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Comments from Academics, Scientists and Clinicians on the Draft Scopes for 20 Designated High Priority Chemical Substances Under the Toxic Substances Control Act

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These comments are submitted on behalf of the undersigned academics, scientists, and clinicians. We declare collectively that we have no direct or indirect financial or fiduciary interest in any chemical or product that is the subject of these comments. The co-signers' institutional affiliations are included for identification purposes only and do not imply institutional endorsement or support.

We appreciate the opportunity to provide written comments on the 'Draft Scopes for 20 Designated High Priority Chemical Substances Under the Toxic Substances Control Act (TSCA)' (hereafter referred to as the 'Draft Scopes'), as amended by the Frank R. Lautenberg Chemical Safety for the 21st Century Act ('amended TSCA').[1] TSCA defines a high-priority chemical as "a chemical substance that the Administrator concludes, without consideration of costs or other nonrisk factors, may present an unreasonable risk of injury to health or the environment because of a potential hazard and a potential route of exposure under the conditions of use, including an unreasonable risk to a potentially exposed or susceptible subpopulation."[2] All 20 of the Draft Scopes meet this definition.

Collectively, these chemicals represent an aggregate production volume of more than 22 billion pounds a year in 2015, if using the most conservative estimate found in the scoping documents.[3] Some of these chemicals have assessments, and in some cases even restrictions, under other federal programs—but none of these other programs has the mandate given to EPA under amended TSCA: to comprehensively evaluate chemicals and ensure that they do not pose an unreasonable risk to human health and the environment, with special consideration to those most vulnerable amongst us. For the risk evaluation, both TSCA[4] and EPA's regulation[5] require adequate information to make a determination of whether or not a chemical poses an unreasonable risk. To set a chemical as high priority, the regulation also requires the evaluation of "relevant" potential human and environmental hazards.[6] We agree with EPA's "low bar" to designate a chemical as high-priority, as it is consistent with modern science-based decision-making.[7]

[1] 84 FR 44300
[2] 15 USC §2605
[3] This is the aggregate production volume estimate calculated using the lowest end of the range for the 18 chemicals with production volume information available. For 1,1 – dichloroethane and 1,2-dichloropropane, manufacturers/ importers claimed production volumes as confidential business information (CBI). Confidential Business Information (CBI) claims should not be used to obscure critical information from the public.
[4] 15 USC §2601 (b)(1)
[5] 40 CFR § 702.41 (b)
[6] 40 CFR § 702.41 (d)(3)
[7] US EPA. (2017). Procedures for Prioritization of Chemicals for Risk Evaluation under the Toxic Substances Control Act; Comment submitted by J. Lam et al. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0636-0071

Accordingly, EPA has developed scoping documents for evaluating the risks of the designated high priority chemicals. We have concerns around the methodology that EPA has used in the Draft Scopes with regard to consistency and transparency, specifically, regarding inadequacies in EPA's risk evaluation process and systematic review methods, which we have previously discussed in detail in our comments on the first ten chemicals that have undergone draft risk evaluations under TSCA.[8,9,10, 11,12,13,14]

Certain health hazards are specifically designated in TSCA as adverse health effects and envisioned that EPA should assess them: "cancer/ carcinogenesis, mutagenesis/ gene mutation, teratogenesis, behavioral disorders, and birth defects."[15] At a minimum these specific health hazards should be evaluated, however this list does not include other important health effects which we have previously highlighted. Finally, because adequate information is critical for decision-making on the high-priority chemicals, it is imperative that EPA determine the completeness of the database of the High Priority Chemical Substances, and quickly move forward to fill identified data gaps.

Based upon the first ten draft risk evaluations, EPA has set a concerning precedent with regard to the implementation of systematic review, consideration of science under TSCA, and consideration of vulnerable populations such as children and workers. The health impacts of EPA's previous and current decisions will be borne by generations of children, workers, families, and communities. With so much at stake, we recommend concrete approaches for EPA to embed the most current scientific principles in its methods to assess the hazards and risks of environmental chemicals.

Our comments address the following main points in the Draft Scopes for the High Priority Chemical Substances:

[8] US EPA. (2019). Toxic Substances Control Act (TSCA) Science Advisory Committee on Chemicals Review of Risk Evaluation for Pigment Violet 29 (PV 29). Comment submitted by Hanna Vesterinen, Research Consultant to UCSF PRHE et al. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2018-0604-0043

[9] US EPA. (2019). Draft Toxic Substances Control Act (TSCA) Risk Evaluations and TSCA Science Advisory Committee on Chemicals (SACC) Meetings; Cyclic Aliphatic Bromide Cluster (HBCD) and 1,4-Dioxane; Notice of Availability and Public Meetings. Comment submitted by Swati Rayasam, Science Associate, Program on Reproductive Health and the Environment, Department of Obstetrics, Gynecology and Reproductive Sciences, University of California, San Francisco et al. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0237-0059 and https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0238-0056

[10] US EPA. (2019). Toxic Substances Control Act (TSCA) Science Advisory Committee on Chemicals Review of Risk Evaluation for 1-Bromopropane. Comment submitted by Swati Rayasam, Science Associate, Program on Reproductive Health and the Environment, Department of Obstetrics, Gynecology and Reproductive Sciences, University of California, San Francisco et al. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0235-0053

[11] US EPA. (2019). Toxic Substances Control Act (TSCA) Science Advisory Committee on Chemicals Review of Risk Evaluation for Methylene Chloride. Comment submitted by Swati Rayasam, Science Associate, Program on Reproductive Health and the Environment, University of California, San Francisco (UCSF PRHE) et al. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0437-0069

[12] US EPA. (2020). Meetings: N-Methylpyrrolidone; Draft Toxic Substances Control Act (TSCA) Risk Evaluation and TSCA Science Advisory Committee on Chemicals. Comment submitted by Veena Singla, Associate Director, Program on Reproductive Health and the Environment, School of Medicine, University of California, San Francisco. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0236-0040

[13] US EPA. (2020). Toxic Substances Control Act (TSCA) Science Advisory Committee on Chemicals Review of Risk Evaluation for Carbon Tetrachloride. Comment submitted by Swati Rayasam, Science Associate, Program on Reproductive Health and the Environment, Department of Obstetrics, Gynecology and Reproductive Sciences, University of California, San Francisco et al. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0499-0041

