February 28, 2022

The Honorable Michal Freedhoff
Assistant Administrator
Office of Chemical Safety and Pollution Prevention
Environmental Protection Agency
1200 Pennsylvania Ave NW
Washington, DC 20460

Re: National PFAS Testing Strategy: Identification of Candidate Per- and Poly-fluoroalkyl Substances (PFAS) for Testing

Dear Assistant Administrator Freedhoff:

Environmental Defense Fund is providing comments on the *National PFAS Testing Strategy: Identification of Candidate Per- and Poly-fluoroalkyl Substances (PFAS) for Testing*[1] (Testing Strategy), which is intended to help fill data gaps and enable the agency to regulate PFAS in a way that is protective of both human health and the environment.

Given the established threat of PFAS such as PFOA and PFOS, as well as some of their replacements like GenX, many people, particularly in communities exposed to multiple PFAS, are legitimately concerned about the potential risks presented by the entire class. Thus, it is essential that there be a robust testing approach to obtain the needed information on these chemicals.

We support a properly designed and implemented testing strategy. Such a strategy would help address some of the significant data gaps that exist for the very large PFAS chemical class. We commend EPA for developing a strategy and committing to using its testing authorities under TSCA. In its current state, however, the Testing Strategy is too narrow and opaque to fulfill the agency's intended purpose.

We would like to highlight the following opportunities to make the testing strategy more transparent and effective. Our recommendations include:

[1] EPA. (2021). "National PFAS Testing Strategy: Identification of Candidate Per- and Poly-fluoroalkyl Substances (PFAS) for Testing." https://www.epa.gov/system/files/documents/2021-10/pfas-natl-test-strategy.pdf

I. Expand the universe of PFAS addressed.

The current strategy is intended to be representative of 2,350 PFAS out of the broader universe of more than 12,000 PFAS that EPA has identified,[2] or about one in five. This is in part because the agency has chosen to apply a narrow definition of PFAS. We believe that EPA should modify its definition of what constitutes a PFAS and adopt a definition that is consistent with that used by other authoritative bodies in the United States and around the world, such as the Organization for Economic Cooperative Development (OECD).[3]

II. Provide more detail on core elements of the strategy.

Many aspects of the Testing Strategy are opaque or lack sufficient detail. Our recommendations for providing greater transparency to help stakeholders understand core elements of the strategy follow.

A. Structural filters

Structural Filter 1: Substances without a defined structure

Starting from a comprehensive EPA database of chemical substances known as the DSSTox Database,[4] all substances without a defined structure were excluded from consideration, beyond a chain of linked carbon and fluorine atoms. The agency explained that it "did not have sufficient information to determine whether they should be considered a PFAS," but the Testing Strategy provides little additional explanation.

It would be helpful if the Testing Strategy were to explain whether this group of substances refers to the 1,200-plus[5] individual chemicals in EPA's DSSTox Database identified as PFAS "without explicit structures" — including polymers and other chemicals of unknown and variable composition, complex reaction products, or biological materials — or if there were other potential PFAS excluded.

The Testing Strategy should include more detail on the substances excluded under this filter and develop an approach for how it will include and address PFAS that lack a defined structure to ensure potentially harmful chemicals are not excluded from the Testing Strategy.

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[2] EPA. (n.d.). "PFAS Master List of PFAS Substances." *CompTox Chemicals Dashboard*. Accessed February 24, 2022, https://comptox.epa.gov/dashboard/chemical-lists/pfasmaster

[3] OECD. (2021). "Reconciling Terminology of the Universe of Per- and Polyfluoroalkyl Substances: Recommendations and Practical Guidance." https://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=ENV/CBC/MONO(2021)25&docLanguage=en

[4] EPA. (n.d.). "Distributed Structure-Searchable Toxicity (DSSTox) Database." Accessed February 24, 2022, https://www.epa.gov/chemical-research/distributed-structure-searchable-toxicity-dsstox-database

[5] EPA. (n.d.). "PFAS chemicals without explicit structures." *CompTox Chemicals Dashboard*. Accessed February 24, 2022, https://comptox.epa.gov/dashboard/chemical-lists/PFASDEV1

Structural Filter 2: Substances that fall outside of OPPT's definition of PFAS

After excluding substances described as lacking a defined structure, the Testing Strategy applied OPPT's working definition of PFAS, defined as chemicals with at least two consecutive fully fluorinated carbon atoms, to identify PFAS. The application of this definition may have resulted in the exclusion of potentially public health relevant PFAS with only one fully fluorinated carbon atom. Furthermore, given that data generated under the Testing Strategy would likely benefit a range of EPA program offices, it would be appropriate to adopt a more widely recognized definition such as the OECD PFAS definition.[6] This is particularly a concern because other EPA programs may not decide to use OPPT's PFAS definition.

