nongenotoxic Hepatocarcinogens Phenobarbital and Chlordane In Vivo*, 116 *Toxicological Sciences* 452 (2010).
[47] U.S. EPA, *Health Effects Support Document for Perfluorooctane Sulfonate (PFOS)* (2016), https://www.epa.gov/sites/production/files/2016-05/documents/pfos_hesd_final_508.pdf.
[48] B. Alexander et al., *Mortality of Employees of a Perfluorooctanesulphonyl Fluoride Manufacturing Facility*, 60 *J. of Occupational & Env't Med.* 722 (2003).

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EXHIBIT A

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October 19, 2020

VIA ELECTRONIC SUBMISSION

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

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

3M Comments on Prioritization of Perfluorooctane Sulfonate (PFOS)

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

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

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

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

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

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

- 3M was one of the main manufacturers of PFOS in the United States. The company initiated a voluntary phase-out of these chemicals in 2000, effectively eliminating a significant portion of the available PFOS to discharge into sources of drinking water and use in consumer and other products originating in the U.S. PFOS has not been reported to US EPA as manufactured or imported into the United States since at least 2006.[3]
- Countless countries have signed onto the international Stockholm Convention, including China, which now requires the elimination of PFOS in essentially all consumer and other goods originating in member countries.
- Significant federal action relating to PFOS and PFOS precursors has been underway since 2002, and US EPA has imposed and continues to ratchet up strong restrictions on the manufacture, import and use of PFOS and PFOS precursors pursuant to its Significant New Use Rule authority under the Toxic Substances Control Act, effectively eliminating any likelihood that consumer and other products originating internationally and containing PFOS will be sold in California.
- As a result of all the steps in the U.S. and internationally to eliminate PFOS, substantial evidence supports the conclusion that further PFOS regulation under Proposition 65 is unnecessary. For example, there is an unmistakable downward trend in residues of PFOS in human blood since 2000, reflecting the results of 3M's voluntary phase-out and US EPA's restrictions. And, since PFOS' listing as a reproductive toxicant under Proposition 65, there has not been a single PFOS notice of Proposition 65 violation issued alleging discharge of or exposure to PFOS.
- The overall weight of the evidence with respect to PFOS fails to clearly show that this chemical causes cancer in humans and therefore does not warrant the extensive resources necessary for the preparation of hazard identification materials.

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[1] Cal. Health & Safety Code § 25249.8(b).
[2] Process for Prioritizing Chemicals for Consideration under Proposition 65 By The "State's Qualified Experts" https://oehha.ca.gov/media/downloads/proposition-65/document/finalpriordoc.pdf, (December 2004) (emphasis added).
[3] https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/fact-sheet-20102015-pfoa-stewardship-program#mfg.

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

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

Regards,

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

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

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

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

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

[2] *Id.* at i.

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

[4] *Id.*

[5] *Id.* (emphasis added).

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

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

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

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

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

[7] Process at 3.

[8] *Id.* (emphasis added).

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

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

[11] Guidance Criteria for Identifying Chemicals for Listing as "Known to the State to Cause Cancer," https://oehha.ca.gov/media/downloads/crnr/revcriteria.pdf.

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

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

1. 3M's Voluntary Efforts and Commitments.

3M was one of the main manufacturers of PFOS in the United States. In May 2000, 3M announced that it was voluntarily phasing out of production of PFOS. That phase out was largely complete in the United States by the end of 2002 – a full 18 years ago. PFOS has not been reported to US EPA as manufactured or imported into the United States by any entity since at least 2006.[12]

2. Federal Regulations.

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

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

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

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

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

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

[14] Prioritization Document at 83.

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

The National Health and Nutrition Examination Survey ("NHANES") prepared by the United States Centers for Disease Control ("CDC") National Center for Environmental Health), which is a nationally representative sample of the U.S. population (noninstitutionalized), provides data[16] which demonstrates the following declines:

Serum Perfluorooctane sulfonic acid (PFOS) (1999 – 2010)

CAS Number 1763-23-1

Geometric mean and selected percentiles of serum concentrations (in µg/L) for the U.S. population from the National Health and Nutrition Examination Survey.

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

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

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

Study Group: Adults

Sample Collection Date: 2018

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

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

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

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

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

Based on data available in 2015, PFOS was listed as a reproductive toxicant under Proposition 65.[19] As relevant here, that listing effectively prohibited the discharge of PFOS into sources of drinking water in California, and triggered a warning obligation before exposing California consumers to PFOS. Yet, of the nearly 5,500 notices of Proposition 65 violations issued since the PFOS listing was effective under Proposition 65, 3M is not aware of a single one alleging a Proposition 65 violation based on a PFOS exposure or discharge.

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

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

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

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

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

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[17] Agency for Toxic Substances and Disease Registry, PFAS in the U.S. Population, https://www.atsdr.cdc.gov/pfas/health-effects/us-population.html (last accessed October 16, 2020).
[18] United States Environmental Protection Agency, Drinking Water Health Advisory for Perfluorooctane Sulfonate (PFOS), https://www.epa.gov/sites/production/files/2016-05/documents/pfos_health_advisory_final_508.pdf (May 2016).
[19] As detailed in this Section II, substantial additional data on the impact of the PFOS phase out was not yet available in 2015.
[20] Prioritization Document at 83.

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

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

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

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

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

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

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

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[21] U.S. Food and Drug Administration, Questions and Answers on Per and Polyfluoroalkyl Substances (PFAS) in Food, https://www.fda.gov/food/chemicals/questions-and-answers-and-polyfluoroalkyl-substances-pfas-food (July 31, 2020).
[22] *Id.*
[23] Prioritization Document at 83.
[24] *Id.*

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Hurley et al. (2018)

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

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

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

[29] Hurley et al. 2018. Environmental Health17:83 https://doi.org/10.1186/s12940-018-0426-6.

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

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

Ghisari et al. (2014)

The Ghisari et al. (2014) published study[30] was not included among the epidemiology studies cited in OEHHA's Prioritization Document. Ghisari et al. is a follow-up study to Bonefield-Jørgensen et al. (2011), which examined breast cancer risk in Inuit women in a hospital-based case-control study of 31 cases and 115 controls. (Note: Wilsøe was the additional case-control study that included those subjects from Bonefield-Jørgensen et al. (2011)). Ghisari et al. conducted phenotyping for CYP1A1, CYP1B1, COMT, CYP17A1, and CYP19A1 genes and the Greenlandic founder mutation BRCA1. Ghisari et al. reported an increased breast cancer risk with women who had high PFOS and PFOA and carriers of at least one CYP1A1 variant allele (OR = 2.63, 95% CI 1.46, 4.75) one variant COMT Met allele (OR = 2.65, 95% CI 1.44, 4.89) or the common CYP17A1 A1A2+A2A2 allele (OR = 2..21, 95% CI 1.19, 4.12). See Supplemental Table 2 in Ghisari et al (2014). No combined effects were seen between PFOS/PFOA exposure and CYP1B1 and CYP19 polymorphisms. As would be expected, the frequency of the BRCA1 mutation was higher in the cases than controls.

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

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

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

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

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

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

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

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

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

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

- Because OEHHA categorically defines "perfluorooctane sulfonate (PFOS) and its salts and transformation and degradation precursors" in its Prioritization Document, the long-term feeding studies in rats with N-ethyl-perfluorooctanesulfonamidoethanol (N-EtFOSE) should also be included.[33]

    - N-EtFOSE is the precursor molecule that metabolically degrades to form PFOS as end-stage metabolite.[34]

    - Similar to the observation in the PFOS 2-year study in Sprague Dawley rats, increased incidence of liver adenoma was observed in rats in both studies.

    - In the first study,[35] there was a sporadic increase in the incidence of pituitary gland adenoma in the male rats that received N-EtFOSE; however, there was no dose- response and this finding was not observed in the female rats or in the second 2-year study. The study authors noted that "there did not appear to be any meaningful relationship of these to the dose administered". It is worth noting that in the second study, there was a statistically significant decreasing trend in pituitary adenoma incidence in female rats.

    - In the second study,[36] there was a statistically significant increase in the thyroid follicular cell adenoma in male rats that received 100 ppm N-EtFOSE in the diet at the end of 2-year study. This observation lacked a clear dose-response, was not observed in female rats and was not previously observed in the first N-EtFOSE 2-year study either. The study authors specifically noted that "The relationship of this finding to treatment is questionable for several reasons: thyroid follicular cell tumors in historical controls from this laboratory are relatively common (occur with an incidence of 1%), however, no thyroid follicular cell tumors occurred in male controls from this study, there was no evidence on nonneoplastic lesions of the thyroid, the increase at 100 ppm was within the range of historical controls, and a clear dose-response was not present".

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

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

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

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

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

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

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

Under "Is genotoxic" (pages 92 – 94)

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

- *In vivo* mouse micronucleus assay[38];
- Chromosomal aberrations in human whole blood lymphocytes[39];
- Mammalian microsome reverse mutation using *Salmonella-Saccharomyces*[40];
- Mammalian microsome reverse mutation using *Salmonella*- Escherichia; and
- Unscheduled DNA synthesis in primary rat hepatocytes.[41]

Under "Induces chronic inflammation" (page 95)

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

- Studies by Qazi et al. (2009a; 2009b) were only ten days in exposure duration and the other three studies[42] were based on tissue culture (*in vitro*).

- Because chronic inflammation is often being associated with detrimental effect such as increased mortality, the survival data in the long-term chronic animal study should be considered. Based on the only chronic mammalian laboratory animal data in rats that received dietary PFOS for up to 2 years[43], there was a statistically significant decreasing trend in mortality (increasing trend in survival) in male rats and no statistically significant trends in mortality in female rats through 2 years.

Under "immunosuppressive" (page 96)

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

[37] Butenhoff et al. 2012 Toxicology 293 1-15; Covance Study No. 6329-212, 2001; US EPA AR226-1051a.
[38] Corning Hazleton study No. 17403-0-455, 1996.
[39] Covance study No. 20784-0-449, 1999.
[40] Covance study No. 20784-0-409, 1999.
[41] Covance study No. 20784-0-447, 1999.
[42] Sorli et al. 2020; Gimenez-Bastida et al. 2015; and Brieger et al. 2011.
[43] Butenhoff et al. 2012; see also Thomford 2001.

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

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

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

- Two-generation study in rats → no effects on estrous cycles[46]; and
- Developmental studies in rats and mice → no effects on estrous cycles[47].

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

- Clinical evaluation of in monkeys after PFOS exposure → no change in thyroid hormone parameters[48]; and
- Investigation of thyroid hormone measurement issues in laboratory animals exposed to PFOS → negative bias observed with conventional immunoassay measurement on FT4, no effects on TSH or thyroid pathology.[49]

[44] https://www.epa.gov/sites/production/files/2016-05/documents/pfos_health_advisory_final_508.pdf.
[45] Peden-Adams et al. 2009 Reproduct Toxicol 27 307-318; Qazi et al. 2010 Toxicology 267 132-139; Zheng et al. 2011 J Immunotoxicol 8 30-38; Dong et al. 2011 Arch Toxicol 85 1235-1244.
[46] Luebker et al. 2005 Toxicol 215 126-148.
[47] Lau et al. 2003 Tox Sci 74 382-392.
[48] Chang et al. 2017 Toxicol Sci 156 387-401.
[49] Seacat et al. 2002 Toxicol Sci 68 249-264; Luebker et al. 2005 Toxicol 215 149-169; Chang et al. 2007 Toxicology 234 21-33; Chang et al. 2008 Toxicology 243 330-339; Chang et al. 2009 Reproduct Toxicol 27 387-399.

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October 28, 2021

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

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

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

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

[1] For example, EPA has issued Drinking Water Health Advisories for PFOA and PFOS at 70 ppt which is 10,000 times greater than the proposed PHG for PFOA.
[2] Indeed, OEHHA has set notification levels 6.5 ppt for PFOS and 5.1 ppt for PFOA in drinking water which were "the lowest levels at which they can be reliably detected in drinking water using currently available and appropriate

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

TECHNICAL COMMENTS

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

A. PFOA

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

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

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

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

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

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

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

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

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

[8] Gilliland and Mandel 1993 JOM 35 950-954

[9] Lundin et al. 2009 Epidemiology 921-928

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

The Raleigh et al. study used two referent populations for the mortality study: 1) the state of Minnesota that used traditional summary-based Standardized Mortality Ratio ("SMR") analyses; and 2) a 3M plant in St. Paul that manufactured tape and abrasives but was not involved with PFOA manufacturing, was the referent group used in the Cox proportional hazard models. Only the St. Paul plant was used as the referent group for the cancer incidence analyses, again, using Cox regression models. Unlike the prior mortality studies of this plant, the construction of the exposure matrix for PFOA in the Raleigh et al. study was noted as reasonable by IARC in their Monograph 110 on PFOA[10] where they wrote,

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

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

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

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

Page 214, 3rd paragraph:

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

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

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

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

[11] Steenland and Winquist 2021 Environ Res 194 110690

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

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

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

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

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

[12] Steenland and Woskie 2012 Am J Epidemiol 176 909-917
[13] Leonard et al. 2008 Ann Epidemiol 18 15-22

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

Page 214, 4th paragraph:

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

Page 214, 4th paragraph:

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

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

[14] Vieira et al. 2013 Environ Health Perspect 121 318-323
[15] Barry et al. 2013 Environ Health Perspect 121 1313-1318
[16] Rothman et al. 2008 Modern Epidemiology, chapter 4

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

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

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

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

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

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

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

Page 215, 1st paragraph:

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

Page 215. 2nd Paragraph:

OEHHA suggests that little to no information is available on the degree to which inhaled PFOA is absorbed in humans or the inter-individual factors that might affect his absorption. While there have not been inhalation studies of PFOA in humans, in their review paper, Griffith and Long (1980)[19] and Kennedy et al. (1986)[20] unquestionably concluded that PFOA is efficiently absorbed in laboratory animals following inhalation exposure and that it is not metabolized and is eliminated intact (as reviewed by Kennedy et al, 2004[21]). The findings from Griffith and Long (1980) and Kennedy et al. (1986) demonstrate that effective serum uptake of PFOA has been shown under both acute and repeated inhalation exposures in rats.

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

[18] Raleigh 2013 PhD thesis
[19] Griffith and Long 1980 Ame Ind Hyg Ass J 576-583
[20] Kennedy et al. 1986 Fd Chem Tox 24 1325-1329
[21] Kennedy et al. 2004 Crit Rev Toxicol 34 351-384

Table 1

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

Page 215, 2nd paragraph 2:

OEHHA also criticized the method of exposure assessment in Raleigh because "the PFOA exposure estimates … were not based on actual PFOA measurements." While no specific biomonitoring validation data were presented, there is strong collaborative evidence that the jobs and tasks with the highest air exposure monitoring data in Raleigh et al. study were, indeed, consistent with the higher PFOA serum concentrations measured. This can be inferred from reading Raleigh et al. (2013[22], 2014[23]), Olsen et al. (2000)[24], and Olsen et al. (2003)[25].

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

[22] Raleigh et al. 2013 PhD thesis
[23] Raleigh et al. 2014 Occup Environ Med 71 500-506
[24] Olsen et al. 2000 Drug Chem Tox 23 603-620
[25] US EPA docket AR-226-1351

a salt slurry; converting the slurry to a salt cake; drying the cake; and packaging. The greatest likelihood for exposure occurred in the drying area (Olsen et al. 2000; Raleigh et al. 2014). This is substantiated by Raleigh et al. (2013) who provided the range of TWA (mg/m^3) for APFO exposure by specific job titles and years. While Raleigh et al. (2012) reported job titles affiliated with electrochemical fluorination (head cell operator, APFO kettle room operator) that had ranges of APFO TWAs (mg/m^3) up to 0.04 mg/m^3 APFO, those involved with the operation of the spray dryer had measurements that ranged up to 100 fold higher (0.124 mg/m^3). Less exposed job titles including clerk, custodian, and finished good checkers had TWAs much lower (<= 0.002 mg/m^3).

