Environmental Defense Fund

Comments on the Toxic Substances Control Act (TSCA) Collaborative Research Program to Support New Chemical Reviews

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Introduction

The Environmental Defense Fund (EDF) appreciates the opportunity to provide comments to the U.S. Environmental Protection Agency (EPA) on the Toxic Substances Control Act (TSCA) Collaborative Research Program to Support New Chemical Reviews (Collaborative Research Program).[1] We appreciate the Office of Chemical Safety and Pollution Prevention's (OCSPP) efforts to collaborate with the Office of Research and Development (ORD) given the breadth of scientific expertise in ORD.

EDF commends EPA for its focus on updating their approach to using data from structurally-similar chemicals. The agency already has a new chemicals category document which they use for many structurally similar chemicals. We hope this will be rigorously and transparently updated and expanded.

It is encouraging that the agency will be digitizing data and studies in hard copy and consolidating information in different databases. This will increase efficiency and ensure that OCSPP staff have more complete information when assessing the risk of a new chemical. We hope EPA will also use this opportunity to ensure that data claimed as CBI is in fact eligible for CBI claims under TSCA.

In updating and augmenting the models used in new chemical assessments, EPA should use the best available science and increase transparency in the agency's use of models to assess new chemicals, as EPA relies heavily on these models given the paucity of data that often accompanies new chemical submissions. As part of this effort, we encourage EPA to consider adapting some of the approaches being developed for existing chemicals, such as the methodology for estimating exposures and risks to fenceline communities.

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[1] EPA. (2022, February 25). "Toxic Substances Control Act (TSCA) Collaborative Research Program To Support New Chemical Reviews; Notice of Public Meeting and Request for Comments," 87 Fed. Reg. 10784. https://www.federalregister.gov/documents/2022/02/25/2022-04039/toxic-substances-control-act-tsca-collaborative-research-program-to-support-new-chemical-reviews

Additionally, EPA should consider exposures throughout the life-cycle of the chemical, including from downstream use, release and disposal, and how physical-chemical properties and the environmental fate impact the magnitude of the exposure potential. The decisions made in the TSCA new chemicals program impact people who are exposed or otherwise affected by the chemical throughout its entire life-cycle. It is important that the impacts on all stakeholders be fully considered when developing new chemical decisions.

We support the use of new approach methods (NAMs) to generate mechanistic, hazard, and toxicokinetic data to inform the hazard assessment of new chemicals. Indeed, the legal, financial, and ethical concerns around animal testing make NAMs an attractive option. However, ultimately, NAMs must be utilized in a manner that prioritizes public health. We hope that subsequent drafts of this Collaborative Research Program include more details on how NAMs will be used.

While we are excited about EPA's plans to improve the scientific basis of its new chemical reviews, we are concerned about a potential over-reliance on modeled or predicted toxicity and exposure data in which the agency limits or halts use of its TSCA information authorities to fill data gaps on new chemicals. Under TSCA, when reviewing a premanufacture notice (PMN), EPA is obligated to identify whether significant information gaps on hazards or exposure exist for a new chemical. In the case that there is not enough information on a new chemical to make a reasonable evaluation of risk, EPA must issue an insufficient information finding under Section 5(e).

EPA's heightened emphasize on categories, QSAR models, exposure models, and state-of-the-art NAMs begs the question of how EPA will interpret "insufficient information" in new chemical reviews. For instance, will the existence of one NAM for one particular health endpoint be judged as "sufficient?" EPA should clearly document its decision-making logic in deciding whether information is sufficient to review the new chemical in question. Further, EPA should clarify how exactly the results of this Collaborative Research Program will change EPA's evaluation of information sufficiency in new chemical reviews.

In addition to TSCA Section 5, EPA also has authority under Section 4 to require the development of information on new chemicals. EPA should use its TSCA Section 4(a)(2)(A)(i) authority to require the development of data to aid in developing and augmenting categories and read-across methods.

In sum, rather than rely solely on predictive methods, EPA should use its information development authorities under TSCA to ensure that new chemical submissions contain sufficient information to adequately assess hazard, exposure, and risk. Further, EPA's use of its information development authorities under TSCA will be critical to the success of this Collaborative Research Program, as measured test data could prove extremely valuable in validating NAMs (including chemical categories, read-across, and QSAR models) against other, more well-studied toxicity tests (such as animal tests).

1. Research Area 1: Update and Refine Chemical Categories

EPA's New Chemical Category Document has been an important tool for the TSCA new chemical's program. EPA has relied on it extensively to help support Section 5 decisions.

We support the collaboration between OPPT and ORD to develop a "systematic, transparent, and reproducible approach for modernizing both chemical categories and read-across methods."[2] In doing so, EPA's approach should be consistent with the OECD's Guidance on Grouping of Chemicals.[3]

In developing each category, it is critical that the applicability domain of the category and any sub-categories within the category (i.e., which chemicals are covered by the category assessment) be explicit and precise. Specifically, as described by OECD, "the precise composition of the category (e.g., carbon number range, branching and position of branching, aromatic content, cyclicity, position and frequency of double bonds, functional group(s)) of category members) should be defined where possible to set the boundaries that are used as inclusion/exclusion criteria."

Sub-categories may be developed within a category, for example based on different hazard potentials for different groups within a category. For these cases the rationale and the parameters of each of the subcategories should be precisely defined.

The applicability for the category should be identified, e.g., specific hazard endpoint(s), environmental fate, etc.

EPA should clearly explain how it will identify the types of scientific information the agency will use to support chemical categories and read-across methods. EPA provided examples of the types of scientific information it will use including structural (and other) boundaries; physical-chemical properties; structural alerts for hazard, fate, exposure, and/or functional uses; mechanistic and toxicokinetic data from NAMs; and/or, existing hazard data, but did not explain how it will identify or use these data sources. EPA should specifically describe how it intends to use these types of data.