[14] US EPA. (2020). Trichloroethylene; Draft Toxic Substances Control Act (TSCA) Risk Evaluation and TSCA Science Advisory Committee on Chemicals (SACC) Meetings; Notice of Availability, Public Meetings, and Request for Comment. Comment submitted by Swati Rayasam et al., Science Associate, Program on Reproductive Health and the Environment, Department of Obstetrics, Gynecology and Reproductive Sciences, University of California, San Francisco (UCSF PRHE). Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0500-0106

[15] 15 USC §2603 (b)(2)(A); 15 USC §2603 (e); 15 USC §2605 (b)(2)(D)

1. **EPA states it is using the systematic review process described in the 'Application of Systematic Review in TSCA Risk Evaluations' to guide the process of searching for and screening reasonably available information, including information already in EPA's possession, for use and inclusion in the risk evaluation. However, the approach EPA has proceeded to outline is not consistent with the systematic review process described in the 'Application of Systematic Review in TSCA Risk Evaluations' and in fact contradicts it in fundamental and critical ways.**
2. **EPA has failed to use or mention the future use of a protocol that outlines the pre-established methods to be used throughout the systematic review process as required by EPA regulation under TSCA.**
3. **EPA has failed to publish a sufficiently detailed 'analysis plan' in the Draft Scopes, despite explicitly stating that it would.**
4. **EPA has already excluded 'unacceptable data sources' from the body of evidence for all Draft Scopes when prioritizing these substances. However, EPA has failed to publish these excluded data sources or the rationale for their exclusion. Of further concern is that EPA has not published the data quality criteria it will now use to evaluate these 20 chemical substances in the risk evaluations and may therefore be applying two different data quality criteria to evaluate the data within the same evaluation.**
5. **EPA's TSCA systematic review methodology continues to have serious scientific flaws and is inconsistent with established, validated methods. This flawed methodology lacks transparency and is not empirically based, making it likely to result in biased evaluations of the evidence for these 20 chemical substances. EPA must address the comments from the Science Advisory Committee on Chemicals (SACC) in its previous Peer Reviews of EPA's first 10 draft risk evaluations under TSCA and incorporate the recommended changes to its systematic review prior to finalizing the Draft Scopes for the next 20 chemical substances and for all future TSCA risk evaluations.**
6. **EPA should use existing IRIS assessments as a starting point for assessment of these chemical substances but fails to cite existing IRIS assessments for over half of the 20 chemical substances which possess them. Further, EPA must release the stalled Formaldehyde IRIS Assessment.**
7. **EPA should use a cumulative approach, and at a minimum, assess all common adverse health outcomes for the risk evaluations of phthalates and chlorinated solvents.**
8. **EPA must consider aggregate exposure within and across populations; otherwise it will underestimate risk. Aggregate exposure should include legacy uses, uses where a chemical is present as a contaminant/by-product, and uses already assessed.**
9. **EPA should follow recommendations from the National Academies of Sciences (NAS) to identify susceptible sub-populations based on established extrinsic and intrinsic factors that increase vulnerability.**
10. **For risk characterization, EPA should use health protective defaults and methods that generate risk estimates.**

We appreciate the opportunity to provide public input. Please do not hesitate to contact us with any questions regarding these comments.

Sincerely,

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DETAILED POINTS

1. **EPA states it is using the systematic review process described in the 'Application of Systematic Review in TSCA Risk Evaluations' to guide the process of searching for and screening reasonably available information, including information already in EPA's possession, for use and inclusion in the risk evaluation. However, the approach EPA has proceeded to outline is not consistent with the systematic review process described in the 'Application of Systematic Review in TSCA Risk Evaluations' and in fact contradicts it in fundamental and critical ways.**

For brevity, we have used the Draft Scope of the Risk Evaluation for **1,3-Butadiene** throughout this document as an example to highlight the issues identified across each of the Draft Scopes for these 20 chemical substances. When differences in the approaches used were identified across the scope documents, we have highlighted this in the footnotes.

EPA has stated in every Draft Scope that:[16,17,18,19,20,21,22,23,24,25,26,27,28,29,30,31,32,33,34,35]

[16] US EPA (2020). Draft Scope of the Risk Evaluation for 1,3-Butadiene CASRN 106-99-0 April. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2018-0451-0023
[17] US EPA (2020). Draft Scope of the Risk Evaluation for o-Dichlorobenzene (CASRN 95-50-1). Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2018-0444-0019
[18] US EPA (2020). Draft Scope of the Risk Evaluation for p-Dichlorobenzene (CASRN 106-46-7). Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2018-0446-0025
[19] US EPA (2020). Draft Scope of the Risk Evaluation for 1,1-Dichloroethane (CASRN 75-34-3) Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2018-0426-0015
[20] US EPA (2020). Draft Scope of the Risk Evaluation for 1,2-Dichloroethane (CASRN 107-06-2) Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2018-0427-0029
[21] US EPA (2020). Draft Scope of the Risk Evaluation for trans-1,2-Dichloroethylene (CASRN 156-60-5) Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2018-0465-0026
[22] US EPA (2020). Draft Scope of the Risk Evaluation for 1,2-Dichloropropane (CASRN 78-87-5) Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2018-0428-0020
[23] US EPA (2020). Draft Scope of the Risk Evaluation for Ethylene Dibromide (CASRN 106-93-4) Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2018-0488-0024
[24] US EPA (2020). Draft Scope of the Risk Evaluation for 1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[γ]-2-benzopyran (HHCB) (CASRN 1222-05-5) Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2018-0430-0023
[25] US EPA (2020). Draft Scope of the Risk Evaluation for 4,4'-(1-Methylethylidene)bis[2, 6-dibromophenol] (TBBPA) (CASRN-79-94-7) Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2018-0462-0025
[26] US EPA (2020). DRAFT Scope of the Risk Evaluation for Phosphoric acid, Triphenyl Ester (TPP) (CASRN-115-86-6) Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2018-0458-0021
[27] US EPA (2020). Draft Scope of the Risk Evaluation for 1,1,2-Trichloroethane (CASRN 79-00-5) Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2018-0421-0019
[28] US EPA (2020). Draft Scope of the Risk Evaluation for Tris(2-chloroethyl) Phosphate (TCEP) (CASRN 115-96-8) Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2018-0476-0022
[29] US EPA (2020). Draft Scope of the Risk Evaluation for Di-ethylhexyl Phthalate (1,2-Benzenedicarboxylic acid, 1,2-bis(2-ethylhexyl) ester) (CASRN 117-81-7) Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2018-0433-0026
[30] US EPA (2020). Draft Scope of the Risk Evaluation for Dicyclohexyl Phthalate (1,2- Benzenedicarboxylic acid, 1,2-dicyclohexyl ester) CASRN 84-61-7. Available: https://www.epa.gov/sites/production/files/2020-04/documents/casrn-84-61-7_dicyclohexyl_phthalate_draft_scope_4-15-2020.pdf
[31] US EPA (2020). Draft Scope of the Risk Evaluation for Di-isobutyl Phthalate (1,2-Benzenedicarboxylic acid, 1,2-bis(2-methylpropyl) ester) (CASRN 84-69-5) Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2018-0434-0028
[32] US EPA (2020). Draft Scope of the Risk Evaluation for Butyl Benzyl Phthalate (1,2-Benzenedicarboxylic acid, 1-butyl 2-(phenylmethyl) ester) (CASRN 85-68-7) Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2018-0501-0036
[33] US EPA (2020). Draft Scope of the Risk Evaluation for Dibutyl Phthalate (1,2-Benzenedicarboxylic acid, 1,2-dibutyl ester) CASRN 84-74-2. Available: https://www.epa.gov/sites/production/files/2020-04/documents/casrn-84-74-2_dibutyl_phthalate_draft_scope_4-15-2020_2.pdf
[34] US EPA (2020).Draft Scope of the Risk Evaluation for Phthalic Anhydride (1,3-Isobenzofurandione) (CASRN 85-44-9) Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2018-0459-0030
[35] US EPA (2020). Draft Scope of the Risk Evaluation for Formaldehyde (CASRN 50-00-0) Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2018-0438-0029