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

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

Table 2

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

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

[26] US EPA docket AR-226-1351
[27] Woskie et al. 2012 Ann Occup Hyg 56 1025-1037

Page 217, 1st paragraph:

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

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

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

[28] Raleigh et al. 2014 Occup Environ Med 71 500-506
[29] Barry et al. 2013 Environ Health Perspect 121 1313-1318
[30] Steenland and Woskie 2012 Am J Epidemiol 176 909-917
[31] Vieira et al. 2013 Environ Health Perspect 121 318-323
[32] Steenland and Winquist 2021 Environ Res 194 110690
[33] https://ntp.niehs.nih.gov/ntp/htdocs/lt_rpts/tr598_508.pdf
[34] Butenhoff et al. 2012 Toxicology 298 1-13
[35] Biegel et al. 2001 Toxicol Sci 60 44-55

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

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

As will be discussed below, several studies in the scientific literature that have suggested an elevation of ALT remain well-within the expected physiologic range of measured ALT and therefore, using the term "damage" is misleading. It is also possible to have quite modest but statistically significant increases in ALT that are not toxicologically relevant (Cattley and Cullen, 2013[37]). The human half-life of ALT is approximately 47 hours with significant variation of 10 – 30% on a day-to-day basis with circadian variation (Cordoba et al. 1999[38]; Kim et al. 2008[39]). Most cohort studies examining estimated serum PFOA concentrations when there is only a single ALT measurement period fail to note this variation in half-life.

From a disease standpoint, nonalcoholic fatty liver disease is the most common cause of mild elevations of liver enzymes (Giannini et al. 2005[40]). Liver function should be considered in the context of many different biological processes that occur within the liver including: 1) production of proteins for plasma; 2) regulating blood clotting; 3) production of cholesterol and lipoproteins; 4) conversion of excess glucose to glycogen for storage; 4) regulation of blood amino acids; 5) metabolism of toxins; 6) production of bile; and 7) clearance of bilirubin.

Collectively, the studies assessed by OEHHA do not suggest "liver damage" (see above definition of a 2 to 4- fold increase) as measured by ALT associated with increasing serum concentrations of PFOA. As discussed in detail below, none of these studies, except Convertino et al. (2018), measured aspects of liver function that involved measures of blood clotting. Although some studies' regression coefficients for PFOA may be statistically significant, the percent variation of ALT explained by PFOA is often minimal, at best, and the increase of ALT is very modest (generally an increase of 1 to 5 IU ALT). Nor was there evidence of increased mortality from increased liver disease in epidemiologic analyses of a community-based exposure to PFOA from drinking water, (Darrow et a. 2016) or in occupational cohort mortality studies (Steenland and Woskie 2012[41] and Raleigh et al. 2014[42]). These later two studies are limited by the number of deaths reported.

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

[36] Hall et al. 2012 Toxicologic Pathol 40 971-994
[37] Cattley, R.C., Cullen, J.M., 2013. Liver and gall bladder. In: W.M. Haschek, C.G. Rousseaux and M.A. Wallig (Eds), Toxicologic Pathology, Elsevier, New York, pp. 1509-1566.
[38] Cordoba et al. 1999 Hepatology 28, 1724-1725
[39] Kim et al. 2008 Hepatology 47, 1363-1370
[40] Giannini et al. 2005 CMAJ 172, 367-379
[41] Steenland and Woskie 2012 Am J Epidemiol 176 909-917
[42] Raleigh et al. 2014 Occup Environ Med 71 500-506

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

Specific Responses to Liver Toxicity Studies

Gallo et al. (2012)

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

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

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

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

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

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

Darrow et al. (2016)[43]

In their cross-sectional analysis, Darrow et al. (2016) suggested the results of the C8 Science Panel's community worker cohort study were consistent with the Gallo et al. (2012) (above) showing an increasing trend in the β coefficients across quintiles. The estimated serum PFOA in 2005-2006 was Quintile 1 2.6-<5.8 ng/mL PFOA; Quintile 2 5.8-<11.4 ng/mL; Quintile 3 11.4-<26.7 ng/mL PFOA; Q4 26.7-<81.5 ng/mL PFOA; and Q5 81.5-3558.8 ng/ml PFOA. There were up to 11 covariates in these models, which were the same as model 3 in Gallo et al. Darrow et al. (2016) did not provide R^2 or partial R^2 values in these cross-sectional analyses. Neither study adjusted for serum lipids (see below discussion by Deb et al. 2018[44]).

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

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

Additional Studies Showing Lack of Relationship between PFOA and Liver Enzymes

Sakr et al. (2007a)[45]

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

[43] Darrow et al. 2016 Environ Health Perspect 124 1227-1233
[44] Deb et al. 2018 Int J Hepatol 2018 1286170
[45] Sakr et al. 2007 J Occup Environ Med 49 1086-1096

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

Sakr et al. (2007b)[46]

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

Costa et al. (2007)[47]

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

Olsen and Zobel (2007)[48]

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

[46] Sakr et al. 2007 J Occup Environ Med 49 872-879
[47] Costa et al. 2009 J Occup Env Med 51 364-372
[48] Olsen and Zobel 2007 Int Arch Occup Env Hea 81 231-246

Olsen et al. (2012)[49]

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

Convertino et al (2018)[50]

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

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

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

[49] Olsen 2018 JOEM 60 e563-e566
[50] Convertino et al. 2018 Toxicol Sci 163 293-306
[51] Sobus et al. 2015 Environ Health Perspect 123 919-927
[52] Lin et al. 2010 Am J Gastroenterol 105 1354-1363
[53] Gleason et al. 2015 Environ Res 136 8-14

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

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

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

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

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

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

Page 140,4th paragraph.

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

[54] Deb et al. 2018 Int J Hepatol 2018 1286170
[55] Jain and Ducatman 2019 J Occup Environ Med 61 293-302
[56] Fisher et al. 2013 Environ Res 121 95-103
[57] Melzer et al. 2010 Environ Health Perspect 118 686-692

Page 141, 2nd paragraph.

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

Page 141, 2nd paragraph.

Unlike liver cancer and TFE reported in rodent studies discussed in this paragraph, OEHHA did not mention in the previous paragraph on kidney cancer that TFE caused an increased incidence of renal cell adenoma or carcinoma (combined) at the highest dose of TFE in both male and female rats compared to controls. See pages 121-124 of IARC Monograph 110[59]. OEHHA should correct this oversight.

Page 142, 2nd paragraph.

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

Page 202, 1st Paragraph with Figure 6.2.1.

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

[58] Eriksen et al. 2009 JNCI 101 605-609
[59] IARC Monograph 110, pgs. 121-124, https://publications.iarc.fr/Book-And-Report-Series/Iarc-Monographs-On-The-Identification-Of-Carcinogenic-Hazards-To-Humans/Some-Chemicals-Used-As-Solvents-And-In-Polymer-Manufacture-2016, accessed 23 October 2021
[60] Raleigh et al. 2014 Occup Environ Med 71 500-506
[61] Barry et al. 2013 Environ Health Perspect 121 1313-1318

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

Page 203, Table 6.2.2.

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

Page 204, 2nd Paragraph

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

Page 207, Table 6.2.3

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

Page 207, Table 6.2.3.

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

[62] https://seer.cancer.gov/archive/studies/surveillance/study6.html, accessed 23 October 2021
[63] Dourson et al. 2020 Regul Toxicol Pharmacol 110 104502
[64] Shearer et al. 2021 J Natl Cancer Inst 113 580-587

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

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

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

Page 211, 7th Paragraph

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

[65] Steenland et al. 2020 Environ Int 145 106125
[66] Eriksen et al. 2009 JNCI 101 605-609
[67] Andersen et al. 2021 Environ Res 197 111183
[68] Vieira et al. 2013 Environ Health Perspect 121 318-323
[69] Steenland and Woskie 2012 Am J Epidemiol 176 909-917

Page 220

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

B. PFOS

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

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

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

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

[70] https://www.cdc.gov/exposurereport/pdf/FourthReport_UpdatedTables_Volume1_Mar2021-508.pdf, accessed 23 October 2021
[71] https://www.cdc.gov/exposurereport/pfas_early_release.html, accessed 23 October 2021
[72] Butenhoff et al. 2012 Toxicology 293 1-15
[73] Proposed OPPTS science policy: PPARa-mediated hepatocarcinogenesis in rodents and relevance to human health risk assessments, USEPA, 2003.

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

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

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

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

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

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[74] https://ntp.niehs.nih.gov/whatwestudy/assessments/cancer/criteria/index.html, accessed 22August 2021
[75] Bjork et al. 2011 Toxicology 288 8-17
[76] Bjork and Wallace 2009 Toxicol Sci 111 89-99
[77] Elcombe et al. 2012 Toxicology 293 16-29
[78] Elcombe et al. 2012 Toxicology 293 30-40
[79] Vanden Heuvel et al. 2006 Toxicol Sci 92 476-489
[80] Proposed Public Health Goals for Perfluorooctanoic Acid and Perfluorooctane Sulfonic Acid in Drinking Water, Office of Environmental Health Hazard Assessment at 153 (July 2021).
[81] Proposed Public Health Goals for Perfluorooctanoic Acid and Perfluorooctane Sulfonic Acid in Drinking Water, Office of Environmental Health Hazard Assessment at 159 (July 2021).
[82] Corton et al. 2014 Crit Rev Toxicol 44 1-49
[83] Elcombe et al. 2014 Crit Rev Toxicol 44 64-82
[84] Gonzales and Shah 2008 Toxicology 246 2-8
[85] Klaunig et al. 2012 Reprod Toxicol 33 410-418
[86] Lake 2009 Xenobiotica 39 582-596
[87] Ross et al. 2010 Toxicol Sci 116 452-466

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

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

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

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

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

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

[88] https://www.epa.gov/sites/production/files/2016-05/documents/pfos_hesd_final_508.pdf, accessed 22 August 2021
[89] Alexander et al. 2003 Occ Env Med 60 722-729
[90] Butenhoff et al. 2012 Toxicology 293 1-15

Table 3

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

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

In the 2-year cancer bioassay study for PFOS where food was given *ad libitum*, Butenhoff et al. 2012[93] reported that the control and K^+PFOS-treated male rats had generally similar food consumption rates. However, there were intermittent lower body weights observed in the 20 ppm-treated group animals. While the actual metabolic caloric balance was not evaluated in that study, it is possible that the subtle difference in food consumption per body weight may have, in part, contributed to the observation of intermittent lower body weights.

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

[91] Suzuki et al. 1979 J Cancer Res Clin Oncol 95 187-196
[92] Dillberger 1994 Toxicol Path 22 48-55
[93] Butenhoff et al. 2012 Toxicology 293 1-15
[94] Butenhoff et al. 2012 Toxicology 298 1-13
[95] Biegel et al. 2001 Toxicol Sci 60 44-55

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

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

USEPA, 2016[97]

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

Health Canada, 2018[98]

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

EFSA, 2020[99]

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

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

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

OEHHA considered four cross-sectional studies (Dong et al. 2019);[100] Steenland et al. (2009);[101] Frisbee et al. (2009);[102] and Starling (2014)[103] in their determination of a PHG and PHC for PFOS based on increased serum total cholesterol in the human. 3M believes the use of these studies, and particularly Steenland et al. (2009) study to evaluate an HPC is highly premature given recent scientific literature , which OEHHA did not consider. Recent studies include include two workshop panel reports, published in 2021 (Fragki et al. 2021;[104] Andersen et al. 2021[105]), that related to the question what might be the underlying reasons why many

[96] Myer et al. 2014 Toxicol Pathol 42 260-274.
[97] https://www.epa.gov/sites/production/files/2016-05/documents/pfos_hesd_final_508.pdf, accessed 22 Ocrtober 2021
[98] https://www.canada.ca/en/health-canada/services/publications/healthy-living/guidelines-canadian-drinking-water-quality-guideline-technical-document-perfluorooctane-sulfonate/document.html, accessed 23 October 2021
[99] Schrenk et al. 2020 EFSA J 18 e06223
[100] Dong et al. 2019 Ecotoxicol Environ Saf 173 461-468
[101] Steenland et al. 2009 Am J Epidemiol 170 1268-1278
[102] Frisbee et al. 2009 EHP 117 1873-1882
[103] Starling et al. 2014 Environ Int 62 104-112
[104] Fragki et al. 2021 Crit Rev Toxicol 51 141-164
[105] Andersen et al. 2021 Toxicol 459 152845

epidemiological studies, primarily cross-sectional, have reported positive association between serum concentrations of perfluoroalkyl substances (in particular PFOS, PFOA, PFHxS) and modestly elevated serum cholesterol. In addition, the recent scientific opinion by a regulatory body, EFSA[106], also did not consider this association (observation of increased cholesterol with PFAS in humans) to be a driver in its calculation of a TWI because of the uncertainies that have recently arisen in the literature. More recently, Dzierlenga et al. (2021)[107] reported an association with increased dietary fiber and decreased PFAS levels using NHANES data. Dietary fiber is known to reduce serum cholesterol levels. This raises the question, which was not examined in the four studies evaluated by the OEHHA (Dong, Steenland, Frisbee, or Starling) as to the confounding presence of dietary fiber in studying the association between PFOS/PFOA and serum total cholesterol.

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

3M is not aware of other state, federal, or international regulatory agencies that have chosen to use the Steenland et al. (2009) cross-sectional study on PFOS and lipids as their Point of Departure to calculate a health-based guidance value. We are not aware of any regulatory agency that has declared a causal association between low concentrations of PFAS and modestly elevated serum total cholesterol. Many of the questions raised by others (Fragki et al. 2021;[108] Andersen et al. 2021;[109] EFSA 2020;[110] ATSDR 2021;[111] Dzierlenga et al. 2021;[112] Chang et al. 2017;[113] and Canova et al. 2020[114]) need to be addressed for further elucidation of this epidemiologic association. Thus, there is insufficient evidence of an association with cholesterol in humans at general population levels, to warrant it as a POD for the calculation of a PHG for PFOS by OEHHA

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

[106] Schrenk et al. 2020 EFSA J 18 e06223
[107] Dzierlenga et al. 2021 Environ Int 146 106292
[108] Fragki et al. 2021 Crit Rev Toxicol 51 141-164
[109] Andersen et al. 2021 Toxicol 459 152845
[110] Schrenk et al. 2020 EFSA J 18 e06223
[111] https://www.atsdr.cdc.gov/toxprofiles/tp200.pdf, accessed 10-19-2021
[112] Dzierlenga et al. 2021 Environ Int 146 106292
[113] Chang et al. 2017 Toxicol Sci 156 387-401
[114] Canova et al. 2020 Environ Int 145 106117

Fragki et al. 2021[115] and Andersen et al. 2021[116]

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

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

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

[115] Fragki et al. 2021 Crit Rev Toxicol 51 141-164
[116] Andersen et al. 2021 Toxicol 459 152845
[117] Steenland et al. 2010 Environ Health Perspect 118 1100-1108
[118] Sakr et al. 2007 J Occup Environ Med 49 1086-1096
[119] Bijland et al. 2011 Tox Sci 123 290-303

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

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

Fragki et al. 2021.

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

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

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

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

Andersen et al. 2021

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

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

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

ATSDR (2021)[121]

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

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

EFSA (2018[122], 2020[123])

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

[121] https://www.atsdr.cdc.gov/toxprofiles/tp200.pdf, accessed 10-19-2021
[122] Knutsen et al. 2018 EFSA J 16 5194
[123] Schrenk et al. 2020 EFSA J 18 e06223

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

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

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

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

Pages 88 and 98.

It is unclear why the study by Chang et al. 2017[124] was included in Table 5.2.3 (a table animal studies of liver effects) but excluded from Table 5.3.2 (a table of animal studies that reported lipid effects). See detailed comments below regarding the Chang et al. 2017 study as related to the findings from Steenland et al. 2009.

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

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

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

Pages 105, 194, and 196:

OEHHA writes about cross-sectional studies being "frequently criticized based on their potential for reverse causation." OEHHA appears to be confusing concepts of reverse causation with temporality. One of the primary criticisms of cross-sectional studies is that they cannot assess temporality – *i.e.*, did the exposure precede the condition being studied. We refer OEHHA to a paper on pharmacokinetic bias that can occur from either confounding or reverse causation (Andersen et al. 2021a) that provides both PFAS and non-PFAS examples. In their workshop, Andersen et al. (2021b) examined reverse causality as one of their 4 hypotheses but this has to do with the possible mechanism of incorporation of PFAS into cholesterol containing particles such as LDL. PFAS would then increase proportionally with the LDL. OEHHA acknowledges that the major transport proteins for cholesterol in the blood are the lipoproteins (not albumin). OEHHA dismisses PFAS binding to lipoproteins because of the results from Butenhoff et al. 2012.[125] While this one study investigated the issue, it was based on a blood sample from only one individual and cannot reasonably be relied upon to support the conclusion OEHHA attempts to draw. Andersen et al. also briefly mentioned the co-distribution – hypothesis.