EPA should also identify whether and how it intends to use any "bright lines" or "rules of thumb," such as for bioavailability. While these may apply for many chemicals, it should not be assumed that they apply for all. For example, in the past the TSCA program has used a molecular weight for 1,000 as a cut-off for bioavailability. This was not always appropriate given there are

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[2] EPA. (2022, March 9). *Draft for Public Comment – Modernizing the Process and Bringing Innovative Science to Evaluate New Chemicals Under TSCA*, p. 5. https://www.regulations.gov/document/EPA-HQ-OPPT-2022-0218-0004

[3] OECD. (2014, April 14). *Guidance On Grouping Of Chemicals, Second Edition*, Series on Testing & Assessment No. 194, ENV/JM/MONO(2014)4. https://www.oecd.org/publications/guidance-on-grouping-of-chemicals-second-edition-9789264274679-en.htm

instances where higher molecular weight chemicals have been found to be bioavailable.[4] In developing chemical categories and implementing read-across, EPA should assess and validate any other "bright lines" or "rules of thumb" before it continues to use them in the new chemicals program.

The importance of the precision and clarity of the applicability domain of each category and sub-category, the purpose of the category, the information that will be used to support categories, and how categories will be used in the future cannot be overstated. These are key to stakeholders' confidence in the use of these categories to support decisions under Section 5.

Category for Per- and Poly-fluoroalkyl Substances (PFAS)

EPA should create a new chemical category for PFAS using the OECD definition[5] as the broadest parameter for the category. Within the broader PFAS category, EPA should include sub-categories of PFAS based on toxicity and, as appropriate, separately for environmental fate, including transport and bioaccumulation.[6]

We encourage EPA to provide a descriptive name for each sub-category and clearly identify the boundaries for each PFAS sub-category consistent with the approach in EPA's New Chemical Category Document. This is needed so that stakeholders can determine what is within the sub-category and what is not. We request that EPA not take the opaque approach for identifying categories used in its *National PFAS Testing Strategy: Identification of Candidate Per- and Poly-fluoroalkyl Substances (PFAS) for Testing*[7] in which no category definitions were provided, and category names were minimally descriptive and vague.

Use of TSCA Section 4(a)(2)(A)(i) testing authority

TSCA Section 4(a)(2)(A)(i) provides EPA with the authority to "require the development of new information relating to a chemical substance or mixture if the Administrator determines that the information is necessary- (i) to review a notice under [Section 5]..."

EPA has not included in its draft Collaborative Research Program the use of this authority to require the development of data to aid in developing and augmenting categories and read-across.

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[4] For example, polybrominated flame retardants such as 1,4-bis(pentabromophenoxy)tetrabromobenzene (MW 1364) have been found in gulls' eggs.

[5] As provided in OECD. (2021, July 9). *Reconciling Terminology of the Universe of Per- and Polyfluoroalkyl Substances: Recommendations and Practical Guidance*, ENV/CBC/MONO(2021)25. https://www.oecd.org/officialdocuments/publicdisplaydocumentpdf/?cote=ENV/CBC/MONO(2021)25&docLanguage=En

[6] We note that many PFAS are persistent and bioaccumulative and thus these will also fall within the PBT category.

[7] EPA. (2021, October). *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

EPA should use this authority to improve the reliability of its chemical categories. The reliance of the new chemicals program on chemical categories and read-across in the assessment of the many data-poor new chemical submissions warrants the use of this authority to increase the strength of the chemical categories and ability to review a notice under TSCA Section 5.

2. Research Area 2: Develop and Expand Databases Containing TSCA Chemical Information

We are encouraged by EPA's stated plans to digitize, consolidate, and expand the amount of information available to the agency to make health-protective and timely new chemical risk determinations under TSCA. However, the current lack of detail in the draft Collaborative Research Program begs many questions related to the extent to which data sources will be integrated into new chemical reviews, the ability of such sources to capture reasonably foreseen uses, whether EPA intends to make the new chemical database public, and whether illegal redactions will be addressed during the digitization of CBI records. Our recommendations related to each follow.

Integration of data sources into new chemical reviews

EPA should clarify at which stage of the new chemical review process each data source is expected to be reviewed and by whom, and require reviewers to transparently document their findings, or lack thereof, from each data source. The process for using the expanded databases in new chemical reviews should be incorporated into standard operating procedures and made public to improve transparency in new chemical reviews and restore public confidence in the program.

Reasonably foreseen uses

EPA should standardize, document, and make public its process for identifying chemical structural analogs and reasonably foreseen uses of a new chemical, including which data sources will be searched within the expanded database for analogs and related reasonably foreseen uses. Under the amended TSCA, EPA must conduct an upfront evaluation of reasonably foreseen conditions of use alongside intended conditions of use (Sections 3(4) and 5(a)(3)).[8] It is therefore critical that new chemical risk assessors have access to regularly updated functional use data sources, including new chemical submissions, Chemical Data Reporting Rule data, and ORD resources such as CPDat. Furthermore, EPA should consider how it can capture expected production volume increases in its assessment of a new chemical, with a focus on the potential risk posed by aggregate production volume increases across multiple sites and manufacturers. Using historical chemical production data, EPA should be able to model, and examine through

[8] TSCA Section 3(4) is the definition of "conditions of use," which doesn't provide any basis for separately (temporally or otherwise) considering reasonably foreseen vs. intended conditions of use; both are relevant to understanding the future risk posed by a new chemical once it is on the market, since both may occur at the same time or expose the same individuals or groups. Section 5(a)(3) in turn specifies the requirement to conduct the review and make the determination for the new chemical under its conditions of use.

quantitative sensitivity analysis, the risk posed by various future production volumes, and regulate that risk using the risk management tools available under TSCA.

Public data transparency

EPA should commit to making all non-CBI data available to the public via a single, user-friendly database and specify whether this will occur through the existing ChemView database. In the draft Collaborative Research Program, EPA focuses primarily on *internal* database integration and expansion, with only one reference to making ORD data public via newly mapped IUCLID templates. We believe there needs to be a much greater focus on public access. While we appreciate EPA's commitment to standardizing the presentation of data based on an internationally recognized template, most if not all ORD data sources are already public, limiting the impact of this action on public access.