> *"To further develop this draft scope document,* ***EPA conducted a comprehensive search to identify and screen multiple evidence streams*** *(i.e., chemistry, fate, release and engineering, exposure, hazard) and the search and screening results are provided in Section 2.1…..****EPA is using the systematic review process described in the Application of Systematic Review in TSCA Risk Evaluations document*** *(U.S. EPA, 2018a)* ***to guide the process of searching for and screening reasonably available information, including information already in EPA's possession, for use and inclusion in the risk evaluation***." [36]

And goes on to say:

> ***"Eligibility criteria were applied in the form of PECO (population, exposure, comparator, outcome) statements. Included references met the PECO criteria, whereas excluded references did not meet the criteria (i.e., not relevant), and supplemental material was considered as potentially relevant****."* [37,38,39]

However, in 'Application *of Systematic Review in TSCA Risk Evaluations'* EPA states:

> *"Scoping and problem formulation helps shape the systematic review approaches and/or methods* ***that will be used*** *to identify, evaluate, analyze, and integrate evidence. For example,* ***the outcomes of scoping and problem formulation are used to tailor a data search and screening strategy (including eligibility criteria) to identify relevant data and information*** *while winnowing out those that are irrelevant for the risk evaluation".*[40]

In every Draft Scope for the High Priority Chemical Substances, however, EPA states it has already *"conducted a comprehensive search to identify and screen multiple evidence streams"* and used a PECO (population, exposure, comparator, outcome) statement to assess the eligibility of the included studies before completing the scoping and problem formulation step in the systematic review process. It is therefore deeply concerning that EPA is either not aware of their own explicitly stated method or they have chosen not to adhere to it and inappropriately conducted comprehensive searches of the literature and screened and excluded studies based on PECOs statement before completing the scoping and problem formulation step. Validated/peer reviewed systematic review methods transparently define the inclusion/exclusion criteria, typically using a PICO or PECO statement, in the protocol and before the conduct of the systematic review to reduce bias in the identification of the literature for the review.

Of further concern is that it is not clear if EPA intends on conducting future searches to identify new data for inclusion in the evaluation of these 20 substances. EPA states in the *'Analysis Plan'* for *'Draft Scope of the Risk Evaluation for 1,3-Butadiene'* that:

[36] US EPA (2020). Draft Scope of the Risk Evaluation for 1,3-Butadiene CASRN 106-99-0 April. Pp 8 Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2018-0451-0023

[37] US EPA (2020). Draft Scope of the Risk Evaluation for 1,3-Butadiene CASRN 106-99-0 April. Pp 13 Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2018-0451-0023

[38] The exact wording of how the PECO statement is described varies across the scoping documents, however it is used as the eligibility criteria in every one to include and exclude data sources.

[39] For Draft Scope of the Risk Evaluation for Formaldehyde EPA states "Eligibility criteria were applied in the form of PECO (population, exposure, comparator, outcome) statements. Included references will meet the PECO criteria, whereas excluded references will not meet the criteria (i.e., not relevant), and supplemental material will be considered as potentially relevant. EPA is in the process of screening the identified literature for the different disciplines; the search results are not yet ready for review."

[40] EPA (2018) Application of Systematic Review in TSCA Risk Evaluations. Pp 12.

> *"The analysis plan is based on EPA's knowledge of 1,3-butadiene to date* ***which includes a partial, but ongoing, review of identified information*** *as described in Section 2.1.* ***EPA plans to continue to consider new information submitted by the public****. Should additional data or approaches become reasonably available, EPA may update its analysis plan in the final scope document."* [41]

It appears EPA is stating on the one hand the searches conducted in Section 2.1 "*includes a partial, but ongoing, review of identified information"* which would suggest that these searches are not final and that there will be further searches conducted. However, EPA then defines this "*partial, but ongoing, review of identified information"* as "*new information submitted by the public."* It is therefore unclear if EPA is intending on conducting further searches of the evidence or if it will develop new PECO statements following the completion of the scoping and problem formulation steps as is recommended in the '*Application of Systematic Review in TSCA Risk Evaluations*'. This ambiguity and lack of transparency is confusing and deeply concerning.

Regardless of whether EPA continues to conduct future searches or not, they must immediately for each of these Draft Scopes publish: 1) the search strategies used, the list of data bases that have been searched and the dates that the searches were conducted; 2) the PECO statement that has already been used as the eligibility criteria to include and exclude data sources as EPA does not define what their PECO statement is; and 3) the full list of studies that have been identified for each evidence stream and those that have been excluded at the title and abstract stage.

2. EPA has failed to use or mention the future use of a protocol that outlines the pre-established methods to be used throughout the systematic review process as required by EPA regulation under TSCA.