Pages 104, 105, and 193:

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

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

[125] Butenhoff et al. 2012 Toxicol Letters 210 360-365
[126] Dzierlenga et al. 2021 Environ Int 146 106292

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

Page 191, Table 6.1.16

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

Page 193, 1st Paragraph

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

Page 193, 3rd Paragraph

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

[127] http://www.c8sciencepanel.org/pdfs/Probable_Link_C8_Heart_Disease_29Oct2012.pdf, accessed 10-19-2021
[128] Winquist and Steenland 2014 Environ Health Perspect 122 1299
[129] Canova et al. 2020 Environ Int 145 106117
[130] Li et al. 2020 Environ Health 19 33
[131] Fragki et al. 2021 Crit Rev Toxicol 51 141-164

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

Page 194, 2nd Paragraph.

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

Page 194, 3rd Paragraph.

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

* * *

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

[132] Andersen et al. 2021 Toxicol 459 152845

Exhibit A

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

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

Study Population

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

Production Process

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

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

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

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

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

Work History

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

Exposure Data

There were a total of 205 personal and 659 area APFO/PFOA (APFO $C_8HF_{15}O_2NH_3$; and PFOA $C_8HF_{15}O_2$) air measurements used in the quantitative exposure assessment. Air data collection for APFO/PFOA began in 1977 and ended in 2000 (Table 2). Both PFOA and APFO were sampled depending on the process step and exposure (i.e., vapor or particulate phase). The following sampling media were used to collect PFOA vapors; Impinger (0.01N NaOH methanol), silica gel tubes, and ethylene glycol coated Tenax tubes through the 1980s. After the 1980s, PFOA was captured using Tenax tubes, silica gel acid tubes and finally OVS–XAD-4 resin tubes. From 1977-1999, APFO was collected with tared 0.8 micrometer pore size Nuclepore filters; with a switch to OVS-XAD-4 resin tubes in 2000. The PFOA anion (PFO^-) was the measured analytic compound using gravimetric gas chromatography, flame ionization and electron capture analyses.

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

Exposure Values: Daily Time-Weighted Averages

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

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

The daily TWA exposure in mg/m3 of air was calculated as:
$C_j = \Sigma_{ni=1}\, c_i t_i / \Sigma_{ni=1}\, t_i$ Equation (1)

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

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

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

EXHIBIT H

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

The 3M Company ("3M") writes to follow up on its prior submission of written comments on the meeting materials published in association with the Environmental Protection Agency ("EPA" or the "Agency") Science Advisory Board's ("SAB") public meetings to review data and analysis prepared by EPA as it considers setting Maximum Contaminant Level Goals ("MCLGs") and National Primary Drinking Water Regulations ("NPDWR") for Perfluorooctanoic Acid ("PFOA") and Perfluorooctanesulfonic Acid ("PFOS").

As noted in its prior submission, 3M is providing these supplemental comments because it was unable to provide the full scope of its technical comments in its December 30, 2021 submission due to the inadequate comment period. This document includes certain of 3M's comments on some aspects of the meeting materials, specifically toxicokinetic models (human and animal), EPA's proposed cancer classification for PFOA, potential non-cancer effects such as cardiovascular disease and birth-weight, and EPA's mixtures framework.[1] 3M is continuing to review the lengthy meeting materials and may provide additional supplemental technical comments on the meeting materials given the limited time provided by SAB. 3M incorporates by reference its prior comments related to the inadequacy of the comment period and further notes that even with the additional time taken to provide these supplemental comments, the opportunity for public review has been wholly insufficient.

Overall, consistent with other commenters, 3M has observed a number of broad, persistent issues that are prevalent across the SAB PFAS Panel's meeting materials from EPA. These themes are presented here and detailed examples of each are discussed in 3M's December 30, 2021 submission as well as in the supplemental technical comments below.

[1] 86 Fed. Reg. 62526 (Nov. 10, 2021).

- **Failure to Comply with Health Risk Assessment Principles, Guidelines, and Policies**

  For more than 40 years, EPA has adopted and followed certain health risk assessment and risk management policies as a basis for assessing scientific evidence for public health protection. From 1976 until today, the assessment of potential health risk associated with any agent is essentially a two-step process: (1) assessment of the weight of evidence that a substance can cause health effects, considering all evidence, including human, animal, and mechanistic studies; and (2) on the assumption that the agent can cause harm, describe quantitatively the levels at which harm might be induced (dose response).

  All of EPA's draft reports currently under review by the SAB PFAS Panel fall short of this established health risk assessment process. The draft reports do not clearly consider all lines of evidence, both positive and negative studies from human, animal, and mechanistic information, to provide a weight of evidence assessment for each endpoint for which EPA presents a point of departure ("POD"), in a two-step process. EPA's failure to carry out these assessment steps and presentation of results raises concerns that EPA is simply searching for the lowest theoretical POD, without regard for whether the endpoint being assessed poses a real risk.

  Also, there has been a typical practice in cancer potency/slope factor development to avoid quantitative assessment when the weight of evidence is weak or where data are too poor on which to base a quantitative assessment. EPA's 2005 cancer guidelines state that "[w]hen there is suggestive evidence, *the Agency generally would not attempt a dose-response assessment*, as the nature of the data generally would not support one; however, when the evidence includes a well-conducted study, quantitative analyses may be useful for some purposes, for example, providing a sense of the magnitude and uncertainty of potential risks, ranking potential hazards, or setting research priorities." P. 3-1 (emphasis added). Non-cancer health endpoint assessment in EPA's draft reports should adhere to similar approaches.

- **Lack of Clarity and Transparency**

  Repeatedly throughout EPA's draft reports, EPA has failed to be clear and transparent in its approach. Numerous examples are described in 3M's initial and supplemental submissions, as well as by many other commenters and by SAB Panel members themselves.[2,3]

[2] 3M's initial and supplemental submissions and those of other commenters may be found on the SAB website at: https://sab.epa.gov/ords/sab/f?p=100:19:5099513780240:::RP,19:P19_ID:963#materials.
[3] *Revised and Preliminary Individual Comments SAB PFAS Review Panel*. January 24, 2022, https://sab.epa.gov/ords/sab/apex_util.get_blob?s=31551561024923&a=100&c=5659346460770746&p=19&k1=5934&k2=&ck=eQOnA_wpq7AMDmRHV6wbKbqVujmVHVZrA3Z1rldaBKMZxSP361uDnP-xKmDgE_4EeXDyt0SKANMAGPvXzL9okw&rt=IR.

In the SAB Charge questions, EPA asked the SAB Panel whether there is agreement with specific labels for both carcinogen and non-carcinogen evidence but no definitions for the non-carcinogen classification are provided. The draft MCLG Documents do not clearly define strong versus suggestive or any weaker weights of evidence.[4] In its health assessments, EPA uses various terms such as "association," "impact," and "effect" somewhat interchangeably and inconsistently, which creates confusion and hampers the ability to judge the different conclusions.

- **Inconsistencies in Analysis and Approach**

EPA's draft reports include a number of significant and unexplained inconsistencies. For example, EPA identified cholesterol as a critical endpoint despite noting that verification of cardiovascular disease is negative in human studies. Nonetheless, EPA's documents call for a benefit analysis of cardiovascular disease cases avoided by prescribed reduction in PFAS exposure. This is but one example of circular and inconsistent analyses that plague the draft reports.

As mentioned above, EPA should also ensure it uses consistent, well-defined protocols for non-cancer weight of evidence characterization. Only where there is clear evidence, and where studies of sufficient quality are available, should EPA proceed to the next step of evaluating protective quantitative toxicity levels from a POD. Selection of studies for PODs should be based on the strength of and confidence in the potential hazard, not just the availability of studies that are amenable to dose-response (and vice versa) or provide the lowest POD.

We also note, for POD selection (notwithstanding the quality of the studies involved) EPA mixes clinically relevant disease endpoints (liver necrosis) with changes in response, biomarker levels of potential exposure but not of effect. The latter include candidate PODs based on vaccine response, not on infections, birth-weight, but not for later life problems arising from thyroid hormone levels, but not thyroid disease, and increased total cholesterol, but not CVD. 3M's December 30, 2021 comments, as well as those included here, discuss EPA's use of PODs that are derived for elevated cholesterol, and antibody response to vaccines. Attention should be focused on the evidence for the actual endpoints to provide support to any POD derivations based on changes in clinical biomarkers of exposure.

[4] The charge question does not provide a term for weaker than suggestive evidence: "Please comment on the health effect/outcome categories identified from the review of the available literature. Do you agree with the strong vs. suggestive evidence designations for the various health outcome categories?"

- **Consideration of All Relevant Evidence**

  EPA's draft reports do not consistently use or evaluate all relevant published studies, nor do they explain why certain studies were not included in its analysis.

- **Failure to Identify Relationship Between Current and Prior Assessments**

  EPA's draft reports represent a significant departure from its 2016 health risk assessments of PFOA and PFOS. Consistent with past practice, EPA should present the relationship of the current assessment of evidence and quantification recommendations to its earlier 2016 health risk assessments. EPA should describe the basis for reaching different conclusions in the current draft reports, particularly focusing on differing interpretations and weight given to what are in most cases essentially the same sets of studies as in 2016 and explain the differing approaches that have led to the significant changes in EPA's current draft reports.

3M encourages SAB to consider the information presented in its December 30, 2021 submission and the comments below when providing EPA with SAB's technical input on the meeting materials. As indicated in 3M's December 30, 2021 submission, EPA's approach is deeply scientifically flawed, substitutes non-scientific judgments for science, and employs unprecedented approaches to reach an illogical outcome. SAB should make these technical deficiencies clear to EPA in its response and should recommend that the Agency use scientifically sound approaches in considering these important regulatory levels and meaningfully engage relevant stakeholders in any future actions.

SUPPLEMENTAL TECHNICAL COMMENTS

Given the extremely limited comment period and the complex nature of the meeting materials published by EPA, 3M supplements it previously submitted comments with the comments below. These comments address EPA's Proposed Approaches to the Derivation of a Draft Maximum Contaminant Level Goal for Perfluorooctanoic Acid ("PFOA) in Drinking Water, and EPA's Proposed Approaches to the Derivation of a Draft Maximum Contaminant Level Goal for Perfluorooctanesulfonic Acid ("PFOS") in Drinking Water (collectively, the "Draft MCLG Documents"), as well as EPA's Analysis of Cardiovascular Disease Risk Reduction as a Result of Reduced PFOA and PFOS Exposure in Drinking Water ("CVD Risk Analysis"), and EPA's Draft Framework for Estimating Noncancer Health Risks Associated with Mixtures of PFAS ("Mixtures Framework").

I. SUPPLEMENTAL COMMENTS ON DRAFT MCLG DOCUMENTS

A. Toxicokinetic Models

1. Human Modeling: Fetal to maternal partitioning and partitioning to breastmilk

In the charge questions posed to the SAB, the PFAS Panel was asked to "comment on the choice to assume that fetal to maternal partitioning and partitioning to breastmilk did not vary in time [and] describe whether there are other methods you would recommend to account for these changes over time and across development."[5] 3M believes that it is imperative that SAB provide input on EPA's assumption that the partitioning does not vary over time and must ask the Agency to look at the timing of collection of samples across available literature as well as whether or not a constant partitioning is consistent with the data on cord blood, milk, and maternal and infant serum samples that were analyzed at different times during gestation. In addition, the SAB should provide input on the duration of breastfeeding that EPA assumed. Finally, SAB should encourage EPA to evaluate and discuss whether there are other modeling approaches that are more fit for this purpose than a constant dose, including whether a drinking water concentration is more appropriate.

In particular, the SAB should focus EPA's attention on data in the scientific literature on the volume/amount of breastmilk that is typically consumed by an infant during lactation and the average duration for breastfeeding in the US. In fact, the 2011 US EPA Exposure Factors Handbook (chapter 15) has an entire section on human milk intake.[6] This shows that as a child grows the volume/amount consumed per kg of body weight decreases over time. EPA's analysis does not account for this fact, nor does it adequately describe why it was discounted. Likewise, EPA assumed that breastfeeding lasted 1 year, and that weaning was an immediate process (i.e., EPA assumed the child's sole diet for 1 year was breastmilk and then immediately stopped). The SAB should suggest that EPA incorporate data on the decrease in consumption relative to body weight and weaning to better reflect actual potential exposure. As the SAB's PFAS Panel itself

[5] Toxicokenitic Models, Charge Question 1.C.
[6] https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=236252

recognized during its public meetings, EPA failed to adequately discuss its the calculation of early life stage exposures and the uncertainty with EPA's approach.

Failure to consider these factors is an important gap in the EPA analysis and is something the SAB should recommend EPA correct.

2. Animal Modeling: EPA's selection of the Wambaugh et al. (2013) model

SAB should recommend that EPA clarify why it believes a single compartment model is a better choice than one of the available PBPK models. As the PFAS Panel itself noted in response to charge questions[7] related to use of the Wambaugh et al. (2013) model, EPA's discussion in the Draft MCLG Documents is cursory at best and does not provide the necessary detail to allow adequate public input. The Draft MCLG Documents state:

> "Typically, PBPK models are preferred because they can provide individual tissue information and have a one-to-one correspondence with the biological system which can be used to incorporate additional features of PK including tissue specific dosimetry and local metabolism. In addition, though PBPK models present a great increase in complexity, many of the additional parameters are chemical-independent and have widely accepted values. The decision to not use one of the PBPK models for PFOA/PFOS was motivated in part by previous issues identified when evaluating the application of PBPK models to other PFAS compounds for the purpose of risk assessment…. However, while these errors usually don't substantially alter the results of the model, correction of the free-fraction error was judged to result in a significant impact which could not be easily resolved" (EPA Document No. 822D21001, p. 332; EPA Document No. 822D21002, p. 303).

The Agency does not explain what this error is and why this could not be "easily resolved." The PFAS Panel should recommend that EPA use a PBPK model (which EPA acknowledges is generally a better approach) and explicitly state why it finds that the "error" could not be easily resolved. With sufficient time, outside commenters could conduct these modeling efforts and provide assistance to EPA in an effort to fully understand the differences and consequences of model choice. No final decisions should be made before taking account of these flaws.

3. Animal Modeling: EPA incorrectly assumed no sex differences in clearance in neonatal animals

In response to charge questions posed to SAB regarding the validity of EPA's assumption that there were no sex differences in clearance in neonatal animals[8], SAB should recommend that EPA review Hinderliter et al. 2006, where the study authors looked at PFOA clearance in post-weaning rats. This study demonstrates that contrary to EPA's assumption, there are some sex-

[7] Toxicokenitic Models, Charge Question 2.A.
[8] Toxicokenitic Models, Charge Question 2.C.

and age-dependent differences, at least for PFOA in rats. The PFAS Panel should recommend that EPA should modify their models accordingly. At a minimum SAB should recommend that EPA more adequately describe the uncertainty associated with its assumptions.

4. Animal Modeling: Transfer of chemical from the mother to her pup and from the mother to the fetus

It is unclear whether the parameters EPA used are appropriate (both the values and whether more description is needed—i.e., is the description of maternal-pup transfer sufficient). It is also unclear on what literature EPA relied (for the cord blood: maternal serum ratio, apparently EPA used only reports where the ratio was actually reported in the study. It is unclear how many measurements EPA actually used and how many were disregarded. In this regard, the Agency assessment lacks transparency. The gaps in the Agency assessment could be filled by outside experts and results submitted to assist the Agency unless the Agency undertakes this effort itself. Either way, the PFAS Panel should recommend that EPA clearly disclose the parameters, measurements, and literature it relied on in reaching its conclusions. EPA should be encouraged to engage with knowledgably stakeholders to help ensure a transparent, scientifically, valid approach.

B. RfD Derivation: Decreased Birthweight is not a Causal Effect of PFOA and PFOS

EPA identifies decreased human birth-weight as a candidate critical effect for development of RfDs for both PFOA and PFOS.[9] In doing so, EPA ignores the foundational problem that decreased birth weight is not established as a causal effect of PFOA or PFOS. Again, without a known causal link to a given health outcome, an RfD will not serve its purpose of protecting against the risk of that health outcome. SAB should recommend that EPA reevaluate this RfD analysis.