While many OCSPP and ORD resources used in the new chemical review process are already public,[9] data sources are isolated from one another, leading the public to the same inefficient process of having to search multiple data sources to gather information on a given new chemical. To meaningfully increase public access, EPA should commit to providing the public with *all* relevant data sources used in a new chemical review in a single, easy-to-use database.

Traditionally, this has occurred through EPA's ChemView database, a public-facing database that includes new and existing chemical information related to TSCA, including PMN documents, submitter test data, new chemical determinations, and significant new use rules. In fact, ChemView also links to other publicly available chemical information, including release and pollution prevention data from the Toxics Release Inventory and hazard data from ORD's IRIS program. While the potential of ChemView is huge, its utility is limited due to the fact that many data sources within the database have not been updated for years, ranging all the way back to 2014 for some sources, such as health and safety studies.[10] The public needs and deserves better access to information used in new chemical reviews. EPA should improve and expand upon ChemView.

Illegal CBI claims

In the draft Collaborative Research Program, EPA indicates that it plans "to identify, extract, curate and catalog available ***CBI data on chemistry, hazard, fate, and exposure*** from different TSCA CBI databases and information"[11] (emphasis added). We are concerned about EPA's characterization of hazard, fate, and exposure data as CBI, as such data are not eligible for being

[9] For example, PMN documents and decisions are available to the public via the Federal Register and web tables. ORD databases like Comp Tox or CPDat are also available to the public.

[10] See "Date Last Updated" (02/21/2014) for the "Health and Safety Studies" export file on ChemView. https://chemview.epa.gov/chemview/ (Accessed 2022, May 9)

[11] EPA. (2022, March 9). *Draft for Public Comment – Modernizing the Process and Bringing Innovative Science to Evaluate New Chemicals Under TSCA*, p. 6. https://www.regulations.gov/document/EPA-HQ-OPPT-2022-0218-0004

considered CBI under TSCA. TSCA provides that health and safety information is not eligible for CBI protection, with only two narrow exceptions, for information "that discloses processes used in the manufacturing or processing of a chemical substance or mixture or, in the case of a mixture, the portion of the mixture comprised by any of the chemical substances in the mixture."[12] Otherwise, health and safety information – which is broadly defined to include information related to chemical hazard, fate, and exposure – must be disclosed.[13]

We urge EPA to recognize the digitization of CBI information as a unique opportunity to systematically review CBI claims to determine whether the associated information is in fact eligible for CBI protection under TSCA Section 14. In the draft Collaborative Research Program, EPA states that "safeguards for CBI will be maintained as appropriate in this process." In considering whether CBI maintenance is "appropriate," the agency should first determine whether the CBI is eligible for CBI protection under TSCA. As noted above, much of the information appears to constitute health and safety information that is not eligible for such protection.

Over the years, we have come across many documents that are fully or heavily redacted, such as safety data sheets, and clearly constitute health and safety information, which is ineligible for protection from disclosure under TSCA. Denying the public access to such information not only leaves the public in the dark, but it also violates TSCA. EPA should work to address illegal redactions in new chemical information during its effort to digitize and consolidate TSCA CBI under the Collaborative Research Program.

3. Research Area 3: Develop and Refine QSAR and Predictive Models for Physical-Chemical Properties, Environmental Fate/Transport, Hazard, Exposure, and Toxicokinetics.

We encourage EPA to improve or replace the models it uses in the review of new chemicals. Models should be both up-to-date and able to effectively estimate values for a broad range of chemicals, such as those that are persistent and mobile in the environment.

EPA should also be more transparent about the applicability of the models and the uncertainty in the estimated values. EPA consistently characterizes its models as conservative, but these models are often conservative only in certain aspects but not conservative overall. For example, an exposure model may use conservative parameters, but the exclusion of particularly important exposure pathways for certain chemicals, e.g., dermal exposure via vapor deposition, may actually results in an underestimation of exposure. Another example is when a model is used even though it may not be adequate or fit for purpose for certain groups of chemicals, e.g., PBTs.

A. Physical-Chemical and Environmental Fate/Transport Models

EPI Suite™ is a suite of estimation programs for physical-chemical and environmental fate values. However, the models in EPI Suite™ lack transparency in performance and applicability.

[12] 15 U.S.C. § 2613(b)(2) ("TSCA Section 14(b)(2)")

[13] *See* 15 U.S.C. § 2602(8) ("TSCA Section 3(8)"); 40 C.F.R. §§ 716.3, 720.3(k)

While performance of the individual property estimation methods used in EPI Suite™ are available in the EPI Suite™ help files, the property model performance estimations are only presented in terms of overall performance and do not describe whether or not the model is applicable for any specific chemical.[14] For example, the accuracy and domain section in the help file for KOWWIN (the Log Octanol-Water Partition Coefficient Program) describes the domain for the model as having "no universally accepted definition..." and that the user "may wish to consider the possibility" that property estimates are less accurate for compounds with molecular weights higher or lower than those used in the training set. Similar disclaimer statements are found in each program that uses quantitative structure property relationships (QSPR). The newer QSPR model, EPA's OPEn structure-activity/property Relationship App (OPERA), includes the reporting of a chemical-specific applicability domain, and was built using a newer database of physical-chemical parameters.[15] We recommend that EPA use this newer, more transparent model for its estimation of physical-chemical properties and environmental fate endpoints.

When considering physical-chemical properties and environmental endpoints, EPA should be attuned to those properties of a chemical that make it persistent and resistant to remediation. These factors should be considered as part of the risk assessment for new chemicals, so as to minimize future problems such as those presented by PFAS.

As discussed previously in section 1 of these comments on categories, EPA should also identify whether and how it intends to use any "bright lines" or "rules of thumb." EPA should assess and validate any bright lines or "rules of thumb" before it continues to use them in the new chemicals program.