To ensure that the Testing Strategy includes all potentially public health relevant PFAS and maintains consistency with other authoritative bodies, the Testing Strategy should adopt OECD's comprehensive PFAS definition prior to its initiation of testing.

Structural Filter 3: Removal of PFAS with unlikely human exposure or environmental presence

In Structural Filter 3, all chemicals with "unlikely exposure or environmental presence" were then removed from further evaluation. Structural Filter 3 presents two problems. First, the Testing Strategy document does not explain what it means by "unlikely human exposure or environmental presence," as no definition or standard is provided.

Second, this filter appears to be inconsistent with the purpose of the Testing Strategy, which is to develop needed information to understand and characterize risks presented by PFAS, including exposure-related information. Given the dearth of information available for PFAS, how can EPA confidently determine whether human exposure or environmental presence is unlikely? If anything, it seems that more exposure information would need to be developed. Again, the limited detail provided makes it difficult to assess the confidence associated with applying this filter.

EPA should provide the specific data, methods, and criteria used to determine whether a PFAS has "unlikely exposure or environmental presence."

Structural Filter 4: Removal of PFAS for which vapor pressure cannot be calculated

In Structural Filter 4, chemicals for which vapor pressure could not be calculated were removed. Unfortunately, the agency did not provide any explanation or justification for applying this filter.

EPA should explain the rationale for excluding chemicals for which vapor pressures are "not calculable," as well as the approaches and underlying information it used to make such determinations.

[6] OECD. (2021). "Reconciling Terminology of the Universe of Per- and Polyfluoroalkyl Substances: Recommendations and Practical Guidance." https://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=ENV/CBC/MONO(2021)25&docLanguage=en

Structural Filter 5: Removal of PFAS where toxicity is likely primarily due to the non-perfluorinated part of the chemical

PFAS were removed where the toxicity of the substance was assumed to be likely primarily due to the non-perfluorinated part of the compound. The Testing Strategy would be improved if there were a more fulsome discussion of the basis and scope of this Structural Filter. Additionally, in the case where both the non-perfluorinated and perfluorinated parts of the substance are toxic, it is unclear if there were considerations of factors other than structure in differentiating between toxicity due to the perfluorinated part and that due to the non-perfluorinated part of the PFAS. Relatedly, it is not clear what the threshold for "primarily" is for toxicity being driven by the fluorinated part of the substance versus the non-perfluorinated part. This exclusionary filter also appears to discount the potential additive or synergistic effect of the non-perfluorinated and perfluorinated parts of certain PFAS.

We find this filter rather concerning and advise that it be dropped from the Testing Strategy. At the very least, the Testing Strategy should more fully explain the rationale for this filter and, as with the other filters, provide much more specificity as to the associated criteria and chemical-specific results of applying this filter.

In sum, the Testing Strategy should provide more detail on the methodology used to develop, and the assumptions associated with, the Structural Filters applied to exclude PFAS from further consideration in the Testing Strategy. The agency should additionally share a list of PFAS excluded by each filter to instill public confidence that the PFAS EPA excluded are not those presently impacting our communities.

B. PFAS categories considered for testing

We urge EPA to provide greater detail and transparency around its chemical categorization and selection process.

The Testing Strategy does provide a clear explanation of the method – structural similarity modeling – used to create PFAS categories. It should similarly include a clear description for each PFAS category. As it has done for its TSCA new chemical categories,[7] the agency should provide a category definition and a description of the boundaries for each category.