EPA states in the '*Draft Scope of the Risk Evaluation for 1,3-Butadiene'* that:

> "EPA plans to publish supplemental documentation on the systematic review methods supporting the 1,3-butadiene risk evaluation to explain the literature and screening process presented in this document in the form of literature inventory trees. ***Please note that EPA focuses on the data collection phase (consisting of data search, data screening, and data extraction) during the preparation of the TSCA scope document, whereas the data evaluation and integration stages will occur during the development of the draft risk evaluation and thus are not part of the scoping activities described in this document."*** [42,43]

Firstly, as highlighted in point #1, it is not appropriate that *"EPA focuses on the data collection phase* ***during the preparation*** *of the TSCA scope document"*, as it should be conducted **after** the Scoping and

[41] US EPA (2020). Draft Scope of the Risk Evaluation for 1,3-Butadiene CASRN 106-99-0 April. Pp 10 Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2018-0451-0023

[42] US EPA (2020). Draft Scope of the Risk Evaluation for 1,3-Butadiene CASRN 106-99-0 April. Pp 12 Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2018-0451-0023

[43] In the Draft Scope of the Risk Evaluation for Tris (2-chloroethyl) Phosphate it does not mention that EPA focuses on the data collection phase during the preparation of the TSCA scope document. Rather it states: "After completing the screening of all identified reasonably available information, the Agency will evaluate the quality of relevant information, synthetize and integrate it to form overall conclusions about the potential hazards and exposures to support the risk characterization for TCEP. This systematic review process will be documented and made public as EPA undergoes the risk evaluation process. The details are not part of this document but will be provided in a supplemental document that EPA anticipates releasing prior to the finalization of the scope document."

Problem Formulation steps are completed EPA fails to explicitly say they will develop and publish a protocol for any of the 20 scoping documents. They do not mention a protocol in 19 of the documents, and in one, '*Draft Scope of the Risk Evaluation for 1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-Hexamethylcyclopenta[γ]-2-Benzopyran (HHCB)*' [44] This is the only mention of a protocol and it is not clear how it will be used.

This contradicts how EPA has explicitly stated it is conducting these Draft Scopes for the High Priority Chemical Substances according to its own systematic review method. In the draft scoping document for 1,3 Butadiene EPA states:

> *"**EPA is using the systematic review process described in the Application of Systematic Review in TSCA Risk Evaluations document (U.S. EPA, 2018a) to guide the process of searching for and screening reasonably available information**, including information already in EPA's possession, for use and inclusion in the risk evaluation"* [45]

However, as shown, in '*Figure 3-1 TSCA Systematic Review Process*' in '*Application of Systematic Review in TSCA Risk Evaluations*' [46] EPA highlights "Protocol Development" as the first step of the systematic review process and goes on to state that:

> *"**Protocol Development is intended to pre-specify the criteria, approaches and/or methods for data collection, data evaluation and data integration. It is important to plan the systematic review approaches and methods in advance to reduce the risk of introducing bias into the risk evaluation process.** TSCA requirements and the results of scoping/problem formulation (i.e., conceptual model(s), analysis plan) frame the specific scientific risk assessment questions to be addressed in each TSCA risk evaluation**. Likewise, the statutory requirements and scoping/problem formulation inform how the data are searched, evaluated and integrated in the assessment**."* [47]

Further, the justification that EPA has previously offered in '*Application of Systematic Review in TSCA Risk Evaluations*' for not producing protocols for the first ten chemical substances that have now undergone draft risk evaluations, no longer applies to these 20 chemical substances as EPA states:

> *"**The timeframe for development of the TSCA Scope documents has been very compressed. The first ten chemical substances were not subject to prioritization**, the process through which EPA expects to collect and screen much of the relevant information about chemical substances that will be subject to the risk evaluation process. **As a result, EPA had limited ability to develop a protocol document detailing the systematic review approaches and/or methods prior to the initiation of the risk evaluation process for the first ten chemical substances**. For these reasons, the protocol development is staged in phases while conducting the assessment work."*

These **20 chemicals have gone through the prioritization process** and **EPA has had sufficient time to develop protocols** detailing the systematic review approaches and/or methods **prior to the initiation of**

[44] US EPA (2020). Draft Scope of the Risk Evaluation for 1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta[γ]-2-benzopyran (HHCB) (CASRN 1222-05-5) Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2018-0430-0023

[45] US EPA (2020). Draft Scope of the Risk Evaluation for 1,3-Butadiene CASRN 106-99-0 April. Pp 8 Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2018-0451-0023

[46] EPA (2018) Application of Systematic Review in TSCA Risk Evaluations. Pp 15.

[47] EPA (2018) Application of Systematic Review in TSCA Risk Evaluations. Pp 19.

the risk evaluation process (it has been two years since EPA released the *'Application of Systematic Review in TSCA Risk Evaluations')*. Therefore, EPA has commenced this process without a detailed protocol that is likely to significantly bias these evaluations.

In order for EPA to adequately address these issues relating to its lack of transparency, **the Agency must immediately implement protocols for each of the Draft Scopes for the High Priority Chemical Substances**. The use of pre-established protocols minimizes such biases in the evidence base by explicitly pre-defining how: the questions will be formulated, the searches will be conducted, the eligibility criteria will be applied, and the quality of the included studies will be assessed.[48] Most importantly, it allows greater transparency in the decision-making process throughout the systematic review and it is a fundamental element required to ensure the integrity of evidence-based evaluations and it is a critical methodological step absent again in EPA's risk evaluations. Further, not using predefined protocols directly contradicts the EPA's 2017 framework rules mandating that the agency use "a pre-established protocol" to conduct risk assessments.[49]

There are multiple well-developed, evidence-based, peer-reviewed and validated methods for conducting systematic reviews in environmental health that EPA could readily apply, including the National Toxicology Program's Office of Health Assessment and Translation (NTP OHAT) method [50] and the Navigation Guide Systematic Review Method, which has been demonstrated in six case studies. [51,52,53,54,55, 56,57,58] The National Academies of Sciences, Engineering, and Medicine (NASEM) has cited both of these systematic review methods as exemplary of the type of methods EPA should use in hazard and

[48] National Research Council. (2014). Review of EPA's Integrated Risk Information System (IRIS) Process. Washington, DC: National Academies Press.