B. Hazard/QSAR Models

EPA states that QSAR models will be developed and refined for use in estimating "physical-chemical properties, exposure, environmental fate/transport, and hazard" of new chemicals.[16] Similar to NAMs, QSAR models should be deemed adequate or fit-for-purpose for use. EPA states that QSAR models will be developed, updated, and evaluated for use using OECD principles. EPA should make public how these models were validated, and which measured data was used to validate the QSAR models. This is important for transparency and to ensure that the QSAR model predictions are deemed acceptable for their intended purposes.

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[14] "The classical approach of comparing models by global R^2/Q^2 fitting performance may or may not reflect higher predictive ability, especially when dealing with different sizes of datasets, for example. Therefore, comparisons of model fit should be local and specific, not based on overall statistics." Mansouri K, Grulke CM, Judson RS, Williams AJ. (2018). OPERA models for predicting physicochemical properties and environmental fate endpoints. *J Cheminform*. 10(1):10. https://doi.org/10.1186/s13321-018-0263-1

[15] *Id.*

[16] EPA. (2022, March 9). *Draft for Public Comment – Modernizing the Process and Bringing Innovative Science to Evaluate New Chemicals Under TSCA*, p. 6. https://www.regulations.gov/document/EPA-HQ-OPPT-2022-0218-0004

C. Exposure Models

i. Assess all relevant exposure pathways, including those that relate to reasonably foreseen conditions of use and background exposures.

General population exposure pathways and sources of exposure

EPA considers only ambient air, drinking water and fish ingestion as exposure sources in its assessment of general population exposures to a new chemical substance. Other relevant exposure pathways and sources of exposure that could substantially contribute to exposure and subsequent risk are excluded from consideration, including:

- land/groundwater contamination from sources other than releases to landfill (e.g., direct land application of contaminated sludge),
- indoor air contamination from vapor intrusion,[17]
- contaminated soil and dust[18]
- contaminated food (e.g., fruits and vegetables grown on contaminated soil), in addition to wild-caught fish,
- showering/bathing in contaminated tap water, and
- spills, leaks, facility start-ups and shutdowns, and other accidental or peak releases.

It should be noted that the above listed exposure sources are not merely hypothetical "worst-case scenario" assumptions, but rather reflect the multitude of sources that contribute to a person's chemical exposure. Therefore, they must be considered if EPA intends to accurately assess general population exposure and risk.

"Negligible" and "below modeling threshold" language

Even in its narrow assessment of only ambient air, drinking water and fish ingestion for the general population, the agency often dismisses environmental release pathways as not applicable

[17] EPA has the resources and tools to model vapor intrusion (*see* https://www.epa.gov/vaporintrusion/epa-spreadsheet-modeling-subsurface-vapor-intrusion). The EPA New Chemical Program should adapt current site-specific vapor intrusion models to a more generic screen for new chemicals.

[18] "The ingestion of soil and dust is a potential route of exposure to environmental chemicals for both adults and children. Children, in particular, may ingest significant quantities of soil and dust due to their tendency to play on the floor indoors and on the ground outdoors and their tendency to mouth objects or their hands. For example, children may ingest soil and dust through deliberate hand-to-mouth movements, or unintentionally by eating food or mouthing objects that have dropped on the floor. Adults may also ingest soil or dust particles that adhere to food, cigarettes, or their hands. Other vulnerable populations may include pregnant women and populations engaging in wilderness and traditional rural lifestyles. Thus, understanding soil and dust ingestion patterns is an important part of estimating overall exposures to environmental chemicals." EPA. (2017, September). *Exposure Factors Handbook: Chapter 5 (Soil and Dust Ingestion) 2017 update.* https://www.epa.gov/sites/default/files/2018-01/documents/efh-chapter05_2017.pdf; Further, Chapter 7 (Dermal Exposure Factors) of the Exposure Factors Handbook includes soil and dust as potential sources of dermal exposure. EPA. (2011, November). *Exposure Factors Handbook: Chapter 7 (Dermal Exposure Factors).* https://www.epa.gov/sites/default/files/2015-09/documents/efh-chapter07.pdf

due to expectations that exposures are "negligible" and/or "below modeling threshold." For example, the TSCA Section 5 order for PMN number P-21-0013 (signed May 6, 2021) indicates that "[e]xposure to the general population was not evaluated via inhalation of stack or fugitive air because exposures were below modeling thresholds (expected to be negligible)."

This language also shows up in Section 5(a)(3) determinations ("not likely to present an unreasonable risk"), (P-21-0012), which uses the same (seemingly boilerplate) language: "Exposures to the general population via stack air or fugitive air inhalation were not assessed because releases to these media were expected to be negligible (below modeling thresholds)." No further explanation is provided.

We suggest EPA disentangle "negligible" from "below modeling threshold," rather than group them together using parentheses as shown in the above examples, as the two terms are distinct from one another. "Negligible" is rooted in physical-chemical properties, while "below modeling threshold" implies a limitation of the exposure models, including in applicability. EPA should clarify the distinction between these two terms and precisely state the criteria used to determine whether each are applicable during a new chemical review.

Regarding claims of "negligible" exposures, EPA should consider the implications of dismissing exposure pathways based on physical-chemical properties alone. This is especially the case for data-poor new chemicals, whose properties are often themselves modeled. As discussed above, EPI Suite™ property estimates are less accurate for compounds with molecular weights higher or lower than those used in the training set. The uncertainty derived from using estimated data as both model inputs and outputs should be considered in the agency's decision to not evaluate a given exposure pathway.

Finally, EPA regularly uses the phrase "below modeling threshold" to dismiss exposure pathways; however, the agency does not define "below modeling threshold" in its working approach document to new chemical reviews, its exposure model guidance documents, nor on its website. In the case of a model limitation, EPA should prioritize updating exposure models before others to ensure they are able to model low-level environmental exposures. In the case of a policy decision, we strongly urge EPA to stop its practice of dismissing exposure pathways based on unspecified exposure thresholds, as there is potential to underestimate risk that may arise from the combination of multiple low-level exposures.