For PFOA:

> EPA uses equivocal language in summarizing the epidemiology of PFOA and fetal growth, concluding that "there is *suggestive* evidence that PFOA *may* impact fetal growth restriction across a variety of [birthweight]-related measures" (EPA Document No. 822D21001, p. 100; emphasis added). EPA acknowledges that there is even "less consistent evidence" of an effect of PFOA on postnatal growth (EPA Document No. 822D21001, p. 100), and that "evidence for any association with PFOA and metabolic outcomes," including body size in childhood or adulthood, is "inconsistent" (EPA Document No. 822D21001, p. 240). Regarding fetal growth and other developmental outcomes, EPA adds: "Collectively, across these various endpoints there is *moderate* evidence of developmental effects related to PFOA based on the more recent epidemiological literature. However, as noted previously there is some uncertainty as to what degree the evidence may be impacted by pregnancy hemodynamics and sample

[9] Reduced birth weight is one of only two health effect endpoints selected by EPA for candidate RfDs, the other being vaccine response. (See Table 23 of the Draft MCLG Documents).

> timing differences across studies as this may result in either confounding or reverse causality {Steenland, 2018, 5079861}. Additional uncertainty exists due to the potential for confounding by other PFAS" (EPA Document No. 822D21001, pp. 100–101; emphasis added).

For PFOS:

> EPA's language regarding the epidemiology of PFOS and fetal growth is similarly ambivalent: "As noted in the epidemiological fetal growth restriction summary, there is *suggestive* evidence that PFOS may impact fetal growth restriction in humans" (EPA Document No. 822D21002, p. 90; emphasis original). Regarding postnatal growth, EPA identifies "inconsistent evidence of PFOS impacts" (EPA Document No. 822D21002, p. 90), and the Agency notes that for endpoints such as body size after early childhood, "evidence for any association with PFOS and metabolic outcomes was inconsistent" (EPA Document No. 822D21002, p. 230). The following language regarding associations between PFOS and developmental outcomes, such as fetal growth, is nearly identical to that used for PFOA: "Collectively across the various endpoints outlined in the human epidemiological sections, there is *moderate* evidence of developmental effects related to PFOS based on the more recent epidemiological literature. As noted previously there is some uncertainty as to what degree the available evidence may be impacted by pregnancy hemodynamic and sample timing differences across studies, as this may result in either confounding or reverse causality {Steenland, 2018, 5079861}. Additional uncertainty exists due to the potential for confounding by other PFAS" (EPA Document No. 822D21002, p. 90; emphasis original).

In response to the charge question posed to it about approaches to addressing potential confounding, as mentioned during the public meeting, SAB should recommend that EPA review or conduct a meta-analysis of the literature relating to birthweight effects. Conducting such an analysis of certain bodies of literature but not others is not scientifically sound. Such an analysis should consider that the interpretation of associations between PFAS and measures of fetal growth is complicated because these associations are susceptible to confounding by maternal physiological mechanisms, such as glomerular filtration rate ("GFR"), (i.e., the flow rate of fluid being filtrated by the kidneys), glucose metabolism, and plasma volume expansion, as well as maternal nutrition, which can produce spurious, non-causal associations with fetal growth (Savitz 2007, Morken et al. 2014, Verner et al. 2015). Such relationships with shared physiological mechanisms can distort results even in studies with prospective exposure assessment; that is, the bias is not limited to cross-sectional or retrospective studies. In particular, circulating PFAS levels are dependent on GFR, since these chemicals are eliminated by the kidneys (Han et al. 2012). GFR generally increases by about 50% during the first half of pregnancy and declines slightly during the second half of pregnancy, and insufficient GFR during pregnancy has been shown to be associated with poorer fetal growth (Verner et al. 2015). Lower maternal GFR may also contribute to greater placental transfer of PFAS (Pan et al. 2017). Thus, maternal GFR can be responsible for a spurious association between higher fetal PFAS exposure and impaired fetal growth. Maternal plasma volume also typically expands during pregnancy, and greater plasma volume expansion is associated with lower circulating PFAS

levels and lower risk of fetal growth restriction (Salas et al. 1993, Salas et al. 2006), again biasing the observed association toward an association between PFAS and poorer fetal growth.

Few epidemiological studies of fetal growth adjusted for maternal estimated GFR or plasma volume expansion, leaving nearly all of the results susceptible to confounding by these physiological factors. The expected bias toward an association between higher PFAS levels and lower fetal growth would be magnified in studies that measured maternal PFAS levels later in pregnancy (Verner et al. 2015, Steenland et al. 2018b). One study that reanalyzed the association between PFOA exposure and birth weight in a prospective Danish cohort found that the observed association was attenuated by 66% after adjustment for maternal eGFR in the second trimester of pregnancy (Morken et al. 2014). Four other studies (including two from the same cohort) did not detect a strong positive confounding effect of maternal eGFR estimated in the first trimester of pregnancy (Manzano-Salgado et al. 2017a, Rokoff et al. 2018, Sagiv et al. 2018, Costa et al. 2019), and another did not observe substantial confounding by maternal eGFR estimated three weeks after delivery (Gyllenhammar et al. 2018). However, these authors and others acknowledged that measurement of PFAS and estimation of eGFR at other times, especially later during pregnancy, might reveal a greater impact of confounding. Additionally, the single measurement of PFAS used in nearly all studies, and the variability across studies in the timing of exposure assessment, limits the ability of these studies collectively to capture the true relationship between PFAS exposure during gestation and fetal growth.

While EPA acknowledges in the Draft MCLG Documents the potential confounding between the timing of the maternal blood sampling and its role in the inverse associations with birth weight and measured maternal serum PFOS/PFOA concentrations, EPA needs to justify why it did not consider Sagiv et al. 2018, which attempted to reduce confounding bias due to pregnancy hemodynamics by measuring maternal PFOS and PFOA only during the 1st trimester, in keeping with its own assessment (highlighted above) as well as the recommendations of Steenland et al. (2018) and Dzierlenga et al. (2020). On a more extensive scale and as noted above, 3M recommends EPA conduct a meta-analysis of all studies, including those that met EPA's systematic review of *high quality* epidemiologic studies that measured maternal serum PFOS and PFOA concentrations only during the first trimester (to minimize pregnancy hemodynamic bias) in its modelling assessment on the clinical outcome of low birthweight which has not been shown to be an adverse health outcome associated with maternal PFOS or PFOA measurements determined in the individual epidemiologic studies that have been published to date.

Another consideration EPA failed to address is that GFR varies through the day and can be affected by age, sex, diet, timing of a meal, medication use, and other factors. eGFR is an approximation of actual kidney function, derived from regression equations that in some cases were developed on small numbers of subjects using broad assumptions (Stevens et al. 2008, Soares et al. 2009, Fesler and Mimran 2011). Therefore, it is well known that the accuracy of eGFR as an estimate of kidney function varies by person, and adjustment for eGFR therefore may not sufficiently account for individual-level kidney function.

Likewise EPA does not address the separate issue relating to control for confounding by gestational age or preterm birth. Although the appropriateness of adjusting for gestational age

has been debated (Wilcox et al. 2011), the majority of studies of PFAS and fetal growth adjusted for gestational age through statistical adjustment, standardization of fetal growth measures by gestational age, or restriction of analyses to full-term births, sometimes in secondary analyses. Several other studies, however, did not report any results adjusted for gestational age, thus failing to address concerns about confounding by this strong determinant of fetal growth. At a minimum, SAB should recommend that EPA discuss why felt it did not need to consider this issue.

A 2018 meta-analysis of 24 studies that EPA should review, co-authored by two of the three members of the C8 Science Panel, found no significant association between PFOA and birth weight after restricting the analysis to studies where PFOA was measured early in pregnancy or shortly before conception, when pregnancy-related changes in maternal GFR and plasma volume expansion (in women with otherwise healthy kidney function) would have little influence (Steenland et al. 2018b). By contrast, a significant inverse association was found in studies where blood sampling was conducted late in pregnancy, when the confounding impact of maternal GFR would be greater. Moreover, inclusion of a large study that used estimated instead of measured serum PFOA levels in Mid-Ohio Valley pregnant women (Savitz et al. 2012b) led to a statistically non-significant association in the combined analysis of all 24 studies. The authors concluded: "Present human evidence provides only modest support for decreased birthweight with increasing PFOA. Studies with a wide range of exposure, and studies with blood sampled early in pregnancy, showed little or no association of PFOA with birthweight. These are studies in which confounding and reverse causality would be of less concern" (Steenland et al. 2018b).

Similarly, SAB should encourage EPA to review Dzierlenga et al. (2020) where the authors conducted a meta-analysis on maternal serum PFOS concentrations and birth weight and their findings were consistent with the conclusion offered by Steenland et al. (2018) on maternal serum PFOA and birth weight. Dzierlenga et al. (2020) conducted a meta-analysis of 29 published studies and reported the random effects summary was −3.22 g/ng/mL PFOS (95% confidence interval [CI] = −5.11, −1.33). In a subgroup analysis stratified by when in pregnancy the PFOS concentration was measured, the summary for the "Early" group was −1.35 g/ng/mL PFOS (95% CI = −2.33, −0.37) and for the "Later" group was −7.17 g/ng/mL PFOS (95% CI = −10.93, −3.41). "Early" group included prepregnancy, first trimester, or first and second trimester; and "Later" group included second trimester, third trimester, second and third trimester combined, or cord blood). In a meta-regression model including a term for timing of blood draw, the intercept was slightly positive but essentially zero (0.59 g/ng/mL, 95% CI = −1.94, 3.11). Thus, the model indicated that when blood was drawn at the very beginning of pregnancy, there was no relation of birth weight to maternal serum PFOS. Dzierlenga et al. (2020) concluded the evidence was weakly or not supportive of an association between a reduction in birth weight and maternal serum PFOS concentrations.

The essential message from these meta-analyses indicates physiological aspects of pregnancy, including plasma volume expansion, its role in maternal GFR, and the timing when the maternal PFOS/PFOA measurements are made during pregnancy, are critical points to evaluate in the associations between birth weight and maternal serum PFOA and PFOS concentrations. Both Steenland et al. (2018) and Dzierlenga et al. (2020) concluded the least amount of confounding bias, as a consequence of pregnancy hemodynamics, would require the

examination of the association between birth weight and that of the maternal serum PFOS/PFOA measured early in the pregnancy.

Following the publication of the Steenland et al. (2018) meta-analysis, the C8 Science Panel and co-authors reviewed an additional 12 studies of PFOA and birthweight, and found that "[m]ore recent studies continued to generate mixed findings, some suggesting a reduced birthweight associated with elevated PFOA and others not finding evidence for such an effect" (Steenland et al. 2020). Again they cautioned that "[r]everse causality or confounding would be most likely to affect studies with low exposure contrasts," and that "studies with PFOA measurement later in pregnancy show stronger associations with birth weight than those with measurements earlier in pregnancy, consistent with the possibility that the overall association is distorted by the magnitude of plasma blood volume expansion and glomerular filtration rate" (Steenland et al. 2020). With respect to preterm birth, the authors stated that there were "few studies," and that "[w]hat studies do exist provide little indication of an adverse effect of PFOA" (Steenland et al. 2020).

C. EPA's Proposed Cancer Classification of PFOA is Not Supported by Human Epidemiological Evidence

SAB should recommend that EPA reevaluate its proposed cancer classification for PFOA. As discussed below, EPA does not adequately describe the rationale for its designation and the support identified is not adequate. EPA's failure to provide this information leaves the public in the dark on its analysis and unable to provide appropriately thorough input.

EPA reaches the conclusion that "PFOA is considered *Likely to Be Carcinogenic to Humans*" "based on the evidence of kidney and testicular cancer in humans," combined with tumor studies in rats (EPA Document No. 822D21001, p. 344). In its summary of the available epidemiologic evidence on PFOA and cancer, EPA notes that "one human epidemiological study identified since the 2016 assessment adds support to the previous evidence of an association between PFOA and kidney cancer (Shearer, 2021, 7161466). No new epidemiological studies on testicular cancer were identified" (EPA Document No. 822D21001, p. 315). Thus, EPA appears to have relied entirely on the results of Shearer et al. (2021) to advance the state of the epidemiologic evidence past its status in 2016, when EPA concluded that "*there is suggestive evidence of carcinogenic potential* of PFOA in humans" (EPA 822-R-16-003, p. 3-159; emphasis original).

Such heavy reliance on Shearer et al. (2021), however, is misplaced. Shearer et al. (2021) is a nested case-control study of 324 renal cell carcinoma cases and 324 matched controls identified from a cohort of approximately 148,000 U.S. adults aged 55–74 years participating in the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial. PFOA exposure was classified based on a single prediagnostic serum sample collected at study enrollment in 1993–2001, an average of 8.8 years (range: 2–18 years) prior to case diagnosis. Contrasts in PFOA levels in this study cohort were modest – comparing a top quartile of >7.3 μg/L PFOA to a lowest quartile of <4.0 μg/L PFOA - and substantially smaller than exposure contrasts in more highly exposed populations that showed no significant difference in kidney cancer risk.

Although Shearer et al. (2021) reported positive associates between PFOA and risk of renal cell carcinoma, the results are undermined by the study's reliance on PFAS exposure measured at a single point in time less than a decade prior to cancer diagnosis among cases; and the insufficient adjustment for confounding by key risk factors including smoking history (classified as never, former, or current), hypertension history (classified as no or yes), and body mass index (classified using standard cutoffs for underweight, normal weight, overweight, or obese and above).

In this matched case-control study, according to Shearer et al, the category cut points were assigned based on quartiles of serum concentrations of each PFAS among controls. By standard definition the odds ratio of the least exposed category (referent) is set at 1.0. However, there were only 47 cases in this reference group with the least exposure to PFOA (< 4.0 ng/mL). This distribution seems rather odd where there are 81 controls and only 47 cases in the referent group. One would expect more similar distribution among the least exposed. Neither Shearer et al. nor EPA commented on this referent group which becomes the main driver in the subsequent or calculations for the other 3 exposure categories.

Besides Shearer et al. (2021), most of the remaining body of scientific literature indicates no association between PFOA exposure and kidney cancer risk. No significant association or exposure-response trend was observed between PFOA exposure and kidney cancer mortality (Lundin et al. 2009, Raleigh et al. 2014) or incidence (Raleigh et al. 2014) among highly exposed workers at the 3M chemical plant in Cottage Grove, Minnesota. The initial study of workers at the DuPont chemical plant in Parkersburg, West Virginia, also found no significant association between PFOA exposure and kidney cancer mortality (Leonard et al. 2008). The only study of highly PFOA-exposed workers that found a positive association with kidney cancer was an updated cohort mortality study of DuPont plant employees (Steenland and Woskie 2012). Furthermore, there were no new or additional kidney cancer deaths identified in the study by Steenland and Woskie (2012) because the prior study by Leonard et al. (2008)[10] on the same population had already identified these 12 kidney cancer deaths by the year 2002.

EPA also did not mention that the second highest exposure category in Steenland and Woskie study had zero kidney cancer deaths (SMR = 0.0; 95% CI 0.0 – 1.48). Combining the upper two exposure categories, Raleigh et al. reported an HR for kidney cancer of 0.85 (95% CI 0.36 – 2.06). Steenland and Woskie did not report the combined upper two quartiles of exposure for an SMR but it can be readily calculated from Table 1 of the Steenland and Woskie study. There was a total of 9.4 expected deaths for all quartiles combined. These calculations can then be made for the 1st, 2nd, and 4th quartiles which resulted in approximately 0.9, 2.2, and 3.0 expected deaths which yields 3.3 expected deaths occurring in the 3rd quartile (compared to the 0 observed deaths). Therefore, combining the upper two quartiles in Steenland and Woskie, there were then 8 observed kidney cancer deaths and approximately 6.3 expected deaths (SMR = 1.27; 95% CI 0.39 – 1.76) for estimated cumulative exposure of PFOA >= 1500 ng/mL-years. Thus, there appears to be no substantial differences between estimates of the magnitude of risk between the upper two exposure categories (albeit different measurements of exposure) in Raleigh et al. study for kidney cancer incidence and Steenland and Woskie study for kidney cancer mortality.

[10] Leonard et al. 2008 Ann Epidemiol 18 15-22

A reasonable question for the EPA to have considered is why were there no observed kidney cancer deaths in the second highest exposure category in Steenland and Woskie. Was it chance or could there have been some degree of exposure misclassification? Given the fact there were 8 kidney cancer deaths in this 4th quartile, three of these deaths would have had to been misclassified from the 3rd quartile to make the SMR estimate for the 4th quartile not statistically significant.