In the current form of the Testing Strategy, many of these categories are not clearly defined. There are no definitions provided and category names are minimally descriptive, for example "Others, cyclic, volatile." EPA's description of the frequently used "Others," is that these PFAS "did not meet the conditions of membership for one of the primary categories." Also, the exact same category name is used for multiple terminal categories. Thus, it is difficult to determine what type of PFAS are actually included in each of the "terminal" categories.

The boundaries of each of the categories need to be clearly explained, so that stakeholders can determine what is in a category of similar PFAS and what is out. This would provide information

[7] EPA. (2010). "TSCA New Chemicals Program (NCP) Chemical Categories." https://www.epa.gov/sites/default/files/2014-10/documents/ncp_chemical_categories_august_2010_version_0.pdf

on whether PFAS of concern are included and would also help stakeholders determine whether the PFAS chosen to represent a given category is truly representative.

Increased transparency of the PFAS "terminal" categories would provide the public with the information needed to assess the scope of such categories. **The Testing Strategy should thus include a descriptive name and a description of the boundaries for each category, similar to what is provided in the TSCA new chemical categories document.**

C. Categories excluded from consideration

Categories with any toxicity data

Of the 70 terminal categories created, the Testing Strategy excluded 14 categories for which there was "any data about the toxicity of the PFAS in that category." The document does not describe how much data there was for members of the 14 categories it excluded, whether the data are sufficient for hazard assessment, or whether it intends to revisit these categories during the agency's phased implementation of the Testing Strategy.

To increase public confidence in the exclusion of these categories, EPA should clearly define the excluded categories, disclose the type and amount of toxicity information that exists for each category, and commit to including them in the agency's category refinement process.

Categories without an identifiable manufacturer

The Testing Strategy excluded another 32 terminal categories that lack existing toxicity data, but do not have an "identifiable manufacturer." The Testing Strategy states that additional manufacturers will likely be identified through the agency's upcoming PFAS reporting rule. Concerningly, however, the agency only states that it "may" expand the initial list of candidate PFAS based on new manufacturer information.

EPA should expand its focus beyond those PFAS that have an "identifiable manufacturer," as this criterion excludes substantial numbers of PFAS to which people are exposed. The agency should consider other TSCA authorities it can use to develop data on PFAS without an identifiable manufacturer.

III. Select additional PFAS for testing.

We urge EPA to include additional PFAS as candidates for testing. As written, the Testing Strategy would require testing for only 24 of the nearly 2,400 PFAS characterized as having limited toxicity data and identifiable manufacturers – about ***one percent.*** Only one PFAS will be tested to represent a potentially large number of PFAS in each terminal category. Given to the opaqueness of the scope and boundaries of each of the terminal categories, it is not clear if the candidate for testing for each terminal category is sufficiently representative of the category. In addition, the small number of candidates introduces uncertainties which EPA has not characterized. Further, the candidate PFAS may not be PFAS that communities are actually

exposed to. In effect, the public must take a leap of faith that the PFAS candidates for testing are representative of the terminal categories and representative of what they are being exposed to.

Since EPA intends to test only a limited number of PFAS, it is crucial that the decisions the agency makes to identify candidates for testing are transparent, robust and include the necessary characterizations of uncertainty. In addition to providing additional clarity, we strongly urge EPA to increase the number of candidate PFAS selected for testing. Specifically, for each terminal category, EPA should at least test both the most representative PFAS and the PFAS in the category that communities are exposed to.

IV. Require testing to better characterize PFAS in mixtures.

Given that people are directly and indirectly exposed to different mixtures of PFAS throughout their lifetime, a cumulative risk assessment framework that looks at the combined effects of PFAS co-exposures across chemical lifecycles should be applied to accurately assess environmental and human health risk. One important consideration for cumulative risk assessment is whether the effects of PFAS mixtures are additive, synergistic, or antagonistic. Mixture testing plays an important role in identifying the type of mixture effect to be expected across different combinations of compounds and should be included in the Testing Strategy.

While EPA does not discuss PFAS mixtures in the Testing Strategy document, it does address it in the agency's new *Draft Framework for Estimating Noncancer Health Risks Associated with Mixtures of Per- and Polyfluoroalkyl Substances (PFAS)* (Draft Framework) currently under review by EPA's Science Advisory Board, which provides a "framework that facilitates practical component-based mixtures evaluation of two or more PFAS under an assumption of dose additivity."