Background exposures

EPA's new chemicals program does not consider background exposures from TSCA-uses, such as chemical byproducts and byproducts and intermediates that get carried along, nor background exposures from non-TSCA uses, defined as uses that fall outside of TSCA's definition of "chemical substance,"[19] including but not limited to any existing food, cosmetic, or pesticidal uses of the new chemical in question, in its new chemical reviews. Because background exposures directly contribute to an individuals' total chemical exposure and subsequent health risks, EPA's omission of background exposures leads to an underestimation of risk to the

[19] 15 U.S.C. § 2602(2) ("TSCA Section 3(2)")

chemical being assessed. Therefore, EPA should account for background exposures, regardless of whether the source activity is directly regulated under TSCA.[20]

Notwithstanding findings of inapplicability for certain background exposure pathways for certain chemicals, it is critical that EPA systematically examine all sources of background exposures to ensure that these relevant exposures are captured in risk assessments. Failure to consider exposures from those uses would be inconsistent with scientific standards and weight of the scientific evidence requirements established in TSCA Sections 26(h), (i), and (k).[21] In the case that a background exposure pathway does not lead to significant exposure, it should still be analyzed and discussed.

EPA should consult existing literature, federal agencies (e.g., FDA), and international bodies (e.g., OECD) to obtain and integrate data on background exposures into its new chemical reviews, and ultimately for all risk evaluations conducted under TSCA. The agency has the expertise and experience to account for background exposures, evidenced by the Office of Water's application of a "relative source contribution" (RSC) factor when calculating ambient water quality criteria (AWQCs) or maximum contaminant level goals (MCLGs) for drinking water,[22] which enables the agency to indirectly account for other potential sources that contribute to an individuals' total exposure.

ii. Assess all relevant routes of exposure.

Ingestion

In its assessment of worker exposure and risk, EPA does not assess ingestion as a route of exposure. This is problematic given that most workers in and around where chemicals are manufactured, processed, or used will take breaks to use the restroom, eat lunch, and engage in other such activities. Workers may not carefully wash their face and hands or change out of their contaminated clothes for each break or at the end of the day. Additionally, they may touch surfaces on which a chemical, especially if it is not volatile, may settle. During each of these activities, workers may transfer a chemical to food they then consume or may engage in some other hand-to-mouth activities that result in ingestion. Thus, the ingestion route of exposure is relevant to workers and should be accounted for to ensure that worker risk to the new chemical under review is not underestimated.

Like workers, consumers of products or articles containing the new chemical under review may also be exposed orally through product use via transfer from hand-to-mouth. Thus, the hand-to-mouth oral ingestion exposure route is a relevant concern for consumers who may

[20] National Research Council. (2009). *Science and Decisions: Advancing Risk Assessment*. Washington, DC: The National Academies Press, Chapter 5. https://doi.org/10.17226/12209

[21] 15 U.S.C. § 2625

[22] EPA. (2000, October). *Methodology for Deriving Ambient Water Quality Criteria for the Protection of Human Health, [EPA-822-B-00-004]*. https://www.epa.gov/sites/default/files/2018-10/documents/methodology-wqc-protection-hh-2000.pdf

unintentionally transfer chemical residues from their hands to their mouth by, for example, handling food after handling a new chemical-containing product.

Like workers and consumers, ingestion is also a relevant exposure route that is not assessed for many of the general population exposure pathways included in new chemical reviews. Specifically, ingestion of contaminated soil and dust is a potential route of general population exposure to chemicals for both adults and children that should be considered.

Vapor-to-dermal

To the extent that the new chemical in question is emitted into the air in the vapor or mist phase, EPA needs to assess the risk from vapor-to-dermal[23] uptake in addition to inhalation for workers, consumers, and the general population. Worker exposure models within EPA's ChemSTEER tool only measure inhalation exposure to chemical vapor or mist, not dermal exposure. This should be updated as a part of EPA's Collaborative Research Program

Further, EPA's E-FAST tool used to measure consumer and general population exposures also omits dermal exposures from chemical vapors or mists. The vapor-to-dermal route of exposure, for example, from showering or bathing in contaminated water, should be assessed in EPA's assessment of general population exposures. Further, for consumers, it is important to consider that certain consumer products, for instance, a shower curtain, can off-gas vapor, which can be exaggerated by the presence of heat, such as during a hot shower. Finally, dermal uptake of vapor is also a relevant route of exposure for the general population through vapor intrusion pathways. Dermal exposure via vapor is a particularly important route of exposure for volatile and semi-volatile organic compounds.

iii. Update exposure factors.

EPA's E-FAST webpage indicates that the 2014 tool version reflects the latest exposure factors from the 2011 EPA exposure Factor Handbook. However, it is unclear if EPA has integrated updated exposure factor values from EPA's more recent updates to the *Exposure Factors Handbook*,[24] where appropriate. EPA should ensure that exposure factors are regularly updated to reflect the most recent science and immediately integrate the exposure factor values from the updated *Exposure Factors Handbook* as they become available.

In addition to making regular updates to default exposure factors, EPA should strongly consider developing or obtaining data to inform and enable the use of subpopulation-specific exposure factor profiles for certain potentially exposed or susceptible subpopulations. These factors should take into account the specific lifestyles and diets of certain subsets of the population, including but not limited to tribal and fenceline communities. For the same reasons life-stage-specific exposure factors are critical to understanding exposure and risk at different ages, subpopulation-

[23] EPA. (2011, November). *Exposure Factors Handbook: Chapter 7 (Dermal Exposure Factors).* https://www.epa.gov/sites/default/files/2015-09/documents/efh-chapter07.pdf

[24] EPA. (2011-2019). *Exposure Factors Handbook*. https://www.epa.gov/expobox/about-exposure-factors-handbook

specific exposure factors are needed to fully understand the exposure scenarios, and potentially disproportionate exposure burdens, of different subsets of the population. Obtaining and applying subpopulation-specific exposure factors is also consistent with guidance from the *Exposure Factors Handbook* on reducing data variability by "disaggregating the population into segments with similar characteristics."[25] The use of subpopulation-specific exposure factors will ultimately allow for more effective and equitable risk management.

iv. Aggregate exposure across pathways, routes, and conditions of use.