[49] 40 CFR 702 Pg. 33733

[50] National Toxicology Program Office of Health Assessment and Translation. (2015). Handbook for Conducting a Literature-Based Health Assessment Using OHAT Approach for Systematic Review and Evidence Integration. National Institute of Environmental Health Sciences; 2015

[51]Johnson PI, Sutton P, Atchley DS, Koustas E, Lam J, Sen S, Robinson KA, Axelrad DA, Woodruff TJ. The Navigation Guide - evidence-based medicine meets environmental health: systematic review of human evidence for PFOA effects on fetal growth. Environ Health Perspect. 2014;122(10):1028-39. Epub 2014/06/27. doi: 10.1289/ehp.1307893. PubMed PMID: 24968388; PMCID: 4181929.

[52]Koustas E, Lam J, Sutton P, Johnson PI, Atchley DS, Sen S, Robinson KA, Axelrad DA, Woodruff TJ. The Navigation Guide - evidence-based medicine meets environmental health: systematic review of nonhuman evidence for PFOA effects on fetal growth. Environ Health Perspect. 2014;122(10):1015-27. Epub 2014/06/27. doi: 10.1289/ehp.1307177. PubMed PMID: 24968374; PMCID: 4181920.

[53] Lam J, Koustas E, Sutton P, Johnson PI, Atchley DS, Sen S, Robinson KA, Axelrad DA, Woodruff TJ. The Navigation Guide - evidence-based medicine meets environmental health: integration of animal and human evidence for PFOA effects on fetal growth. Environ Health Perspect. 2014;122(10):1040-51. Epub 2014/06/27. doi: 10.1289/ehp.1307923. PubMed PMID: 24968389; PMCID: 4181930

[54]Vesterinen H, Johnson P, Atchley D, Sutton P, Lam J, Zlatnik M, Sen S, Woodruff T. The relationship between fetal growth and maternal glomerular filtration rate: a systematic review. J Maternal Fetal Neonatal Med. 2014:1-6. Epub Ahead of Print; PMCID: 25382561.

[55] Johnson PI, Koustas E, Vesterinen HM, Sutton P, Atchley DS, Kim AN, Campbell M, Donald JM, Sen S, Bero L, Zeise L, Woodruff TJ. Application of the Navigation Guide systematic review methodology to the evidence for developmental and reproductive toxicity of triclosan. Environ Int. 2016;92-93:716-28. doi: 10.1016/j.envint.2016.03.009. PubMed PMID: 27156197.

[56] Lam J, Sutton P, Halladay A, Davidson LI, Lawler C, Newschaffer CJ, Kalkbrenner A, Joseph J. Zilber School of Public Health, Windham GC, Daniels N, Sen S, Woodruff TJ. Applying the Navigation Guide Systematic Review Methodology Case Study #4: Association between Developmental Exposures to Ambient Air Pollution and Autism. PLoS One. 2016;21(11(9)). doi: 10.1371/journal.pone.0161851.

[57] Lam J, Lanphear B, Bellinger D, Axelrad D, McPartland J, Sutton P, Davidson LI, Daniels N, Sen S, Woodruff TJ. Developmental PBDE exposure and IQ/ADHD in childhood: A systematic review and meta-analysis. Environmenal Health Perspectives. 2017;125(8). doi: doi: 10.1289/EHP1632.

[58] Lam J, Koustas E, Sutton P, Cabana M., Whitaker E., Padula A, Vesterinen H, Daniels N, Woodruff TJ. Applying the Navigation Guide: Case Study #6. Association Between Formaldehyde Exposures and Asthma. In preparation. 2019.

risk assessment.[59,60,61,62] Further, the NASEM has utilized both methods in its 2017 assessment of the potential health impacts of endocrine active environmental chemicals.[63] Specifically, in its 2017 review the NASEM found:

> "The two approaches [OHAT and Navigation Guide] are very similar… and they are based on the same established methodology for the conduct of systematic review and evidence assessment (e.g., Cochrane Collaboration, AHRQ Evidence-based Practice Center Program, and GRADE). Both the OHAT and Navigation Guide methods include the key steps recommended by a previous National Academies committee (NRC 2014) for problem formulation, **protocol development**, specifying a study question, developing PECO statement, identifying and selecting the evidence, evaluating the evidence, and integrating the evidence." [64]

Protocols developed for applying the OHAT method[65] and the Navigation Guide Systematic Review Method have been published and can serve as a template to further expedite EPA's systematic reviews under TSCA.[66, 67]

3. EPA has failed to publish a sufficiently detailed 'analysis plan' in the Draft Scopes, despite explicitly stating that it would.

EPA states in the '*Draft Scope of the Risk Evaluation for 1,3-Butadiene*' that:

> *"**The draft scope for 1,3-butadiene includes the following information**: the conditions of use, potentially exposed or susceptible subpopulations (PESS), hazards, and exposures that EPA plans to consider in this risk evaluation, along with a description of the reasonably available information, **conceptual model, analysis plan and science approaches**, and plan for peer review for this chemical substance."* [68]

Further, in '*Application of Systematic Review in TSCA Risk Evaluations*' EPA states:

> *"**TSCA requires EPA to publish the scope for any risk evaluation it will conduct**….To communicate and visually convey the relationships between these components, the final rule*