Inconsistent findings were reported in studies of the Mid-Ohio Valley population where no significant association or exposure-response trend was observed between PFOA exposure and kidney cancer incidence in analyses restricted to workers or combining community members and workers (Barry et al. 2013). In addition, an apparent non-monotonic trend was found between estimated serum PFOA and kidney cancer incidence in a semi-ecologic geographic analysis (Vieira et al. 2013). Thus, among three occupational analyses (Raleigh et al. 2014; Barry et al. 2013; and Steenland and Woskie et al. 2012), which likely represent the highest exposed individuals based on overall reported biomonitoring data, only one analysis showed a statistically signfiicant associaton with kidney cancer. However, that association was not seen when the two highest exposure categoreies were used. And there remains the confusing possibility of overlapping of kidney cancer cases between Steenland and Woskie (2012)[11], Vieira et al. (2013)[12], and Barry et al. (2013). This was acknowledged by Steenland and Winquist (2021)[13] but they did not provide any insights as to the percentage. And the Shearer et al. (2021) single serum PFOA concentrations measured at general populaton levels are inconsistent with the other 4 studies. Even though an excess of kidney cancer incidence (which, unlike mortality, is not influenced by non-causal prognostic factors) was found among residents of Ronneby, Sweden, who had elevated drinking water exposure to primary to PFOS and PFHxS, and to a much less degree of PFOA, however, this was not based on measured serum PFOA levels amongst those who were diagnosed with kidney cancer in this timeframe study by Li et al. (2022).

Taken together, epidemiological findings on PFOA exposure and kidney cancer are inconsistent: notably, no excess risk was detected among highly exposed workers in several studies (Leonard et al. 2008, Lundin et al. 2009, Barry et al. 2013, Raleigh et al. 2014). The positive association in Shearer et al. (2021) is therefore unexpected, especially given that the study population consisted of adults with background-level exposure to PFOA (CDC 2021), orders of magnitude below that among occupationally exposed workers. Moreover, several established risk factors for kidney cancer, such as cigarette smoking, overweight/obesity, hypertension, and chronic kidney disease, were not controlled for in the Mid-Ohio Valley/Parkersburg studies, and several studies classified PFOA exposure imprecisely, thereby limiting the ability to draw firm causal conclusions based on these results.

In light of the methodological limitations of Shearer et al. (2021), the inconsistent findings across the epidemiological literature as a whole, and the biological implausibility of an effect of background PFOA exposure but not high-level occupational PFOA exposure on kidney cancer, up-classification of the potential human carcinogenicity of PFOA from “suggestive” to “likely” is not scientifically justified.

[11] Steenland and Woskie 2012 Am J Epidemiol 176 909-917
[12] Vieira et al. 2013 Environ Health Perspect 121 318-323
[13] Steenland and Winquist 2021 Environ Res 194 110690

D. The Proposed Cancer Classification of PFOA is Not Supported by Animal Evidence

SAB should recommend that EPA undertake a more in-depth weight of evidence analysis for carcinogenicity given the lack of concordance between human epidemiological data and the animal carcinogenicity studies for PFOA and questions about relevance of the primarily benign neoplasms identified in the animal studies. EPA concluded that PFOA is *Likely to Be Carcinogenic to Humans* based on evidence of kidney and testicular cancer in humans and testicular Leydig cell tumors (LCTs), pancreatic acinar cell tumors (PACTs), and hepatocellular adenomas in rats. This conclusion is noteworthy both because 1) the three available rat carcinogenicity studies have identified tumor types of questionable relevance to humans and that, by and large, do not progress to carcinomas despite lifetime exposures; and 2) evidence for the tumors with presumptive evidence in humans is not replicated in the animal toxicology studies (LCT are rarely observed in the category of human testicular cancer as well as an absence of kidney tumors in rats related to PFOA treatment).

The three lifetime exposure carcinogenicity studies for PFOA (Biegel et al., 2001; Butenhoff, Kennedy, et al., 2012; NTP, 2020) between them identified three types of neoplasms, LCT, PACT, and hepatocellular, primarily in males and almost exclusively benign adenomas. In the first two studies there was not a statistically significant increase in malignant carcinomas in any of these tissues (liver, testes, pancreas) in rats fed diets with 30 ppm (Butenhoff, Kennedy, et al., 2012) or 300 ppm ammonium perfluorooctanoate (AFPO; the ammonium salt of PFOA) (Biegel et al., 2001; Butenhoff, Kennedy, et al., 2012). In fact, the only carcinoma of any type in these tissues reported by Biegel et al. (2001) was a pancreatic acinar cell tumor in a single animal; the statistically significant increase in liver, Leydig cell, and pancreatic acinar cell tumor incidence in this study was wholly attributable to an increase in benign adenomas. Butenhoff et al. (2012) did report liver carcinomas in 5 of 50 male rats fed 300 ppm AFPO, but this was not statistically different than the 3 of 49 animals in the control group with liver carcinomas; liver tumor incidence, benign or malignant, was not increased in any dose for males or females in Butenhoff et al. (2012). Butenhoff et al. (2012) also reported that a pathology review of pancreatic tissues conducted after the original study report using updated diagnostic criteria did identify a slight increase in acinar cell hyperplasia in the 300 ppm dose group, but not adenoma or carcinoma.

The more recent study (NTP, 2020) included two lifetime carcinogenicity studies. In Study 1, time-mated female Hsd:Sprague Dawley® SD® rats were fed diets with 0, 150, or 300 ppm during gestation and lactation, then F1 males were fed diets with 0, 150, or 300 ppm, resulting in perinatal/postweaning exposures of 0/0, 0/150, 0/300, 150/150, and 300/300. Postweaning females were provided diets with a higher dose level (0, 300, or 1000 ppm) because of the faster PFOA excretion rate in female rats compared to males. Due to unanticipated toxicity in male rats, Study 1 was discontinued at week 21 for males and a second study (Study 2) evaluating only males using only perinatal dose levels of 0 and 300 ppm and lower postweaning dose levels (0, 20, 40, and 80 ppm). Therefore, tumor results for females are from Study 1 and for males from Study 2.

There was a statistically significant increase in hepatocellular adenoma 0/40, 0/80, and 300/80 ppm, but not carcinoma in male rats. The rate of combined adenoma or carcinoma was also increased at these dose levels, but that was predominantly driven by adenomas. In female rats, there was not a statistically significant increase in hepatocellular adenoma, carcinoma, or combined adenoma or carcinoma, at any dose up to the high dose of 300/1000 ppm. A similar pattern occurred with PACT, wherein males were more sensitive and neither sex had an increased rate of adenocarcinoma. Male rats had an increased rate of pancreatic acinar cell adenoma at all dose levels, though not clearly demonstrating a dose-response relationship, but not pancreatic adenocarcinomas at any dose. Females had no statistically significant increase in adenomas, carcinomas, or combined adenomas or carcinomas at any dose. Unlike Biegel et al. (2001) and Butenhoff et al. (2012), NTP (2020) did not report an increase in Leydig cell adenomas at any dose. Additionally, it is worth noting, these three bioassays used different rat stocks for the evaluation. Sprague Dawley rats are outbred in that they are characterized by heterozygosity. Therefore, it is inappropriate to consider outbred rat "stocks" to be genetically distinct rat "strains." The rat stock used by the NTP was Hsd:Sprague Dawley® SD®; and the rat stocks used by Butenhoff et al. and Biegel et al. were Crl:COBS CD(SD)BR and Crl:CD BR (CD), respectively. 3M has consulted with two expert laboratory veterinarians at the Charles River Laboratories (which has the largest animal breeding programs in the world) for the technical definition between a rat stock vs. strain. They validated our concern that it is scientifically inappropriate to consider different rat "stocks" as equivalent to different rat "strains". Therefore, these independent bioassays were conducted spanning across approximately 40 years and they collectively demonstrated consistent neoplastic findings in Sprague Dawley rats with chronic dietary exposure to PFOA. The newly released study by the NTP did *not* report any additional neoplastic findings in the rats with chronic dietary exposure to PFOA compared to the previous studies. In addition, there was no early age of onset associated with PFOA exposures, as the NTP study confirmed that additional *in utero* exposure to PFOA did *not* potentiate the neoplastic response.

Of note, EPA reported increased rates of the three tumor types in the PFOA MCLG document, focusing almost exclusively on positive results, and without providing clear delineation of results for benign adenomas vs. malignant carcinomas. However, this approach misses the opportunity to fully evaluate consistency across studies, where the negative results are equally as important as the positive results, and the level of evidence for progression to a carcinoma. The simple presentation in the table below demonstrates a lack of consistency or progression that requires additional discussion to fully the evaluate the weight of evidence.

Statistically significant increased rates of adenomas and carcinomas reported in animal carcinogenicity studies

	Leydig Cell		Pancreatic Acinar Cell		Hepatocellular	
	Adenoma	Carcinoma	Adenoma	Carcinoma	Adenoma	Carcinoma
Biegel et al (2001)	Yes	No	Yes	No	Yes	No
Butenhoff et al. (2012)	Yes	No	No	No	No	No
NTP (2020)	No	No	Yes	No	Yes	No

Adenomas are benign growths arising from glandular epithelial tissue. Although adenomas are not cancerous, they may over time become malignant tumors and as such are considered precancerous and potentially adverse. However, taken in the context of studies in which adenomas did not progress to carcinomas in rats fed very high doses of PFOA over a lifetime, it is apparent that PFOA demonstrated little if any carcinogenic potential. Public health agencies do consider benign tumors in evaluating carcinogenic potential, but sufficient evidence of carcinogenicity requires inducement of malignant tumors as well (EPA, 2005; NTP, 2015). For example, NTP (2015) states that "Sufficient evidence of carcinogenicity from studies in experimental animals" requires "[a]n increased incidence of malignant and/or a combination of malignant and benign tumors." NTP (2015) states specifically that "[t]he spectrum of neoplastic response, from pre-neoplastic lesions and benign tumors to malignant neoplasms of a specific tumor type is relevant for the evaluation of whether increases in benign tumors are likely to progress to malignancy." U.S. EPA (2005) states: "Observation of only benign neoplasia may or may not have significance for evaluation under these cancer guidelines. Benign tumors that are not observed to progress to malignancy are assessed on a case-by-case basis." The PFOA Draft MCLG Document provided no context or nuance regarding the observation that statistically significant increases in tumors, when they occurred, were because of benign tumors, nor does it address the fact that these data do not meet the stated definition of "*Sufficient evidence of carcinogenicity*" described by NTP.

The PFOA Draft MCLG Document provides minimal discussion of potential mechanisms of carcinogenicity as it relates to the human relevance of the three tumor types identified in two of the three animal carcinogenicity studies. Evidence indicates that the hepatocellular tumors, LCT, and PACT are linked to a common mode of action involving PPARα agonism, a mode of action with limited relevance to humans (Biegel et al., 2001; Corton et al., 2018). The only comment on this provided in the Draft MCLG Approach is that IARC "concluded that there is moderate evidence for many potential mechanisms for PFOA-induced toxicity (including PPARα)." In contrast, the (EPA, 2016) assessment highlighted a PPARα-mediated mode of action as likely for rat liver tumors and discussed evidence for a PPARα-mediated mode of action for both LCTs and PACTs. EPA concluded: "There are some data that provide support for the hypothesis that the PPARα agonism MOA is wholly or partially linked to each of the observed tumor types. The data support a PPARα MOA for the liver tumors and thus are indicative of lack of relevance to humans. PPARα activation also could play a role in the other tumor types observed, but more data to support intermediate steps in the proposed MOAs are needed." NTP (2020) also highlights the uncertain relevance of this MOA for humans, stating that the increased rate of hepatocellular neoplasms "could be related at least in part to the PPARα activity, which reviews of studies suggest that the human liver is not as sensitive to PPARα activity as rodents."

The PFOA Draft MCLG Document also does not address the critical point that LCTs are not biologically relevant for humans (Steinbach T.J. et al., 2015). There are important differences between rats and humans in hormonal response and physiology that demonstrate the lack of relevance of rat LCT to humans, described in detail by Steinbach et al. (2015).

The issues associated with the significance and relevance of the animal toxicology findings require more detailed evaluation in the PFOA Draft MCLG Document in order to provide a transparent weight of evidence evaluation. As stated in EPA (2005) cancer assessment guidelines:

> "In borderline cases, the narrative explains the case for choosing one descriptor and discusses the arguments for considering but not choosing another. For example, between "suggestive" and "likely" or between "suggestive" and "inadequate," the explanation clearly communicates the information needed to consider appropriately the agent's carcinogenic potential in subsequent decisions."

A narrative statement clearly communicating the conclusion about cancer classification, according to the guidelines, is a critical aspect of any cancer assessment. The importance is further accentuated because the only new substantive studies available since the 2016 assessment are one human epidemiologic study (Shearer et al., 2021; discussed above) and one animal toxicology study (NTP 2020) that is essentially consistent with the two previous studies (Biegel et al, 2001; Butenhoff et al, 2012) showing statistically significant increases in benign adenomas of 2 of the 3 types (LCT, PACT, hepatocellular, for which human relevance has been debated) identified in one or both of the previous studies, but not increases in carcinomas despite lifetime exposures. SAB should recommend that EPA reevaluate its cancer classification and more clearly articulate its conclusions, identifying the evidentiary support, and consider whether a lower classification is better supported by the scientific literature.

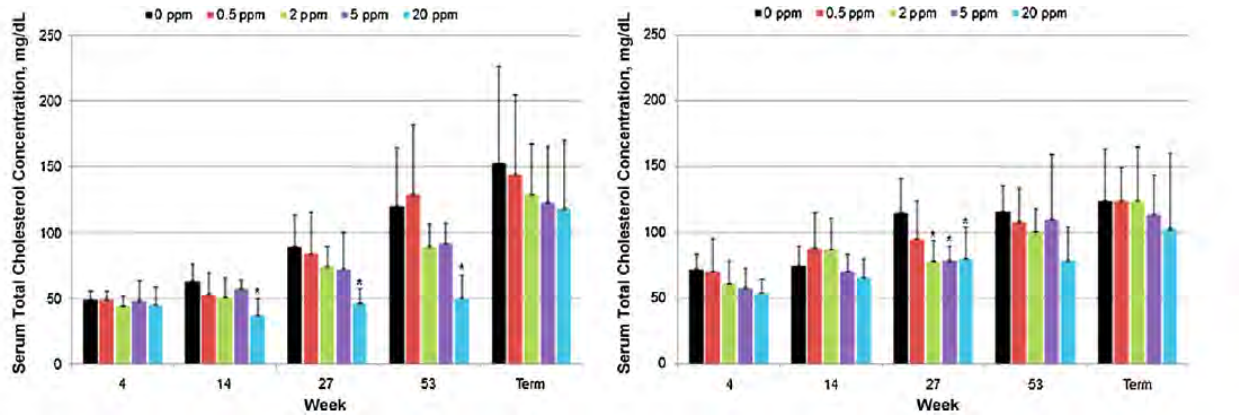
E. Non-Cancer Effects: Cardiovascular Disease and Animal Studies

Animal toxicology studies do not support a relationship between PFAS exposure and elevated serum lipids. In the Draft MCLG Document for PFOS, EPA concluded that evidence from human studies is consistent with a positive association between PFOS exposure and both total and LDL cholesterol. EPA's conclusions regarding PFOA were similar, although noting less consistency in the response. EPA additionally concluded there was a positive relationship for PFOA and serum triglycerides. In all cases, EPA noted that the relationships were population-specific, with some serum lipid markers apparently affected in some sub-populations but not others.

EPA ultimately selected increased serum total cholesterol from the Dong et al., 2019 cross-sectional study as the only outcome/study for deriving PODs for both PFOS and PFOA. Dong et al., 2019, identified as a *medium* confidence study by EPA, analyzed U.S. National Health and Nutrition Examination Survey (NHANES) data to analyze temporal trends in PFAS biomonitoring concentrations and associations between cholesterol levels and PFAS exposure. Dong et at., 2019 reported small, positive associations between PFOS/PFOA and total cholesterol levels in their cross-sectional study.

In terms of the overall weight of evidence, the animal toxicology evidence cited in the Draft MCLG Documents is not in concordance with the human data. Rather, it demonstrates the opposite effect if anything. EPA documents that when serum lipids were affected at all in rat studies, they were generally decreased. For example, in the chronic dietary toxicity and

carcinogenicity studies with PFOS in Sprague Dawley rats, serum total cholesterol was decreased with PFOS exposure, especially in males (Butenhoff, Chang, et al., 2012; see figure below). This negative association with serum cholesterol is consistent with data from other studies with PFOS (Bijland et al., 2011) and in some studies with PFOA (NTP, 2020). Furthermore, a negative associate between PFOS exposure and total cholesterol and other serum lipids has also been reported in non-human primates (Goldenthal et al., 1979; Seacat et al., 2002).