Aggregate exposure across operations, uses, settings, and receptor groups

To meaningfully assess exposure and risk, EPA cannot isolate receptor groups, as workers are also members of the general population and consumers. By assessing exposure and risk separately for different groups of the population, EPA systematically underestimates potential risk, and ignores the lived reality in which people experience chemical exposures. This is especially true for potentially exposed or susceptible subpopulation, who may in fact be more exposed or more susceptible as a result of combined exposures from different uses and settings. Thus, while the agency characterizes models used in new chemical reviews as "conservative," we argue that conservative model parameters (although not always truly conservative at face value) do not equate to a conservative review. Instead, EPA systematically underestimates risk by not aggregating exposure across uses, pathways, routes, and settings.

Aggregate exposure from intended and reasonably foreseen uses by assessing them in combination

EPA should assess all pathways, routes, and sources across the entire chemical life-cycle *in combination*, with a focus on anticipating potential downstream exposures and reasonably foreseen conditions of use. As discussed above, EPA's decision to exclude exposure pathways that are "below modeling threshold" may lead to underestimation of aggregate exposure and ultimately risk. Therefore, EPA should systematically examine all exposure pathways, intended and reasonably foreseen, even if it initially expects exposures to be low, as the aggregation of low-level exposures across exposure pathways can lead to risk. Once an aggregate assessment is conducted, EPA can refine its findings by performing sensitivity analyses removing reasonably foreseen uses, possibly to inform a significant new use rule (SNUR) or necessary restrictions in a Section 5(e) order. However, it is critical that any SNUR resulting from an assessment of reasonably foreseen uses is not used to justify a not likely determination, which the agency committed to stop doing in March 2021.[26]

Further, one important but often overlooked reasonably foreseen condition of use is an increase in the future production volume of the chemical. Evidence clearly shows that once commercialized, the number of industrial sites that manufacture and/or process the chemical

[25] EPA. (2011, September). *Exposure Factors Handbook: Chapter 2 – Variability and Uncertainty.* https://www.epa.gov/sites/default/files/2015-09/documents/efh-chapter02.pdf

[26] EPA. (2021, March 29). "Important Updates on EPA's TSCA New Chemicals Program." https://www.epa.gov/chemicals-under-tsca/important-updates-epas-tsca-new-chemicals-program

increases over time. Any reasonably foreseen increases in releases should be modeled and addressed in an assessment of risks to fenceline communities. Specifically, EPA should model expected future production and use increases as reasonably foreseen uses of the chemical. This can easily be done in EPA's current ChemSTEER tool, and potential risk from expected production volume increases can be assessed through sensitivity analysis.

v. Move toward a cumulative risk assessment framework to ensure potentially exposed or susceptible subpopulations (PESSs) are adequately protected.

EPA's traditional, single-chemical approach ignores how other chemical exposures may impact the risk posed by the specific chemical in question, which underestimates actual risk to public health. This is particularly the case for workers and fenceline communities, who are often exposed to multiple chemicals simultaneously and disproportionally bear adverse health burdens. Failing to account for chemical co-exposures to these receptors groups underestimates their potential risks, as chemical co-exposures may render an individual more susceptible to risks associated with the new chemical being assessed.

Therefore, EPA should develop and implement methods to assess cumulative risks, such as those faced by workers to diisocyanates and by fenceline communities where chemicals with similar effects are produced at the same facility. EPA's in-house new chemical submission databases contain the information needed to determine whether either of these potentially exposed or susceptible subpopulations are exposed to multiple chemicals that have come through the new chemicals program. Furthermore, EPA should attempt to augment hazard and exposure models to account for the impact of non-chemical stressors.

While robust cumulative risk assessment methodologies are still being developed, particularly in the area of incorporating non-chemical stressors, EPA's ORD recently developed draft guidance on implementing cumulative impact assessment in the near-term.[27] This new ORD draft guidance aims to "promote the use of cumulative impact assessment across the Agency," which "aligns with recommendations from the National Environmental Justice Advisory Council and the White House Environmental Justice Advisory Council that urge increased attention to the cumulative impacts of multiple chemical and non-chemical stressors on disadvantaged, underserved, and environmentally overburdened communities, including tribes (NEJAC, 2004, 2014; WHEJAC, 2021)."[28] EPA recently received comments on this draft document from the Scientific Advisory Board (SAB). Some commenters note that there are data and methodologies available to the agency to take action now, including the agency's EJSCREEN: Environmental Justice Screening and Mapping Tool. We recommend that EPA start to use these tools in considering impacts to fenceline communities and other vulnerable subgroups.

[27] EPA. (2022, January). *External Review Draft – Cumulative Impacts: Recommendations for ORD Research.* https://www.epa.gov/healthresearch/cumulative-impacts-research

[28] *Id.*

vi. Analyze and characterize uncertainty associated with the various models used in new chemical reviews.

Uncertainty analysis

EPA should assess and document uncertainties and assumptions associated with exposure model inputs and outputs in a more robust and transparent manner. Specifically, the agency should employ sensitivity analyses to assess how gaps in the exposure assessments affect the risk estimates.[29] Other approaches to quantitative analysis of uncertainty – such as analytical uncertainty propagation, probabilistic uncertainty analysis, and classical statistical methods – are outlined in EPA's *Exposure Factors Handbook*.[30] We suggest that EPA reference this Handbook as it determines the specific steps it will take to assess uncertainty.

Uncertainty factors

EPA should clearly and transparently document its decision-making process for selecting and applying uncertainty factors in the derivation of a point of departure for use in new chemical risk assessments. In the case that an uncertainty factor is not applied, such as a database uncertainty factor (UF_D), EPA should include a robust discussion of why this is the case in its PMN determination documents. The database uncertainty factor accounts for deficiencies in the study database that may have otherwise resulted in the identification of a more sensitive effect for certain endpoints or life stages, which may become increasingly important as the agency transitions away from animal toxicity tests to NAMs.