[59] National Research Council. (2014). Review of EPA's Integrated Risk Information System (IRIS) Process. Washington, DC: The National Academies Press; 2014.
[60] National Academies of Sciences Engineering, and Medicine. (2018). Progress Toward Transforming the Integrated Risk Information System (IRIS) Program: A 2018 Evaluation. Washington, DC: The National Academies Press; 2018.
[61] National Academies of Sciences Engineering, and Medicine. (2017). Application of Systematic Review Methods in an Overall Strategy for Evaluating Low-Dose Toxicity from Endocrine Active Chemicals. Washington, D.C.: The National Academies Press; 2011
[62] National Academies of Sciences, Engineering, and Medicine. 2019. Review of DOD's Approach to Deriving an Occupational Exposure Level for Trichloroethylene. Washington, DC: The National Academies Press. https://doi.org/10.17226/25610.
[63] National Academies of Sciences Engineering, and Medicine. (2017). Application of Systematic Review Methods in an Overall Strategy for Evaluating Low-Dose Toxicity from Endocrine Active Chemicals. Washington, D.C.: The National Academies Press; 2011
[64] National Academies of Sciences Engineering, and Medicine. (2017). Application of Systematic Review Methods in an Overall Strategy for Evaluating Low-Dose Toxicity from Endocrine Active Chemicals. Page. 119.Washington, D.C.: The National Academies Press; 2011
[65] National Toxicology Program Office of Health Assessment and Translation. (2015). Handbook for Conducting a Literature-Based Health Assessment Using OHAT Approach for Systematic Review and Evidence Integration. National Institute of Environmental Health Sciences; 2015
[66] All Navigation Guide systematic review protocols can be found at: https://prhe.ucsf.edu/navigation-guide The National Toxicology Program's protocol for its systematic review to evaluate the evidence for an association between exposure to PFOA or PFOS and immunotoxicity or immune-related health effects is at: https://ntp.niehs.nih.gov/ntp/ohat/pfoa_pfos/protocol_201506_508.pdf
[67] National Toxicology Program. Completed Evaluations. Available: https://ntp.niehs.nih.gov/whatwestudy/assessments/noncancer/completed/index.html
[68] US EPA (2020). Draft Scope of the Risk Evaluation for 1,3-Butadiene CASRN 106-99-0 April. Pp 8 Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2018-0451-0023

> *Procedures for Chemical Risk Evaluation Under the Amended Toxic Substances Control Act (40 CFR Part 702)* requires ***including a conceptual model and an analysis plan for each risk evaluation****."* [69]

However, EPA fails to adequately outline the *'Analysis Plan'* that it intends on using, repeatedly stating that detail on its intended approach is forthcoming:

> *"EPA plans to seek public comments on the systematic review methods supporting the risk evaluation for 1,3-butadiene, including the methods for assessing the quality of data and information and the approach for evidence synthesis and evidence integration supporting the exposure and hazard assessments.* ***The details will be provided in a supplemental document that EPA anticipates releasing for public comment prior to the finalization of the scope document."*** [70]

EPA's failure to publish its analysis plan is repeated through the other sections of the Draft Scopes as well.

In '*Analysis Plan'* for *'Human Health Hazards'* EPA states:

1) *"Review reasonably available human health hazard data, including data from alternative test methods (e.g., computational toxicology and bioinformatics; high-throughput screening methods; data on categories and read-across; in vitro studies; systems biology). EPA plans to use systematic review methods to evaluate the epidemiological and toxicological literature for 1,3-butadiene.* ***EPA plans to publish the systematic review documentation prior to finalizing the scope document"****.* [71,72]

3) *"Conduct hazard identification (the qualitative process of identifying non-cancer and cancer endpoints) and dose-response assessment (the quantitative relationship between hazard and exposure) for identified human health hazard endpoints. Human health hazards from acute and chronic exposures will be identified by evaluating the human and animal data that meet the systematic review data quality criteria described in the systematic review documentation* ***that EPA plans to publish prior to finalizing the scope document."*** [73,74]

5) "Evaluate the weight of the scientific evidence of human health hazard data. During risk evaluation**,** *EPA plans to evaluate and integrate the human health hazard evidence identified in the literature inventory under acute and chronic exposure conditions using the methods*

[69] EPA (2018) Application of Systematic Review in TSCA Risk Evaluations. Pp 12.
[70] US EPA (2020). Draft Scope of the Risk Evaluation for 1,3-Butadiene CASRN 106-99-0 April. Pp 10 Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2018-0451-0023
[71] US EPA (2020). Draft Scope of the Risk Evaluation for 1,3-Butadiene CASRN 106-99-0 April. Pp 49 Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2018-0451-0023
[72] In the Draft Scope of the Risk Evaluation for Triphenyl Phosphate CASRN 115-86-6, Tris(2-chloroethyl) Phosphate CASRN 115-96-8 and 1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-Hexamethylcyclopenta[γ]-2-Benzopyran (HHCB) CASRN 1222-05-5 it does not state *"EPA plans to publish the systematic review documentation prior to finalizing the scope document"*
[73] US EPA (2020). Draft Scope of the Risk Evaluation for 1,3-Butadiene CASRN 106-99-0 April. Pp 49 Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2018-0451-0023
[74] In the Draft Scope of the Risk Evaluation for 1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-Hexamethylcyclopenta[γ]-2-Benzopyran (HHCB) CASRN 1222-05-5 it does not state *"EPA plans to publish prior to finalizing the scope document."*

*described in the systematic review documentation that **EPA plans to publish prior to finalizing the scope document."*** [75,76]

If EPA has already completed the data screening of eligible studies using a PECO statement in the Draft Scopes for these 20 chemical substances then the analysis methods should also be ready to be published as the PECO statement guides the entire review process, including the search strategy, the inclusion/exclusion criteria to be applied, the data to be extracted, and critically, the strategy for the synthesis and reporting of results. [77] It is unclear how this process has taken place without these methods already being established. EPA should therefore immediately publish its analysis plan so that it may be evaluated.

4. **EPA has already excluded 'unacceptable data sources' from the body of evidence for all Draft Scopes when prioritizing these substances. However, EPA has failed to publish these excluded data sources or the rationale for their exclusion. Of further concern is that EPA has not published the data quality criteria it will now use to evaluate these 20 chemical substances in the risk evaluations and may therefore be applying two different data quality criteria to evaluate the data within the same evaluation.**

EPA states in *'A Working Approach for Identifying Potential Candidate Chemicals for Prioritization'*:

> *"The initial emphasis will be the exclusion of unacceptable data sources based on data quality criteria outlined in the Application for Systematic Review in TSCA Risk Evaluations EPA document. Specifically, these criteria identify serious flaws that would make the information unreliable to use for risk evaluation purposes. This increases the efficiency of EPA's systematic review efforts by excluding unacceptable data sources early in the process for those chemical substances that may enter risk evaluation through a high-priority designation*."[78]

We have previously commented, both to EPA and in a peer-reviewed commentary on the scientific flaws in the TSCA systematic review method, that its approach to evaluating the quality of the included data that may lead to the exclusion of a study due to one 'serious flaw'.[79,80,81] However, it is also concerning that EPA has already been 'excluding unacceptable data sources' in these high-priority risk evaluations using an ad hoc method that has not been peer-reviewed or without documenting the evaluation process in any of the Draft Scopes. The process that EPA has already used to assess data quality raises serious concerns for the Risk Evaluations to be conducted for these 20 chemicals, as evidence has been