Mean serum total cholesterol was reduced in male rats (left panel) fed 20 ppm PFOS compared to controls (statistically significantly on Weeks 14, 27, and 53). There were statistically significant reductions in mean serum cholesterol occurred in female rats (right panel) on Week 27 in the 2, 5, and 20 ppm dose groups. Although not statistically significant, cholesterol appeared lower in 20 ppm dose group females on Week 53 and at terminal sacrifice. (*statistically significant compared to the time-matched controls, $p \leq 0.05$) (Butenhoff, Chang, et al., 2012)

Rather than explore the significance of not just inconsistent, but apparently opposite effects (increased total cholesterol in humans, decreased in rats) on the overall weight of evidence, EPA cites both as "a disruption in lipid metabolism" and dismisses the discrepancy as due to "known differences between the serum lipid composition in human and animals" and notes only that "biological significance of the decrease in various serum lipid levels observed in these animal models regardless of species, sex, or exposure paradigm is unclear."

Instead of dismissing the animal data because of its apparent incongruity with the conclusions EPA draws from the epidemiologic data, the Draft MCLG Documents should fully assess both the animal and human data (as well as relevant mechanistic data that might explain such differences) with a detailed, transparent, and systematic weight of evidence review.

II. MIXTURES FRAMEWORK

In EPA's Mixtures Framework[14], the Agency presents methods for risk assessments based on the assumption of dose additivity. These methods include 1) a screening level approach involving summing of hazard indices (HI approach) for all PFAS in a mixture using reference doses (RfDs), regardless of similarity in toxicity endpoint; 2) refinement of the HI approach by grouping and then summing HIs based on toxicity to the same target organ (TOSHI approach); 3) a method using relative potency factors (RPF approach) that incorporates a factor representing the relative potency of individual compounds at inducing a given key effect required to induce the health outcome relative to the potency of an index, data rich chemical; and 4) with limited data, EPA introduces the potential use of a method for developing mixture-based POD using a dose addition mixture benchmark dose modelling (BMD approach).

To commence the mixtures analysis, Step 1 (p.36), Identification of RfDs, EPA proposes four sources of information for identification of a chronic oral RfDs: "off the shelf" RfDs (including MRLs) from federal sources, state and other sources, then where these "off the shelf" assessments are not available, EPA proposes that the "user" find other hazard effect and dose response data for development of reference values ("RfVs").[15] Finally, where previous, traditional sources are not available, it proposes New Approach Methodologies ("NAM").

In the charge questions posed to the SAB, the PFAS Panel was asked to comment on the appropriateness of the proposed approach for a component-based mixture evaluation of PFAS assuming dose additivity, the suitability of the illustrated BMD approach for development of a relative potency factor (RFP), and the fitness of other implied assumptions and factors presented in the Mixtures Framework. 3M recommends that the SAB respond to this charge by noting that frequently the draft Mixtures Framework proposed approaches are at odds with the EPA guidance on mixtures (1986 and 2000)[16], and are otherwise inappropriate or inadequately described. SAB should further recommend that EPA revise the Mixtures Framework to rectify these concerns.

A. Identification of Reference Toxicity Values

For the first two source categories for toxicity values, the draft Framework refers to "off the shelf" assessments to provide toxicity values, e.g., chronic oral RfDs. While the first source is traditional, EPA assessments or other Federal level assessments that have mostly undergone extensive peer review and public comment, under "PFAS 1" a second set of sources for toxicity

[14] EPA, Combined PFAS framework Final 11.5.21_Edited_Formatted_11.9.21 508.pdf

[15] Page 35 of the Framework states: "Many states and others (e.g., international entities) are addressing rapidly evolving PFAS issues under their respective purviews, including the development of toxicological assessment documents. Although there is overlap in the landscape of PFAS evaluated (or currently being evaluated) across federal, state, and international agencies, at the state/international level, there may be assessment values available for a broader array of PFAS in the context of this framework, these will be collectively referred to as "PFAS 1"[..]."

[16] EPA (Environmental Protection Agency). 1986. Guidelines for the Health Risk Assessment of Chemical Mixtures. EPA/630/R-98/002. EPA, Risk Assessment Forum, Washington, DC. https://www.epa.gov/risk/guidelines-health-risk-assessment-chemical-mixtures.
EPA (Environmental Protection Agency). Supplementary Guidance for Conducting Health Risk Assessment of Chemical Mixtures. EPA/630/R-00/002. EPA, Risk Assessment Forum, Washington, DC. August 2000.

values is identified. In a departure from traditional guidance, EPA calls for reliance on 'state or other sources' for assessments. These later sources are observed to provide widely varying toxicity guidance levels that suffer not only from inconsistency, which pose the problem of whether to select the highest, lowest or some median value, but also from high degree of variability in quality, peer review, use of judgmental uncertainty choices, and completeness of study considerations. In a component mixture assessment, not only could outcomes be inconsistent, but a poorly supported, atypically low, outlier reference value (s) could dominate the final health risk assessment outcome. EPA needs to reconsider these recommendations. The lack of data on any particular substance should not lead the risk assessor to provide what could be inappropriate substitutes and unfounded outcomes.

The next source of toxicity values is even more problematic. In the absence of "off the shelf" assessments, EPA guides the mixtures assessor to "study hazard effect and dose-response data" (PFAS -2) to derive reference values. While EPA directed attention to its methods and sought consultation with experts in the field, no adherence to any scientific process is described in detail or assured. Clearly, this could result in derivation of reference values that have not undergone formal peer review and public comment, bringing into question the quality of the toxicity value used in the component HI.

In both PFAS-1 and -2 risk assessment outcomes would be expected to vary enormously across various assessments depending on the choices of the particular assessor. The use of external or assessor-derived values allows for potential cherry-picking and the current discussion in the Framework does not provide guard rails to prohibit bias in the selection of studies to incorporate. This guidance is not reliable and should be reconsidered by the Agency.

For the selection of PODs that are used in the RFP approach, both the Mixtures Framework and the Draft MCLG Documents err on the side of extreme caution, by guiding users to the lowest possible POD without regard for the sufficiency of evidence that the endpoint chosen poses a relevant human health risk. Whether a health threat exists – the hazard assessment - regardless of the dose response characteristics is fundamental to an unbiased and transparent health risk assessment. Every POD derived or used should be accompanied by a hazard identification/weight of evidence for the effect end/disease point, which spells out the several lines of evidence including human, animal, and mechanistic, to assign greater weight to evidence where all lines converge, and lesser weight to weak or suggestive evidence where the lines of evidence are contradictory or missing. As recommended in the 2005 guidelines, quantitation generally is not performed where the evidence is too weak.

The process, as proposed, could lead to selection of a study for a particular component in a PFAS mixture that dominates the mixtures perceived risk, an issue raised in EPA's Supplementary Guidance for Conducting Health Risk Assessment of Chemical Mixtures, August 2000 ("2000 Mixtures Guidance"):

> "The other concern with a large number of chemicals in the mixture is that one poorly studied chemical may dominate the response estimate. An excessive response estimate could arise from improper statistical analysis or toxicological procedures employing highly sensitive animal species." p.124

The 2000 Mixtures Guidance further provides the following cautionary remarks:

> "The component-based procedures discussed earlier for dose-response assessment and risk characterization are intended only for simple mixtures of a dozen or so chemicals. The uncertainties and biases for even a small number of chemical components can be substantial. Component-based methods are particularly susceptible to misinterpretation because the listing of chemical components in a mixture is often misconstrued as implying a detailed understanding of the mixture toxicity and, by inference, the estimated mixture risk. The risk characterization must include a discussion of what is known as well as what is missing or poorly understood in order to convey a clear sense of quality and confidence in the risk assessment." p.76

And,

> "Whenever an assessment is based on component toxicity values, the risk characterization must discuss the quality of the individual chemical estimates that are used." p.79

And,

> "[] an evaluation of the data may lead the user to decide that only a qualitative analysis should be performed. This generally occurs in cases where data quality is poor, inadequate quantitative data are available, data on a similar mixture cannot be classified as "sufficiently similar" to the mixture of concern, exposures cannot be characterized with confidence, or method-specific assumptions about the toxicologic action of the mixture or of its components cannot be met." p.xiv/xv

The Mixtures Framework does not acknowledge any of this guidance. At a minimum, this guidance provides scientific justifications that should be addressed. EPA does not recognize the recommended application to simple mixtures, implications of the lack of an MOA to imply confidence in common toxicity endpoints, requirement for full risk characterization, or consideration of using a qualitative analysis where data quality is poor. EPA resorted to methods for deriving toxicity values based on relative potency approaches without presenting sufficient and complete considerations of weight of evidence, which is not scientifically defensible. In doing so, EPA finds toxicity without providing evidence of a common mechanism of action for the chosen target health effect. Instead, for quantification of relative toxicity values, EPA proposes using PODs from disparate sources (as discussed above) and novel approaches that can bypass natural body defenses (see discussion of NAMs below). The SAB should request the EPA consider these points and the guidance noted above in its proposed procedures for use of "off the shelf" and assessor derived reference/toxicity values.

Where previous, traditional sources of toxicity values are not available, EPA next proposes a "PFAS-3," the development of New Approach Methodologies (NAM) based reference values ("RfVs"). Use of these methods for direct application in deriving a toxicity value is superficial, premature, and lacks precedent. The NAM are outside the realm of standard

practice for chemicals that have not had MOA assessments. Indeed, NAM could potentially include: 1) *in vivo* study types not traditionally considered for risk assessment but rather used as supporting evidence for elucidating mechanisms of action and the relevance of findings in animal studies for humans (e.g., injection studies); 2) *in vitro* models, which bypass normal body defenses and certainly bypass MOA considerations such as understanding common MIEs and KEs; or 3) *in silico* approaches that rely on predictive modeling. This search for a potential common endpoint for PFAS compounds is improper given that these compounds demonstrably have clear differences in pathophysiological effects and common MIE and KEs have not been identified. The proposed application of NAM to reach regulatory decisions is entirely novel and EPA has no precedent for applying these methods in a Tiered approach.

The Mixtures Framework examples of chemical classes where dose additivity and/or relative potency have been used are inapplicable to the circumstances here and do not support EPA's novel action. In most or all of the examples, the chemicals in the class have a shared molecular initiating event ("MIE") (e.g., dioxins and induction of the aryl hydrocarbon receptor) and/or converge on a common KE (e.g., pyrethroids and altered neuronal excitability) in an adverse outcome pathway leading to a shared adverse outcome. EPA's Mixtures Framework states, "in the absence of detailed molecular mechanisms for most PFAS, it is considered a reasonable health-protective assumption that PFAS which can be demonstrated to share one or more KEs [key events] or adverse outcomes will act with toxicological similarity to produce dose-additive effects from co-exposure." Mixtures Framework at p.23. But without some evidence, EPA cannot simply assume a shared key event to justify using dose-additivity. Both the 1986 and 2000 Mixtures Guidance documents are founded on sound scientific principles that emphasize the role of mechanistic understanding when deciding to combine risks for component mixtures. Contrary to EPA's implied suggestion, these examples do not support the concept that evidence is only needed that individual chemicals in the class affect the same organ system or clear health outcome without evidence of a shared MIE and/or KE.

In section 3.4 of the Mixtures Framework document, EPA discusses evidence for shared MIEs and/or KEs for various outcomes, but the discussion lacks a systematic or critical evaluation of the scope and relevance of these data. For example, the Mixtures Framework discusses *in vitro* studies of activation of peroxisome proliferator activated receptor alpha (PPARα) as evidence of a shared MIE but does not provide discussion of the relevance of these data in the context of demonstrated species-specific differences in PPARα and responses related PPARα activation. This lack of context is compounded by the lack of meaningful discussion of this issue in the Draft MCLG Documents. Other potential MIE (activation of constitutive androstane receptor) are introduced briefly, and only in the context of studies of PFOA and PFOS. The Mixtures Framework mentions several outcomes as examples of shared evidence of toxicity, but it is difficult to discern from the discussion which outcomes EPA considers as KEs, which as markers/precursors, and which as apical endpoints. The discussion is cursory and does not include the presentation and full analysis of any one adverse outcome pathway (AOP). This is a critical aspect and should be a precondition for application of an assumption for shared MOA and use of an RPF approach.

The NAM approaches included are not practical, transparent, descriptive, or consistent with current EPA practice and guidance. Rather, they invite nearly any *in vitro* or *in silico* study to be incorporated without the benefit of peer and/or expert review (such as SAB) or public

comment. Indeed, the Mixtures Framework appears to focus far more on finding a way to arrive at the lowest POD and RfD rather than first fully understanding and presenting a full assessment of the available data. SAB should recommend that EPA revise the framework to fully explain its analysis in a revised document and then provide stakeholders an adequate opportunity to review and comment.

B. Assumption of Dose Additivity

EPA's Mixtures Framework does not provide a detailed, transparent, or clear discussion of why the assumption of dose additivity that is the basis for the methods and approaches that follow are appropriate for PFAS. Rather, the rationale seems to be "PFAS are an emerging chemical class of concern" and "MOA data are limited or not available for many PFAS." Instead, the Framework needs to detail the data available that support OR contraindicate a similar MOA, and detail what critical information is necessary to fill the admittedly large data gaps; a roadmap for eventually determining whether an assumption of dose additivity is appropriate.

Notably, the quote from the 2000 Mixtures Guidance used in the Mixtures Framework and Charge to justify bypassing MOA comes from a table in EPA 2000 Section 2.6.1.2 *User Fact Sheet: Relative Potency Factors,* under the heading "Assumptions.".[17] However, neither the Mixtures Framework nor the Charge include the full quote, which is:

> "Based on dose addition which carries with it assumptions of same mode of action and similarly shaped dose-response curves across the components. The common mode-of-action assumption can be met using a surrogate of toxicological similarity, but for specific conditions (endpoint, route, duration)" p.29

Similarly stressing MOA, the 2000 Mixtures Guidance also notes,

> "The minimum data needed for development of an RPF approach include: (1) a known or suspected common mode of action shared by the class of compounds; (2) a quantitative dose-response assessment for the index compound; and (3) pertinent scientific data that allow the components to be meaningfully compared to the index compound in terms of relative toxicity." p.109

And,

> "Included in the definition of the class should be the understanding of the common mode of action leading to the observed toxicologic effects, the chemical similarity of the compounds, and the identification of the spectrum of toxicologic impacts shared by the class." p.110.

[17] It should also be noted that the Framework or Charge do not mention the different wording is used in the table related to Hazard index (HI) (section 2.6.1.1. User Fact Sheet: Hazard Index): "Applies dose addition, which carries with it assumptions of same mode of action and similarly shaped dose-response curves across the components. The "common mode-of-action" assumption can be met by using a surrogate of same target organ."

EPA's Mixtures Framework does not clearly address the criterion of "similarly shaped dose response curves." Whereas the 2000 Mixtures guidance notes,

> "A separate HI should be calculated for each toxic effect of concern (U.S. EPA, 1986, 1989a). The target organs to be addressed by the HIs should be decided for each particular mixture assessment. The assessor should compare the dose-response curves for the different toxic effects with the estimated exposure levels (and routes) to ensure that those effects most relevant to the environmental exposure are addressed. When certain toxic effects are known to occur, but at much higher exposure levels than those being assessed, then the HI for those effects may not need to be evaluated, but an explanatory note should be included in the discussion of assumptions and uncertainties for the mixture assessment." p,86

EPA has not complied with this portion of the 2000 Mixtures guidance.

Additionally, "surrogate of toxicological similarity, but for specific conditions (endpoint, route, duration)" has greater meaning than just showing that certain PFAS in drinking water can be grouped by health endpoint regardless of MOA. The 2000 Mixtures Guidance notes that a "'common mode-of-action' assumption can be met by using a surrogate of same target organ" for the hazard index approach (Figure 2.6.1.1, EPA 2020). However, the bar for dose additivity is higher for the RPF approach (Figure 2.6.2.2, EPA 2020). The assumption for use of an RPF approach must be based on dose addition which carries with it assumptions of same mode of action and similarly shaped dose-response curves across the components. The "common mode-of-action" assumption can be met using a surrogate of toxicologic similarity, but for specific conditions (endpoint, route, duration). Although the 2000 Mixtures guidance is not specific about what would constitute a surrogate of toxicologic similarity to support the RPF method, by its contrast to the hazard index approach it is clearly more than just effects on the same target organ endpoint. At a minimum, the Mixtures Framework needs to fully explore the level of evidence needed and describe why PFAS do or do not meet adequate criteria to fulfill a reasonable assumption for a common MOA. At present, the EPA must consider that this MOA information is largely lacking and, further, that differences in MOA may be indicated by carefully considering the data that are available.