Even though the database uncertainty factor is one of the five uncertainty factors traditionally applied in chemical risk assessment – and is commonly employed by other offices and programs at EPA, including ORD/IRIS – the agency has not historically employed and does not, to our knowledge, currently employ a database uncertainty factor in its new chemical risk assessments. Given the paucity of data available to EPA on new chemicals, EPA should systematically apply a database uncertainty factor in almost all cases, and when one is deemed unnecessary, transparently discuss the rationale for excluding such a factor.

[29] U.S. EPA. (2020, August). *Summary of External Peer Review and Public Comments and Disposition for 1-Bromopropane (n-Propyl Bromide)*, p. 97. https://www.epa.gov/sites/default/files/2020-08/documents/summary_of_external_peer_review_and_public_comments_and_disposition_for_1-bromopropane_n-propyl_bromide.pdf; U.S. EPA. (2020, June). *Summary of External Peer Review and Public Comments and Disposition for Methylene Chloride (MC)*, p. 23 and 30. https://www.epa.gov/sites/default/files/2020-06/documents/2_mecl_peer_review_and_public_comment_response_final.pdf

[30] EPA. (2011-2019). *Exposure Factors Handbook*. https://www.epa.gov/expobox/about-exposure-factors-handbook

vii. Address specific flaws in existing ChemSTEER and E-FAST tools.

ChemSTEER

Generic Scenarios
EPA's ChemSTEER tool used to estimate environmental releases and worker exposures for chemicals manufactured and used in industrial/commercial settings includes many generic occupational-emission-scenarios (OES)-specific models. In general, EPA should ensure that environmental release and worker exposure models reflect real-world scenarios and are regularly updated as new data becomes available.

EPA/OPPT Near-Field/Far-Field Inhalation Exposure Model
Many of the assumptions in the EPA/OPPT Near-Field/Far-Field Inhalation Exposure Model are problematic. In this model, near-field exposures represent potential inhalation exposure to workers, while the far-field exposures represent potential inhalation exposure to Occupational Non-Users (ONUs). This assumes workers spend the entire duration of the activity in their respective exposure zones. This assumption was criticized by the Science Advisory Committee on Chemicals (SACC) during the 1-bromopropane draft risk evaluation peer review meeting (one SACC member with industrial hygiene experience noted that workers and ONUs may regularly pass into each other's space, e.g., to communicate or otherwise interact).[31] We urge EPA to update the Near-Field/Far-Field Inhalation Exposure Model nested within ChemSTEER to reflect a more realistic workplace that represents demonstrated and proven worker and ONU behaviors. To do so, EPA should consider developing data, or integrating existing data sources into its "modern relation database" (research area 2) related to workplace behaviors to better inform model assumptions.

Models that incorporate PELs/RELs
Many of the worker inhalation and dermal exposure models available within ChemSTEER include various Occupational Safety and Health Administration (OSHA) Permissible Exposure Limits (PELs) and National Institute for Occupational Safety and Health (NIOSH) Recommended Exposure Limits (RELs) that may be applicable to a specific substance within a material, product or good. For example, the OSHA PEL-Limiting Model for Substance-Specific Particulates Model "assumes that the worker is exposed to the chemical at a level limited by the OSHA PEL (TWA or C)." A default assumption that worker exposure is limited to a PEL or REL does not reflect the reality of many workplaces and wrongfully considers risk management actions (i.e., a PEL) in the risk assessment of a new chemical. Instead of assuming that PELs and RELs represent upper bounds of potential exposure, EPA should model exposure in the absence of assuming compliance with OSHA requirements. Aside from the fact that OSHA has stated that its PELs are not sufficiently protective,[32] the health standards issued under Section 6(b)(5) of the Occupational and Safety Health Act must reduce significant risk only to the extent that it is

[31] SACC. (2019, September 10-12). *Peer Review for Draft Risk Evaluation for 1-Bromopropane (1-BP) [Meeting Minutes and Final Report No. 2019-03]*, p. 27-28. https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0235-0061

[32] Department of Labor, Occupational Safety and Health Administration. (n.d.) "Permissible Exposure Limits – Annotated Tables." www.osha.gov/annotated-pels

technologically and economically feasible. Thus, even if followed, these standards are not consistent with the requirements of TSCA, incorporate cost or other non-risk factors, and therefore should not be included in any assessment of risks to workers.

E-FAST/Consumer Exposure Module (CEM)

The generic consumer exposure scenarios presented in the most recent E-FAST manual need to be updated. Most of the generic consumer exposure scenarios originate from data collected in the 1980s, with only some newer data from the early 2000s.[33] EPA should consider coordinating new consumer product use surveys to reflect changes in use patterns and product composition that have taken place over the past few decades.

EPA should also get rid of the faulty assumption that kids do not clean. EPA's current Consumer Exposure Module nested within E-FAST does not calculate dermal exposure for non-adults (including youths up to 19 years old) for any scenarios other than the Bar Soap and the User-Defined Scenario because:

> "the [other generic scenarios] scenarios assume active and not passive exposure (e.g., adults are assumed to engage in cleaning and house painting activities; children are not), and individuals other than adults are assumed to have no direct contact with these products. Non-adults (youths, children, small children and infants) have significant changes in their physical qualities (e.g., body weight, surface area) over time. Therefore, for non-adults, CEM will calculate acute dermal exposures for the Bar Soap and User-Defined scenarios only."

While changes in non-adult physical qualities over time are legitimate and would have to be modeled, the claim that children (6-12 years old) and youths (13-19 years old) do not engage in direct cleaning is absurd. Children and youths are often tasked with household chores that include cleaning activities. Ignoring this fact underestimates exposure to a potentially susceptible child or youth who regularly partakes in cleaning activities as part of weekly or even daily home responsibilities. EPA should therefore abandon its inaccurate assumption that children and youths do not clean and model dermal exposures for these life-stages.