[75] US EPA (2020). Draft Scope of the Risk Evaluation for 1,3-Butadiene CASRN 106-99-0 April. Pp 50 Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2018-0451-0023

[76] In the Draft Scope of the Risk Evaluation for 1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-Hexamethylcyclopenta[γ]-2-Benzopyran (HHCB) CASRN 1222-05-5 it does not state "EPA plans to publish prior to finalizing the scope document"

[77] National Toxicology Program Office of Health Assessment and Translation. (2019). Handbook for Conducting a Literature-Based Health Assessment Using OHAT Approach for Systematic Review and Evidence Integration. Pp 8National Institute of Environmental Health Sciences; 2019

[78] US EPA (2018). A Working Approach for Identifying Potential Candidate Chemicals for Prioritization September. Pp 13-14. Available: https://www.epa.gov/sites/production/files/201809/documents/preprioritization_white_paper_9272018.pdf

[79] EPA (2018) Application of Systematic Review in TSCA Risk Evaluations.

[80] US EPA (2018) Problem Formulations for the Risk Evaluations to be Conducted for the First Ten Chemical Substances under the Toxic Substances Control Act, and Application of Systematic Review in TSCA Risk Evaluations; Notice of Availability, Comment submitted by Veena Singla, Associate Director, Science and Policy, Program on Reproductive Health and the Environment, University of California, San Francisco et al. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2018-0210-0107

[81] Singla, V. I., Sutton, P. M., & Woodruff, T. J. (2019). The Environmental Protection Agency Toxic Substances Control Act Systematic Review Method May Curtail Science Used to Inform Policies, With Profound Implications for Public Health. *American Journal of Public Health*, *109*(7), 982–984. doi:10.2105/AJPH.2019.305068

removed from the evidence base without any justification. However, of further concern is EPA's statement in the Draft Scopes that:

> *"**Human health hazards from acute and chronic exposures will be identified by evaluating the human and animal data that meet the systematic review data quality criteria described in the systematic review documentation that EPA plans to publish prior to finalizing the scope document**. Hazards identified by studies meeting data quality criteria will be grouped by routes of exposure relevant to humans (e.g., oral, dermal, inhalation) and by cancer and noncancer endpoints".*[82,83]

Therefore, EPA is indicating that its data quality assessments moving forward from the Draft Scopes will be based on an as-of-yet unpublished systematic review document. This is concerning as it shows EPA may incorporate **two different sets of criteria** to evaluate data quality for **one chemical** between prioritization and scoping. It is likely the criteria will be different given that EPA has published at least **two** new separate updates to how it evaluates the human epidemiological evidence since these 20 chemicals were designated as high-priority substances and since their original publication of their criteria.[84] The first can be found in '*Systematic Review Supplemental File: Updates to the Data Quality Criteria for Epidemiological for the Draft Risk Evaluation for Carbon Tetrachloride'*[85]and the second in *'Risk Evaluation for Trichloroethylene Systematic Review Supplemental File: Updates to the Data Quality Criteria for Epidemiological Studies'* CASRN: 79-01-6.[86]

Of note, the original Data Quality Criteria for Epidemiological Studies used in the prioritization process (before November 2019) as outlined in the *'Application of Systematic Review in TSCA Risk Evaluations*' had 19 criteria which could exclude a study, and now the '*Updates to the Data Quality Criteria for Epidemiological for the Draft Risk Evaluation'* for both Carbon Tetrachloride and Trichloroethylene have 14 criteria which could exclude a study. Therefore, it is likely EPA will evaluate the included studies following full text screening in the Draft Scopes using a *Data Quality Criteria* that 14 criteria which could exclude a study. Further, given that EPA has been evolving their data quality criteria without appropriate external peer review, it indicates that EPA's methods are changing as the documents are being written which opens up the evaluations to bias.

We strongly recommend that EPA present the studies that have already been excluded from the evidence base for these 20 chemicals substances during prioritization under the criteria outlined in the pre-November 2019 *'Application for Systematic Review in TSCA Risk Evaluations*', the rationales for such exclusions, and the quality criteria it now plans to use to assess the data quality of included studies for these chemical substances, so that comparisons can be made to ensure that the criteria are consistent.

[82] US EPA (2020). Draft Scope of the Risk Evaluation for 1,3-Butadiene CASRN 106-99-0 April. Pp 49 Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2018-0451-0023

[83] In the Draft Scope of the Risk Evaluation for 1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-Hexamethylcyclopenta[γ]-2-Benzopyran (HHCB) CASRN 1222-05-5 it does not state "Human health hazards from acute and chronic exposures will be identified by evaluating the human and animal data that meet the systematic review data quality criteria described in the systematic review documentation that EPA plans to publish prior to finalizing the scope document."

[84] US EPA (2018). A Working Approach for Identifying Potential Candidate Chemicals for Prioritization September. Pp 13-14. Available: https://www.epa.gov/sites/production/files/201809/documents/preprioritization_white_paper_9272018.pdf

[85] US EPA. (2020). Systematic Review Supplemental File: Updates to the Data Quality Criteria for Epidemiological Studies. Available: https://www.epa.gov/sites/production/files/2020 01/documents/8_ccl4_updates_to_the_data_quality_criteria_for_epidemiological_studies_updated_january_2020.pdf

[86] Risk Evaluation for Trichloroethylene Systematic Review Supplemental File: Updates to the Data Quality Criteria for Epidemiological Studies' CASRN: 79-01-6. Available: https://www.epa.gov/sites/production/files/2020-02/documents/16_tce-updates_to_the_data_quality_criteria_for_epidemiological_studies.pdf

5. EPA's TSCA systematic review methodology continues to have serious scientific flaws and is inconsistent with established, validated methods. This flawed methodology lacks transparency and is not empirically based, making it likely to result in biased evaluations of the evidence for these 20 chemical substances. EPA must address the comments from the Science Advisory Committee on Chemicals (SACC) in its previous Peer Reviews of EPA's first 10 draft risk evaluations under TSCA and incorporate the recommended changes to its systematic review prior to finalizing the Draft Scopes for the next 20 chemical substances and for all future TSCA risk evaluations.