We commend the agency for its stated intentions to assess toxicity from mixtures of PFAS using component-based approaches and agree that this approach resolves many of the issues related to whole mixture testing. However, we are concerned that EPA is relying on the default assumption of dose additivity rather than developing the needed database to verify this assumption and evaluate cumulative mixture models.

While we understand that dose-additivity is a reasonable default assumption, and that significant deviations from dose additivity are not common among chemicals that produce similar effects, we believe it would be appropriate for EPA to require testing on different mixtures of PFAS, within and between categories, to determine if the default assumption of dose-additivity is warranted for PFAS.

This is critical because if the effects of PFAS mixtures are greater-than-additive, or synergistic, EPA's use of the default assumption of dose-additivity would significantly underestimate the toxicity of PFAS mixtures and potentially lead to risk management actions that fail to sufficiently protect public health and the environment.

In its Draft Framework, EPA acknowledges that "[l]imited work has been conducted on combined exposure to PFAS in experimental systems," such as cell-based and animal tests on mixtures. A recent industry-funded study on PFAS mixtures found critical gaps in mixture

toxicity test data, citing less than a dozen published whole mixture toxicity studies as of 2021, most of which assess legacy PFAS such as PFOA and PFOS.[8] Similarly, in 2018, the Dutch National Institute for Public Health and the Environment (RIVM) argued that mixture toxicity studies "are not available for PFASs" and that the "the assumption made concerning the dose addition of PFAS congeners still needs to be verified."[9]

It is clear from the literature that additional mixture testing across a wide range of PFAS combinations is needed to comprehensively assess potential synergistic effects and validate modeled predictions of dose-additivity in component-based mixture assessment methods. Testing should expand beyond well-studied PFAS to newer compounds and examine low levels of exposure commonly found in the environment.

It should be noted that EPA has the legal authority under TSCA to require manufacturers to develop information on PFAS mixtures. In fact, mixtures are explicitly mentioned in TSCA section 4(a)(1)(A)(i), which authorizes EPA to require testing where it determines that (emphasis added):

> the manufacture, distribution in commerce, processing, use, or disposal of a chemical substance or *mixture*, or that any combination of such activities, may present an unreasonable risk of injury to health or the environment.

For the reasons outlined above, EPA should modify its Testing Strategy to require companies to conduct tests on PFAS mixtures to better understand potential synergistic effects, especially where data are limited as to the type of mixture effect. Mixture testing should be conducted for mixtures of PFAS within and between structural categories.

V. Reduce reliance on new approach methods.

EPA's Testing Strategy provides for a tiered approach to testing identified PFAS candidates that employs various new approach methods (NAMs)[10] and animal-based methods. More specifically, the Testing Strategy consists of three testing tiers where Tier 1 includes physical-chemical property tests and *in vitro* assays; Tier 2 includes additional NAMs and introduces animal testing to determine the appropriate animals and doses of PFAS that will be included in Tier 3; and Tier 3 consists of whole animal testing, where animals are used to investigate complex health endpoints, such as reproductive effects and cancer. Importantly, it is only in Tier

[8] Goodrum, P.E., Anderson, J.K., Luz, A.L., & Ansell. G.K. (2020). "Application of a Framework for Grouping and Mixtures Toxicity Assessment of PFAS: A Closer Examination of Dose-Additivity Approaches." *Toxicological Sciences, 179*(2). https://academic.oup.com/toxsci/article/179/2/262/5879299

[9] National Institute for Public Health and the Environment (RIVM). (2018). "Mixture exposure to PFAS: A Relative Potency Factor approach (RIVM Report 2018-0070)." *https://www.rivm.nl/bibliotheek/rapporten/2018-0070.pdf*

[10] Per *EPA's Strategic Plan to Promote the Development and Implementation of Alternative Test Methods Within the TSCA Program*, NAMs are defined as "any technology, methodology, approach, or combination thereof that can be used to provide information on chemical hazard and risk assessment that avoids the use of intact animals." *See* https://www.epa.gov/sites/production/files/2018-06/documents/epa_alt_strat_plan_6-20-18_clean_final.pdf

3 that the agency will identify dose levels for PFAS that should be used as points of departure in human health risk evaluations.