Although the Mixtures Framework states that MOA is 'optimal", EPA justifies not using MOA because "MOA data are limited or not available for many PFAS"[18] and then presents its approaches "in the interim." EPA's 2000 Mixtures Guidance explicitly states that a common MOA as well as similarly shaped dose-response curves are necessary for the assumption of dose additivity:

> "4.4.2.5.3. Assess mode of action. It is necessary to describe the mode of action of the class of compounds underlying the health effects for which the RPF was developed. A common mode of action for the class is the basis for the assumption of dose additivity. However, in some cases the class may be linked by common effect with only suggestive or indirect information concerning the underlying mode of action. The description of the

[18] The mention of chemical classes for which MOA has been used to support dose additivity does not advance the argument that MOA can be side-stepped for PFAS.

> RPF must answer the question, "to what degree do the scientific data support the assumption of a common mode of action?" p.113

Furthermore, EPA's 2000 Mixtures Guidance notes,

> "For example, Feron et al. (1995) discuss studies where even at the same target organ (the nose), differences in mode of action led to other than dose additive response. Dose-additive models may be an adequate default procedure for chemicals affecting the same target organ but may not be the most biologically plausible approach if the compounds do not have the same mode of toxicologic action." p.66

The Mixtures Framework does not appear to provide an answer to the basic question, "to what degree do the scientific data support the assumption of a common mode of action?" SAB's recommendations to EPA should request that the Agency answer this and allow the public to review EPA's assumptions.

C. BMD Approaches

1. Equation for mixture BMD

EPA uses an equation to calculate the mixture BMD (Equation 4-5 in EPA Document No. 822-21-003, p. 54), which it states is similar to the Berenbaum equation (as cited in the 2000 Mixtures Guidance). When 3M reviewed the Berenbaum equation in the 2000 Mixtures Guidance, Equation 4-5 is not the same, and EPA gives no explanation as to how it modified this Berenbaum equation and derived the equation it is using. (See comparison of equations below). The Berenbaum equation referenced in the EPA 2000 guidance on mixtures is on the top. Equation 4-5 that EPA is using in the current mixtures draft is shown on the bottom. At a minimum, the SAB should recommend the Mixtures Framework clarify the equation use and the changes made from prior guidance. Peer review of this work cannot be completed without further clarification and assessment from the Agency.

$$1 = d_1/D_1 + d_2/D_2$$ where: d_i = dose of i^{th} chemical, and D_i = dose of i^{th} chemical that produce the response of 0.05.
$$t_{add} = \left(\sum_{i=1}^{n} \frac{a_i}{BMD_i}\right)^{-1}$$
In the bottom equation, t_{add} is the mixture dose (I in the top equation) in mg/kg/day, a_i are the fixed proportions of the component PFAS in the mixture, and BMD_i is the *i*th chemical BMD value.

2. Precedent for BMD approach

In Section 1.5 of the EPA Mixtures Framework, EPA outlines) various state, national, and international approaches to address PFAS mixtures. 3M notes there is nothing stated here about this BMD approach, so it would appear, based on information presented by EPA, that such an approach is unprecedented. Time limitations to comment on the EPA Mixtures Framework prevent further research to verify this point, but SAB should recommend that EPA provide a clearer understanding of other applications of the BMD approach, if any.

What is more, the 2000 Mixtures Guidance document mentions BMD analyses, but does not appear to use them in the way that EPA is attempting to use it in the Mixtures Framework. The 2000 Mixtures Guidance discusses use of the BMD approach in the context of applying the BMD to the hazard index, which is considered a separate approach in the Mixtures Framework. The BMD approach in the current mixtures draft document is different and it is not clear how it relates to prior EPA guidance. The SAB should provide comments on this and whether the current approach has been adequately explained given this departure from precedent.

3. EPA's examples of the mixture BMD approach

EPA's examples of the mixture BMD approach are hypothetical and it is unclear how practical they could be in the real world. In these examples, EPA did not even use measured concentration data (although there is a section in Section 1.3 of the Mixtures Framework on the occurrence of PFAS mixtures in the environment, and EPA apparently monitors this). Tables 4-15 and 4-16 of the Mixtures Framework do not identify which PFAS are in the mixture; just PFAS 1, PFAS 2, PFAS 3, or PFAS 4. It is clear that the examples are arbitrary and thus, it is not known how this method would work in practice. The Agency should use a real-world mixture of PFAS to address at least some of the substantial uncertainty in its approach.

In Table 4-15 of the Mixtures Framework, EPA presents its first hypothetical water sample, and BMD values for 3 endpoints (liver weight, reduced pup body weight, and reduced thyroid hormone concentrations) that apparently came from animal studies. EPA does not state what studies these were, which PFAS compound these endpoints came from, and it does not present the BMD analyses (or cite to where they may have performed these). At a minimum, the current assessment is incomplete and lacks clarity.

Also in Table 4-15 of the Mixtures Framework, EPA states that the liver endpoint produced the lowest mixture BMD, so would be the most sensitive effect domain for this mixture; below the table, EPA illustrates its use of Berenbaum equation 4-5 for this liver endpoint. EPA used the liver BMDs for the denominator, but does not explain what was done with the other endpoints for this hypothetical scenario and how those endpoints were incorporated. The SAB should recommend that EPA clarify how it derived the BMD values in their examples and explain its use of the dose-additivity equation.

Table 4-15. Mixture BMD Approach: Hypothetical Water Sample 1

	Measured Water Concentration (ng/L)	Mixing Ratio (Proportion)	Thyroid BMD (mg/kg/d)	Liver BMD (mg/kg/d)	Developmental BMD (mg/kg/d)
PFAS 1	10	0.02	0.24	0.044	0.01
PFAS 2	10	0.02	0.24	0.013	0.0051
PFAS 3	50	0.11	2.1	720	2.1
PFAS 4	400	0.85	70	0.1	0.7
Mixture Total	470	1.0			
DA Mixture BMD Calculation			4.16	0.094*	0.132

*The lowest mixture BMD is converted to a mixture-HBWC for comparison to the measured concentration (i.e., 470 ng/L).

Application of Equation 4-5 to the example water sample in Table 4-15 to derive the DA Mixture BMD. This example is for the liver domain as it was the lowest mixture BMD in this example.

$$t_{add} = \left(\Sigma_{i=1}^{4} \frac{a_i}{BMD_i}\right)^{-1} = \left(\frac{0.02}{0.044} + \frac{0.02}{0.013} + \frac{0.11}{720} + \frac{0.85}{0.1}\right)^{-1} = 0.094 \text{ mg/kg/d}$$

Table 4-16. Mixture BMD Approach: Hypothetical Water Sample 2

	Measured Water Concentration (ng/L)	Mixing Ratio (Proportion)	Thyroid BMD (mg/kg/d)	Liver BMD (mg/kg/d)	Developmental BMD (mg/kg/d)
PFAS 1	5	0.07	0.24	0.044	0.01
PFAS 2	50	0.71	0.24	0.013	0.0051
PFAS 3	10	0.14	2.1	720	2.1
PFAS 4	5	0.07	70	0.1	0.7
Mixture Total	70	1.0			
DA Mixture BMD Calculation			0.299	0.017	0.0068*

*The lowest mixture BMD is converted to a mixture-HBWC for comparison to the measured concentration (i.e., 70 ng/L).

Again, at a minimum, the Mixtures Framework is incomplete and lacks clarity. In this regard, it should not be relied on by EPA for any decision-making. EPA is not clear on how it came to this conclusion about the liver endpoint being most sensitive and having the lowest BMD.

In Table 4-16 of the Mixtures Framework, EPA presents its second hypothetical water sample. In this example, EPA concluded that developmental effects were the most sensitive endpoint and had the lowest BMD. As with the first example, there is no explanation of how EPA arrived at this conclusion.

The Agency seems to be in search of the lowest resulting value without regard to the primary scientific foundations for how likely the effect is to occur in humans from these modeling efforts, i.e., there is no weight of evidence (hazard index) consideration presented.

D. Limitations of EPA's BMD approach.

As with the Relative Potency Factor (RFP) approach (also discussed in the Mixtures Framework), the user/risk assessor needs to have effect data for at least one common endpoint for all the PFAS in the mixture. Thus, this approach cannot be applied if there is no common endpoint. In addition, for most mixtures, the available dose-response data for the different component chemicals will be based on different conditions, such as differences in exposure duration or test species. According to the 2000 Mixtures Guidance, in the context of applying the BMD to the hazard index, the hazard index can use these BMDs only if some sort of standardization is applied so that the 1/BMD scaling factors describe a common scenario (2000 Mixtures Guidance at p. 83). The SAB should comment on the limited utility of this approach and whether a standardization factor should be applied for the different experimental conditions used to derive the BMD values.

EPA also states that for some mixtures with less well-studied PFAS, there may be no available dose-response data for calculating a BMD. Thus, this BMD approach cannot be applied to all PFAS mixtures (it will be limited by the available data). If data are limited on the individual compounds, the endpoints modeled may not capture all possible endpoints..

In the 2000 Mixtures Guidance, EPA states that: "Pharmacokinetic differences among the class of compounds should be identified because differences in the pharmacokinetics across species could substantially change RPFs developed from nonhuman data." 2000 Mixtures Guidance at p. 114. Not only do PFAS differ in pharmacokinetics across compounds as a class (i.e., shorter-chain compounds are eliminated more quickly than longer-chain compounds), but PFAS differ in pharmacokinetics across species (i.e., rodents eliminate them more quickly than humans). The SAB should comment on how these differences in pharmacokinetics might affect the BMD and thus the outcome of this approach.

In the Mixtures Framework, EPA's description of the BMD approach is incomplete, lacks rationale scientific foundations and is fraught with uncertainties. That EPA further fails to provide even minimum practical considerations for application in the real world is troubling. Without adequate scientific analysis and peer review, this approach should not become policy or guidance, nor should it be applied in Agency decision-making. Accordingly, the SAB should recommend that EPA reevaluate its BMD analysis.

III. CVD RISK ANALYSIS

A. Epidemiology of PFOA/PFOS and cardiovascular disease (CVD), including high cholesterol

EPA's CVD Risk Analysis is intended to estimate population-level reductions in cardiovascular disease ("CVD") risk, as well as reductions in total cholesterol levels, that may result from reductions in drinking water exposure to PFOA and PFOS. The premise of this document, however, ignores the fundamental issue that PFOA and PFOS are not known to cause CVD or to increase total cholesterol levels. In the absence of a causal effect, any reduction in drinking water exposure to PFOA and PFOS would be anticipated to have no impact on CVD risk and total cholesterol levels in the target population.

In the Draft MCLG Document for PFOA, EPA acknowledges that the available epidemiologic evidence "did not provide consistent evidence for an association between PFOA and blood pressure"; and was "inconsistent" regarding any association between PFOA and hypertension or other CVD-related outcomes (EPA Document No. 822D21001, p. 191). For total cholesterol, EPA concludes that "the association was consistently positive in pregnant women, positive but less consistently so in adults and children, and generally null in workers" (EPA Document No. 822D21001, p. 192).

In the Draft MCLG Document for PFOS, EPA uses similar language, noting that the available epidemiologic studies "provided evidence for a positive association between PFOS and blood pressure, although the results were not always consistent between [systolic blood pressure] and [diastolic blood pressure], and one study reported an inverse association. The limited evidence for an association between PFOS and increased risk of hypertension was inconsistent … Evidence for other CVD-related outcomes across all study populations was more limited and inconsistent." Draft MCLG Document for PFOS at p. 179. Regarding total cholesterol, EPA states that "the available evidence supports a positive association between PFOS and [total cholesterol] in the general population, including children and pregnant women," and that "[a]lthough PFOS appeared not associated with elevated [total cholesterol and low-density lipoprotein] in workers, this conclusion is uncertain as the occupational studies included in this review are limited in both quantity and quality." *Id.* at p. 179).

3M notes that most epidemiological studies of PFOA or PFOS in relation to total cholesterol levels have been cross-sectional in design, preventing a causal interpretation of their results, especially in light of plausible reverse-causal effects. Even in prospective studies, shared underlying physiological mechanisms that affect circulating PFAS levels and lipid levels can also influence results, leading to spurious associations. Specifically, alternative explanations for observed positive associations between serum PFOA or PFOS and serum lipid levels include common underlying physiological mechanisms (Frisbee et al. 2010), such as shared gut receptors; an effect of total cholesterol, low-density lipoprotein (LDL), and non-high-density lipoprotein (HDL) cholesterol on decreased kidney function (Schaeffner et al. 2003, Morita et al. 2010). They are also subject to confounding by numerous demographic, behavioral, and environmental factors that affect lipid levels (Thelle 1990), such as body size, which can affect PFAS clearance at background exposure levels (Longnecker 2006), and high-fat or low fiber diets, which increase circulating lipid levels and also could affect clearance of PFAS via

gastrointestinal excretion and thus be associated with higher serum PFOA and/or PFOS levels (Buck et al. 2011; Dzierlenga et al. 2021). The ability of cholestyramine to facilitate both PFOA/PFOS and lipid clearance further suggests that a confounding factor impacting the enterohepatic circulation of both PFOA/PFOS and lipids could explain the observed association (Johnson 1984; Ducatman 2021). Binding of PFOA and PFOS to circulating β-lipoproteins and albumin in blood also could be responsible for a non-causal positive association (Olsen and Zobel 2007, Seo et al. 2018). The premise of the CVD Risk Assessment ignores these critical interpretive limitations. SAB should recommend that EPA account for these issues in a revised assessment. Other recent reviews, including one conducted through a project involving 30 countries, the European Environment Agency, and the European Commission (Fragki et al. 2021) and one with co-authors from EPA (Andersen et al. 2021), concur that "the extent to which the relationships between PFOS/PFOA exposure and these altered levels of blood lipids are causal remains uncertain" (Fragki et al. 2021) and that "[t]he extent to which the relationship is causal is an open question" (Andersen et al. 2021). These reviews detail many of the data limitations and plausible alternative explanations that preclude attributing the modest lipid effects observed in some studies to PFAS. SAB should recommend that EPA address these limitations and alternative explanations before basing any risk assessment on lipid effects.

Nearly all epidemiological studies of PFOA or PFOS with respect to total cholesterol levels are also hampered by a one-time measurement of lipid levels, which can vary, sometimes substantially, within individuals over short and long time scales (Hegsted and Nicolosi 1987, Smith et al. 1993, Tolfrey et al. 1999). Additional methodological concerns in these studies are whether analyses were restricted to fasting blood specimens or to individuals not taking lipid-lowering medications. Without such restrictions, associations with total cholesterol levels could be biased in an unpredictable manner due to outcome misclassification, given likely correlations between misclassification error and potential confounders such as socioeconomic status and health care access.

In 2020, the former C8 Science Panel members and collaborators noted that of the "numerous" cross-sectional studies of associations between PFOA and lipid markers, and that most found a "clear positive association between serum PFOA and total cholesterol (TC) or low-density [lipoprotein] (LDL) cholesterol and a minority with positive associations with high-density lipoprotein (HDL) and triglycerides." The authors noted, however, that these findings were susceptible to bias; that is, the apparently consistent statistical association may not be causal:

> The positive association could reflect confounding, if for example regulation of serum level of both PFOA and cholesterol was correlated. Inter-individual variation in enterohepatic cycling of both PFAS and bile acids, the latter affecting serum cholesterol levels, has been postulated as a mechanism for such a correlation between PFAS and cholesterol (EFSA Panel on Contaminants in the Food Chain et al. 2018). Some observations lend support to this view. Correlation between PFAS and cholesterol excretion has been shown in patients with high levels of PFOS, another long chain PFAS, who were given cholestyramine, a drug known to reduce cholesterol, and which led to a sharp decrease in PFOS (Genuis et al. 2014).

Regarding PFOA and CVD, the same authors concluded that there was "no evidence of an association with heart disease," despite the apparent associations with cholesterol (Steenland et al. 2020). The authors reasoned that an association of PFOA with higher levels of HDL cholesterol and/or lower levels of C-reactive protein might mediate a protective effect against cardiovascular disease; therefore, they stated, "it is plausible that there is a positive association of PFOA with raised cholesterol, yet no impact on the risk of cardiovascular disease" (Steenland et al. 2020).

In its MCLG documents EPA notes that it did not find convincing evidence of an associating PFOA or PFOS with CVD in 2016 and, since, then it has assessed 35 and 30 new epidemiological studies, for PFOA and PFOS, respectively, that examined CVD endpoints. EPA's 2021 assessment did not find affirmative evidence for associations with CVD endpoints. [19] Consequently, models that predict risk of CVD outcomes such as the ASCVD model, cannot be assumed to be applicable to PFAS because of the large numbers of studies including newer ones that do not affirm CVD associations with PFAS.