As previously discussed, according to the latest E-FAST User Manual, EPA's Consumer Exposure *Module* within E-FAST does not assess consumer exposure from non-dietary ingestion. However, EPA's latest "Consumer Exposure Model"[34] (version 2.1, published in 2019) includes fifteen new consumer exposure models (in addition to the six models from E-FAST). The 2019 CEM update includes new consumer exposure models that enable the calculation of exposure from (1) additional product and article categories, (2) the non-dietary ingestion route (including ingestion of soil, dust, particulates, as well as article mouthing), (3) the vapor-to-skin route, and (4) product or article off-gassing – among many more improvements.

[33] For example, *see* Westat Inc. 1978a National Usage Survey of Household Cleaning Products.; 1987b Household Solvent Products: A National Usage Survey; Versar, Inc. 2003. Source Ranking Database

[34] EPA. (2019, April). *Consumer Exposure Model (CEM) User Guide*. https://www.epa.gov/sites/default/files/2019-06/documents/cem_2.1_user_guide.pdf

Based on current E-FAST guidance, it does not appear that the improved CEM published in 2019 has been incorporated into E-FAST, and subsequently, new chemical reviews. If EPA is not already in the process of transitioning to the 2019 CEM, EPA should immediately integrate the new CEM modeling capabilities into E-FAST and new chemical reviews. Further, EPA should strongly consider implementing the ideas laid out in the "Areas for Future Enhancements" section in the 2019 CEM, including but not limited to developing or enhancing models to enable the modeling of products added to water during a bath or shower and the modeling of temperature influences during product application and use.

4. Research Area 4: Explore Ways to Integrate and Apply NAMs in New Chemical Assessments

We support the use of NAMs in the draft Collaborative Research Program to generate mechanistic, hazard, and toxicokinetic data to inform the hazard assessment of new chemicals. Indeed, the legal, financial, and ethical concerns around animal testing make NAMs an attractive option. However, ultimately, NAMs must be utilized in a manner that prioritizes public health.

Tiered framework for hazard characterization

The draft Collaborative Research Program states that a suite of fit-for-purpose NAMs could be used for testing and data submissions and to inform the categorization of new chemicals. We commend the use of multiple NAMs that are specifically selected to evaluate an adverse key event or health outcome. During the April 20, 2022 virtual public meeting, EPA introduced a tiered testing framework for using NAMs for hazard characterization. The testing framework consists of three tiers. As you move from Tier 1 to Tier 3, chemicals are evaluated in more complex cell culture models or microphysiological systems, ideally to be linked to an existing adverse outcome pathway (AOP) framework. Ultimately, EPA will use NAMs to calculate a chemical's point-of-departure (POD) based on a likely tissue, organ, or organism effect.

In the draft version of the Collaborative Research Program, EPA did not describe how a chemical will move from Tier 1 to Tier 3. In fact, the tiered structure of the testing framework suggests that all subsequent testing in Tiers 2 and 3 are dependent upon the Tier 1 results. Based on the current framework, if EPA cannot identify a defined biological target or pathway using Tier 1 NAMs, the agency will calculate a POD using available Tier 1 data only. In subsequent versions of the Collaborative Research Program, EPA should consider how calculating PODs from only Tier 1 data could potentially affect the hazard characterization of a chemical. Furthermore, in the event that only Tier 1 data (chemical structure and properties and broad coverage high content assays) are available for a chemical, EPA should consider the implications of using only this information to make decisions about chemical categories and toxicity. Critically, all NAMs have important limitations that could carry significant implications for their proposed use in developing categories and evaluating the toxicity of new chemicals. In subsequent versions of the Collaborative Research Program, EPA should address how uncertainties and limitations associated with using these NAMs will be addressed.

The goal of this draft Collaborative Research Program is to bring innovative science to the review of new chemicals to ensure their safety before entering the marketplace. We recommend

that EPA develop a scientific confidence framework for NAMs that could be used to inform the use of NAMs as tools as to assess health human effects. This framework should describe how a particular NAM or suite of fit-for-purpose NAMs will be reviewed for validity. Unlike other predictive methods, such as QSARs, for which there are available guidelines for validating the models, no such guidance exists for newer NAMs.

Ultimately, we recommend that NAMs be used to screen in chemicals, meaning use as evidence to confirm toxicity, rather than screen them out, or determine a chemical does not cause harm. This is critically important because there are still concerns regarding the agreeability between the results from NAMs and the results from animal models or human studies. In fact, a recent study found that PFOA did not show strong activity in NAMs that measure immune response, yet evidence from both animal and human studies shows that PFOA induces immune system suppression.[35] In short, we still don't know if NAMs are suitable replacements for animal testing for all relevant health endpoints. Since the ultimate objective of NAMs is to assess the potential for chemical risk to human health, human data could have an important role in considering the performance of NAMs. EPA should consider how human data fits into evaluating the relevancy of NAMs, to be certain that NAMs are not missing key molecular initiating events or biological pathways that are relevant to adverse health outcomes in humans.

<u>EPA should use all available NAMs</u>

The draft Collaborative Research Program states that EPA has a list of NAMs that are "scientifically reliable, relevant, and capable of providing information of equivalent or better scientific reliability and quality to that which would be obtained from vertebrate testing." As stated in this list,[36] we hope that EPA considers this to be a starting point, rather than an exhaustive list of NAMs. We recommend that EPA consider and include a variety of NAMs (e.g., *in vitro* assays, predictive *in silico* models, computational models for estimating internal and external exposure) for use in its Collaborative Research Program.

Furthermore, during virtual meeting presentation, EPA commented that it may look to targeted assays used for "a safety pharmacology approach" that are already "in use by cosmetics and pharmaceuticals companies" to develop a testing framework. We recommend that any NAMs developed outside of EPA be validated by a third party before being used by the agency.

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The Environmental Defense Fund appreciates EPA's consideration of these comments.

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[35] Naidenko O.V., *et al.* (2021, March 24). "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):3332. https://doi.org/10.3390/ijerph18073332

[36] EPA. (2021, February 4). "List of Alternative Test Methods and Strategies (or New Approach Methodologies [NAMs], Second Update." https://www.epa.gov/sites/default/files/2021-02/documents/nams_list_second_update_2-4-21_final.pdf