The Testing Strategy lacks sufficient detail as to how the agency intends to implement the tiered approach; however, it appears that the tiers effectively operate as filters where evidence of toxicity or risk is required in a given tier in order for a substance to be considered for testing in a higher tier.

Given the many PFAS in existence, we agree that NAMs have a role in the EPA's Testing Strategy. We recognize that subjecting thousands of PFAS to a suite of animal-based assays is not desirable or viable. However, we are concerned that the agency's current approach to applying NAMs in the Testing Strategy will miss hazards and risks of PFAS and therefore misguide decisions on further actions EPA may take to protect public health and the environment from PFAS.

We believe that an alternative approach to the use of NAMs in the Testing Strategy would more effectively generate health and safety information, while providing public confidence in EPA's characterization of PFAS risk. Specifically, we strongly recommend that the agency subject the very few candidate PFAS identified for testing (at current 24 individual substances) to comprehensive *in vivo* animal studies and employ NAMs to pressure test and support extrapolation of such results more broadly across various PFAS categories.

Presently, there are concerns regarding shortcomings of studies of PFAS in NAMs compared to what has been determined in animal studies. For example, a recent study[11] found that PFOA did not show strong activity in NAMs that measure immune response, yet evidence from both animal and human studies show that PFOA induces immune system suppression. Likewise, in a recent National Academies workshop[12] on PFAS and human health, an EPA scientist highlighted that PFAS may cause adverse health endpoints by affecting stress response pathways or cellular lipid membranes, yet the Testing Strategy does not include NAMs that could investigate these pathways.

At the very minimum, EPA must provide greater clarity as to how it chose the specific NAMs identified in the Testing Strategy (many valuable and informative NAMs developed by EPA's Office of Research and Development, such as high-throughput transcriptomics (HTTr), are not reflected in the current testing battery); how decisions regarding the extent of testing pursued for any particular PFAS will be made; and how existing uncertainties and limitations associated with selected NAMs will be addressed.

We urge EPA to revisit the tiered testing strategy as currently conceived in the Testing Strategy and publish a detailed supplement to the Testing Strategy that provides details necessary to understand the agency's approach to testing candidate PFAS. Further, we

[11] Naidenko O.V., Andrews D.Q., Temkin A.M., Stoiber T., Uche U.I., Evans S., & Perrone-Gray S. (2021). "Investigating Molecular Mechanisms of Immunotoxicity and the Utility of ToxCast for Immunotoxicity Screening of Chemicals Added to Food. *Int J. Environ. Res. Public Health, 18*(7). https://doi.org/10.3390/ijerph18073332

[12] NAS. (2021). *Federal Government Human Health PFAS Research Workshop Proceedings of a Workshop—in Brief*. Washington, DC: The National Academies Press. https://doi.org/10.17226/26054

strongly recommend that the agency subject the very few candidate PFAS identified for testing (at current 24 individual substances) to comprehensive in vivo animal studies and employ NAMs to pressure test and support extrapolation of such results more broadly across various PFAS categories.

VI. Describe how the agency intends to use the data.

Multiple EPA programs are addressing PFAS. Thus, the data generated via the Testing Strategy may have broad applicability. While the Testing Strategy indicates that EPA will use its TSCA section 4 authority to require testing, it does not indicate whether the data will be used beyond TSCA or how it plans to make these data available. Given the multimedia impacts of PFAS, it would be helpful for stakeholders to understand how EPA intends to use the data, including whether the data will be used by programs in addition to TSCA, and whether the data will be publicly available.

The Testing Strategy should describe how EPA intends to use the data generated to characterize and manage risks from PFAS, as well as how it plans to make this health and safety information publicly available and accessible.

Conclusion

We commend EPA again for developing a strategy to fill PFAS data gaps and committing to using its testing authorities under TSCA to do so. We hope these comments and recommendations can be used to help the agency increase the transparency of the Testing Strategy and ultimately increase the representativeness of the PFAS testing. Please contact Lauren Ellis at lellis@edf.org if you have any questions.

Sincerely,

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