For the above reasons 3M recommends the SAB consider the evidence for the lack of a CVD response from exposure to PFAS and the legitimacy of the exposure reduction-benefit analysis proposed by EPA.

Oyebode A. Taiwo, MD, MPH

[19] See conclusory paragraphs in the PFOA MCLG Draft Document on pages 172, 175, and 176, and the conclusory paragraphs in the PFOS MCLG Draft Document on pages 162 and 165.

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EXHIBIT I

NCASI
IMPACT. SCIENCE. SOLUTIONS.

Attn: Environmental Protection Agency Science Advisory Board
Dr. Sue Shallal, DFO
via email: shallal.suhair@epa.gov

December 22, 2021

Re: Proposed Approaches to the Derivation of a Draft Maximum Contaminant Level Goal for Perfluorooctanoic Acid (PFOA) in Drinking Water; Proposed Approaches to the Derivation of a Draft Maximum Contaminant Level Goal for Perfluorooctanesulfonic Acid (PFOS) in Drinking Water; Analysis of Cardiovascular Disease Risk Reduction as a Result of Reduced PFOA and PFOS Exposure in Drinking Water; and Draft Framework for Estimating Noncancer Health Risks Associated with Mixtures of PFAS

NCASI conducts research and technical studies on behalf of forest products companies across the US, and its members represent more than 80% of pulp and paper and two-thirds of wood panels produced nationwide. NCASI has been an active participant at the state and federal levels in technical and scientific aspects of water quality criteria development for many years and, more recently, has collaborated with other researchers to consider approaches to the systematic review of toxicological and epidemiological information when estimating toxicity factors for environmental contaminants.

NCASI appreciates the opportunity to provide technical comments regarding the development of federal drinking water criteria for PFAS. These comments relate specifically to the documents drafted by EPA staff to be considered by the Scientific Advisory Board (SAB) including: *Proposed Approaches to the Derivation of a Draft Maximum Contaminant Level Goal for Perfluorooctanoic Acid (PFOA) in Drinking Water*; *Proposed Approaches to the Derivation of a Draft Maximum Contaminant Level Goal for Perfluorooctanesulfonic Acid (PFOS) in Drinking Water*; and *Draft Framework for Estimating Noncancer Health Risks Associated with Mixtures of PFAS.*

In our comments, we will highlight scientific issues regarding the development of the toxicity values proposed for PFOA and PFOS, the approach for addressing mixtures of PFAS, and issues related to the systematic review approach taken in the development of these documents.

1.0 MCLG Development for PFOS and PFOA

NCASI agrees with the use of systematic review approaches to evaluate causal relationships and dose-response between chemical exposures and potential health outcomes. However, several elements in the systematic review approach relied on in the MCLG development documents for PFOS and PFOA could be improved to ensure

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that the literature used to develop causal conclusions and points of departure for toxicity values are specifically relevant to the needs of these two assessments and that the body of literature selected represents a robust collection of data that can be relied on with high confidence. For instance, the inclusion criteria in the Population, Exposure, Comparator, Outcome (PECO) statement for exposure is the same for both the assessment of general causation as it is for the selection of points of departure (POD). Literature that may be informative for one of these evaluations may not be relevant for the other; in particular, the inclusion criteria allows for 'Any oral exposure to PFOA or PFOS via oral routes'. This broad PECO component will allow many studies to be considered for the selection of a POD that may lack critical data elements for this evaluation, such as an appropriate resolution of measurement of exposure concentrations, appropriate measurements of intake rates, corroborating serum concentrations, and documented temporal/spatial relationships of measured exposures to health outcomes of interest. Observational epidemiology studies are wide ranging in terms of quality and the collection of critical data elements. Without more specific inclusion criteria, there is the potential to consider studies that lack critical data elements for POD selection within a systematic review of this type.

As well, risk of bias criteria could be improved by more prescriptive treatment of studies with specific types of risk of bias elements that could substantially limit the confidence of these studies. For instance, the studies relied upon for selection of a POD include Grandjean et al. (2012, 2017a, 2017b)[1,2,3], which evaluated antibody response to vaccination in the presence of various PFAS exposure concentrations. However, the outcome of antibody response is highly variable at the inter-individual level due to well characterized genetic factors.[4,5] Zimmerman and Curtis, 2019 note a host of factors that potentially impact antibody response from vaccination, "*These include intrinsic host factors (such as age, sex, genetics, and comorbidities), perinatal factors (such as gestational age, birth weight, feeding method, and maternal factors), and extrinsic factors (such as preexisting immunity, microbiota, infections, and antibiotics)*."[6] The studies relied upon in the MCLG documents fail to measure, control, or adjust for most, if not all of these factors that produce variability in the primary endpoint of these studies. Subtle, non-random distribution of these confounding or effect modifying factors could substantially alter the outcomes of these studies and pose a substantial risk of bias. The current risk of bias approach fails to capture this significant threat to study confidence and could be improved to further qualify these studies appropriately.

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It is also important to note, that from a PECO (e.g., defining the outcome) perspective, reduced antibody response from vaccination is not a diagnosable disease outcome. There is no specific criterion for antibody response that can be classified a 'disease or illness' nor is there a threshold where it is understood that an increase in health risk may occur from differential antibody response. The studies considered for a POD selection did not actually identify an increase of the diseases that vaccinations were administered for in any exposure group in the study. Outcomes in systematic reviews for adverse health endpoints should be clearly defined so as to clearly link an exposure response between a specific range of exposures to a specific disease outcome.

The search approach in the review failed to identify an important study that informs the human equivalent dose (HED). When deriving a (HED), it should be understood what the impact of dose is on elimination rate in order to achieve a scientifically defensible value. The kinetics data relied upon by EPA does not capture all the best science available for estimating the half-life of PFAS in humans. Some PFAS are retained in the bloodstream by the kidney, which treats these molecules like fatty acids and uses a similar receptor-based mechanism to prevent their loss from the blood. However, when the concentration of PFAS becomes high enough, this retention system becomes saturated, and the elimination rate of PFAS becomes much higher, shortening the half-life. In animal studies, our observations occur at relatively 'high' concentrations of PFAS compared to observations in humans that are typically much lower. Therefore, the elimination rate we observe in animal studies is faster (because the retention mechanism is saturated) than what occurs in human studies where doses are much lower. However, Elcombe et al. 2013 studied PFAS as a component of a chemotherapeutic regimen for cancer patients and determined that higher doses (more likely to be relevant to human toxicity) of PFAS in humans resulted in faster elimination rates. This study should be captured by the literature search and is important for consideration when developing an HED value.[7]

Potential improvements also exist in the approach to integrate evidence for drawing causal inference and this is particularly notable in the evaluation of PFOA as a carcinogen. The review identifies 8 epidemiological studies that were classified as having 'medium' confidence and one animal model that provided evidence for renal cancer in male rats. However, there is no specified criteria for the integration of these findings, weighted by the risk of bias analysis, to draw a conclusion regarding carcinogenicity. In the absence of a 'high' confidence epidemiological study, an evidence base in the animal toxicology literature should be required to be integrated into the epidemiology evidence base, where the animal toxicology would serve as the primary evidence base and the epidemiology would serve as supporting evidence given the insufficient confidence in that literature. However, only one animal model was identified to support a conclusion of carcinogenicity (among several studies that did not find sufficient evidence of carcinogenicity). Likewise, there is no corroboration of dose-response or specific cancer cell type/site among animal and toxicology studies. A specific evidence integration component in the systematic review protocol would assist in applying these features of the evidence base for drawing conclusions and would perhaps lead to a different conclusion regarding carcinogenicity than is reported in the draft MCLG document for PFOA. NCASI staff have recently coauthored a publication on evidence integration in systematic review that would inform this

[7] Elcombe, C.R., Wolf, C.R., Westwood, A.L., 2013. US Patent Application Publication. Pub. No.: US 2013/0029928. Available at: https://patentimages.storage.googleapis.com/24/ee/73/f58267c7d70dde/WO2011101643A1.pdf

aspect of the systematic review protocol.[8]

Many of these issues could have been addressed by peer review/public comment on the systematic review protocol used in the MCLG development. It is common practice among regulatory agencies to either publish or distribute for comment a proposed protocol that can be revised based on technical feedback as seen in other EPA program areas such as the Integrated Risk Information System (IRIS). Not only does this serve to enhance the transparency of the review process, but also provides additional perspectives on many of the criteria for risk of bias and evidence integration that must be detailed a priori to the actual review. NCASI supports the opportunity to provide technical comments on proposed systematic review protocols.

PFAS Mixtures

NCASI agrees with the general principle that chemicals found to impact the same organ system with the same mechanism of action may be assumed to be additive, proportionate to individual chemical dose response, for the purpose of health protective risk assessment practices. In the tiered approach proposed in the '*EXTERNAL PEER REVIEW DRAFT Draft Framework for Estimating Noncancer Health Risks Associated with Mixtures of Per- and Polyfluoroalkyl Substances (PFAS)*', the target organ specific hazard index (TOSHI) relies on this approach. This approach relies on PFAS to have a toxicity value developed (e.g., RfD) for each substance, compared to extant exposure to calculate a hazard quotient, and then the hazard quotients are summed to calculate the hazard index, which is interpreted to be protective of public health when equal to or less than 1.0. However, the draft document would be improved by more clearly defining the data requirements for this approach and the recognition that the class of substances referred to as PFAS are likely to contain unique substances that should not be treated as additive unless organ specificity and mechanism of action specificity criteria are met.

PFAS, as a group, includes thousands of substances with unique physio-chemical properties, unique fate and transport properties, and unique toxicological profiles. Broadly inclusive criteria are unlikely to produce standards or risk assessment approaches with a well characterized margin of safety or that accurately reflects the hazard posed by individual substances within the group. This has been evidenced in the scientific literature, even in studies that have evaluated PFAS of relatively similar chemical structure. As an example, Pizzurro et al. 2019 examined the toxicokinetics of several PFAS compounds and came to the following conclusions:

> *"Overall, our analysis provides one of the first syntheses of available empirical PFAS toxicokinetic data to facilitate interpreting human relevance of findings observed in animal studies and developing health-based criteria for PFAS from such studies. Our analysis highlighted several notable differences among the different PFAS regarding species and substance-specific tissue partitioning, half-life, and transfer to developing offspring via the placenta or lactation, as well as highlighted data gaps for certain substances."*
>
> *"Lastly, the results of this analysis indicate that there are toxicokinetic differences among the different PFAS based on chain length, and these substances should not be regulated as a group*

[8] Julie E. Goodman, Robyn L. Prueitt, Raymond D. Harbison, Giffe T. Johnson. 2020. Systematically evaluating and integrating evidence in National Ambient Air Quality Standards reviews. Global Epidemiology, Volume 2, 2590-1133, https://doi.org/10.1016/j.gloepi.2020.100019.

> *without careful consideration of how the substance-specific toxicokinetics may impact potential toxicity, including differing specific target organ toxicity and overall body burden."*[9]

Also, the draft document refers to several toxicity values derived from the Agency for Toxic Substances and Disease Registry (ATSDR) Minimal Risk Level (MRL). The ATSDR is explicit in its guidance on the use of the MRL and clearly indicates the intended use of this value is not to define clean up levels, such as water quality criteria. As noted in the ATSDR Toxicological Profile for Perfluoroalkyls regarding MRLs (underline added):

> *"These substance-specific estimates, which <u>are intended to serve as screening levels</u>, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that <u>MRLs are not intended to define clean-up or action levels</u>."*
>
> *"Exposure to a level above the MRL does not mean that adverse health effects will occur."*
>
> *"<u>MRLs are intended only to serve as a screening tool</u> to help public health professionals decide where to look more closely."*[10]

Use of the MRL to derive water quality criteria results in criteria that are more conservative than needed to protect public health and will not provide additional public health benefit over an approach more consistent with that used by EPA to develop toxicity values. The draft document should specify that toxicity values such as the RfD, which are intended to inform public health policy should be relied on in a mixtures assessment and not screening level toxicity values such as the MRL, which are not designed for this purpose.

Please feel free to contact me regarding any questions associated with these technical comments.

Respectfully,

Giffe Johnson, PhD
Program Manager and Principal Scientist

[9] Pizzurro, Daniella M.; Seeley, Mara; Kerper, Laura E.; Beck, Barbara D. 2019. Interspecies differences in perfluoroalkyl substances (PFAS) toxicokinetics and application to health-based criteria. Regulatory Toxicology and Pharmacology 106 239–250.

[10] Agency for Toxic Substances and Disease Registry (ATSDR). 2018. Toxicological profile for Perfluoroalkyls. (Draft for Public Comment). Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service.

EXHIBIT J

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Dear Colleagues

We appreciate the opportunity to provide comments on this review of EPA's draft text entitled "EXTERNAL PEER REVIEW DRAFT, Proposed Approaches to the Derivation of a Draft Maximum Contaminant Level Goal for Perfluorooctanoic Acid (PFOA) (CASRN 335-67-1) in Drinking Water. This text is well written in many places and summarizes most of the literature in a balanced and scientifically appropriate way. We wish to bring to your attention information in three areas that might improve the text.

First, EPA's discussion of critical effect does not fully explain the dose-imbalance in endpoints between human observational studies and experimental animal studies. For example,

- The human observational studies of immune effects and developmental toxicity generally occurred at much lower levels than in the definitive experimental animal studies.
  - This can be due to the differences in kinetics between human and experimental animals, or in sensitivities between humans and experimental animals, or to the fact that many of the human studies are observational, not causal.
  - Therefore, we encourage EPA SAB to carefully review this disparity in dose between epidemiology and toxicological findings, and make recommendations as appropriate.
- Depending on the critical effect, the PFOA or other PFAS half-life analysis may need to be reworked. For example:
  - If the critical effect is judged to be developmental toxicity, or other toxicity related to *in utero* exposure, then the proper dosimeter between experimental animals and humans or among humans may be the Cmax, which is the default position of EPA (1991). An unfunded and award-winning publication describes this situation (Dourson et al., 2019).
  - If the critical effect is judged to be toxicity after a lengthy exposure, such as after 90 days or two years in experimental animals or chronic exposure in humans, then the proper dosimeter between experimental animals and humans may be the clearance by kidney and other organs, or if volumes of distribution are known between experimental animals and humans or among humans, then comparisons of half-life.

Second, the discussion of PFOA half-life is missing significant information, in part due to recent international developments and in part due to misunderstandings. Specifically:

- An unfunded and international collaboration has recently yielded a consensus position on the human half-life of PFOA (*ARA*, 2021a) of 0.5 to 1.5 years. This consensus was

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developed under the auspices of the Alliance for Risk Assessment (https://tera.org/Alliance%20for%20Risk/index.htm) and is attached.

- An older human observational study by Zhang et al. (2013) is actually a clearance study where PFOA and its branch-chain isomers were monitored. The use of this study would avoid problems associated with unmonitored PFOA exposures and unmeasured PFOA isomers since all exposures are integrated into the blood. The average half-life in this study is 1.3 years and would be lower if other sources of elimination would have been monitored (*ARA*, 2021a).
- Most human observational studies do not account for unmonitored PFOA exposures and unmeasured PFOA branched isomers. The former problem would lead to an inflated PFOA half-life, the latter problem would lead to a deflated PFOA half-life. The two problems together result in unreducible uncertainty to the estimated half-lives in most of these observational studies (*ARA*, 2021a).
- A recent and unfunded publication gives a range of the PFOA half-life of 0.5 to 1.5 years based on human observational studies, a human clinical study, and an analysis of likely unmonitored PFOA exposures (Dourson and Gadagbui, 2021). A recent analysis of Nilsson et al. (2010) lends support to the lower limit of this range (*ARA*, 2021b, Figure 4, page 40).

Third, although sundry, the following items need attention:

- The citation of Dourson and Gadagbui (2021) related to the volume of distribution was surprising. The research in this publication was devoted to the PFOA half-life, using in part the only clinical study to date on PFOA. The volume of distribution was described in an appendix of this paper and noted to as an initial volume of distribution. A further analysis of this volume has been summarized in *ARA* (2021b, Figure 3, page 39).
- The draft value of the PFOA RfD given by EPA was shocking, since it is lower that the LD50 for botulin toxin, which is generally acknowledged to be the most toxic chemical known. If true, then EPA will need to carefully justify their position because otherwise it will likely be ridiculed.

Sincerely,

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