We stated previously in comments on the Proposed High-Priority Substance Designation that:

> "**Before beginning the risk evaluation process for the first 20 high-priority chemicals** designated as high-priority substances, EPA must address the comments from the Science Advisory Committee on Chemicals (SACC) on the Draft Risk Evaluations for1,4-Dioxane and Cyclic Aliphatic Bromide Cluster (HBCD) through changes to its systematic review process and implement such changes for future TSCA risk evaluations."[87]

Following our review of the Draft Scopes, we again urge EPA to address these comments, and additional comments made by other SACC committees, including those made in its Peer Review of the Draft Risk Evaluations of the first ten chemicals[88],[89],[90],[91],[92] which echo the comments made by the SACC on the Draft Risk Evaluations for1,4-Dioxane and Cyclic Aliphatic Bromide Cluster (HBCD). The SACC has made several comments and critical recommendations necessary to improve the TSCA systematic review method which EPA has again not addressed in the Draft Scopes; therefore, the scientific flaws in the TSCA systematic review method persist. EPA should incorporate the following comments and recommendations made by EPA's SACC that are relevant to flaws we have identified in the systematic review process for these 20 chemical substances:

The EPA SACC in its Peer Review of PV29 commented: "The Committee discussed the need to publish peer reviewed pre-established protocols for each of the Agency's reviews prior to performing the actual risk assessment. The protocol for PV29 was created concurrently with the review, which is contrary to best practices for systematic reviews" [93]

[87] US EPA. (2019) Proposed High-Priority Substance Designations Under the Toxic Substances Control Act (TSCA). Comment submitted by Swati Rayasam, Science Associate, Program on Reproductive Health and the Environment, Department of Obstetrics, Gynecology and Reproductive Sciences, University of California, San Francisco (UCSF PRHE) et al. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2018-0451-0019

[88] US EPA. (2019). Peer Review for EPA Draft Risk Evaluation of C.I. Pigment Violet 29 (PV29). Available: https://www.regulations.gov/docket?D=EPA-HQ-OPPT-2018-0604 D=EPA-HQ-OPPT-2018-0604

[89] US EPA. (2019). Draft Toxic Substances Control Act Risk Evaluations: 1-Bromopropane. Comment submitted by Swati Rayasam, Science Associate, Program on Reproductive Health and the Environment, University of California, San Francisco et al. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0235-0053

[90] US EPA. (2019). Peer Review for the United States Environmental Protection Agency (EPA) Draft Risk Evaluation for 1-Bromopropane (1-BP). Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0235-0061

[91] US EPA. (2019). Peer Review for the United States Environmental Protection Agency (EPA) Draft for Risk Methylene Chloride. Available:https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0437-0080

[92] US EPA. (2019). Peer Review for the United States Environmental Protection Agency (EPA) Draft for N-Methylpyrrolidone (NMP). Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0236-0066

[93] US EPA. (2019). Peer Review for EPA Draft Risk Evaluation of C.I. Pigment Violet 29 (PV29). Pp 27. Available: https://www.regulations.gov/docket?D=EPA-HQ-OPPT-2018-0604 D=EPA-HQ-OPPT-2018-0604

The EPA SACC in its Peer Review of 1, 4 Dioxane commented: "Committee members did not find the systematic review to be a transparent and objective method for gathering the relevant scientific information, scoring its quality, and integrating the information evaluate."[94]

The EPA SACC in its Peer Review of 1-BP commented: "The Committee generally concluded that it was difficult at best to determine exactly what was done during the SR…..**Committee members expressed that they experienced challenges in trying to follow the actions taken in the SR**, and how the results of the SR were used in the draft risk assessment." [95](emphasis ours)

The EPA SACC Peer Review of 1-BP commented: "Several Committee members discussed in depth that it was not appropriate to determine an "unacceptable" rating during data quality evaluation based solely on one criterion."[96]

The EPA SACC Peer Review of 1, 4 Dioxane recommended: "Do not be overly stringent and exclude studies based on a single criterion."[97]

6. EPA should use existing IRIS assessments as a starting point for assessment of these chemical substances but fails to cite existing IRIS assessments for over half of the 20 chemical substances which possess them. Further, EPA must release the stalled Formaldehyde IRIS Assessment.

As before, we recommend that EPA use the IRIS assessments as a foundation for its review, especially considering that the majority of high priority chemicals have an existing assessment. However, we also recognize that the IRIS systematic review process requires further methodological development to ensure it is in line with other empirically based systematic review methodologies including the Navigation Guide and NTP OHATs method the Office of Health Assessment and Translation (OHAT), and EPA should request IRIS to update and incorporate new evidence where needed, or utilize existing reviews by the NASEM such as the case with DIBP.[98, 99] This approach, that EPA should build on existing reviews to incorporate new studies and then use this updated systematic review as a basis for its assessment, has also been endorsed by the NASEM in 2017.[100]

According to the IRIS Assessment Database, there are existing IRIS assessments for 15 of the 20 chemical substances: Butyl benzyl phthalate (BBP), Dibutyl phthalate (DBP), 1,2-Dichlorobenzene, 1,4-Dichlorobenzene, 1,1-Dichloroethane, 1,2-Dichloroethane, trans-1,2-Dichloroethylene, 1,2-Dichloropropane, Di (2-ethylhexyl)phthalate (DEHP), Diisobutyl phthalate (DIBP), Formaldehyde, Phthalic anhydride, 1,1,2-Trichloroethane, 1,2-Dibromoethane, and 1,3-Butadiene.[101]

[94] US EPA. (2019). Peer Review for EPA Draft Risk Evaluations for 1,4-Dioxane and Cyclic Aliphatic Bromide Cluster (HBCD). Pp 31. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0237-0064

[95] US EPA. (2019). Peer Review for the United States Environmental Protection Agency (EPA) Draft Risk Evaluation for 1-Bromopropane (1-BP). Pp 22. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0235-0061

[96] US EPA. (2019). Peer Review for the United States Environmental Protection Agency (EPA) Draft Risk Evaluation for 1-Bromopropane (1-BP). Pp 21. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0235-0061

[97] US EPA. (2019). Peer Review for EPA Draft Risk Evaluations for 1,4-Dioxane and Cyclic Aliphatic Bromide Cluster (HBCD). Pp 38. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0237-0064

[98] US EPA (2019). Initiation of Prioritization Under the Toxic Substances Control Act (TSCA). Comment submitted by Veena Singla, PhD, Associate Director, Science and Policy, Program on Reproductive Health and the Environment, University of California, San Francisco (UCSF) et al. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0131-0010

[99] The National Academies of Sciences. *Application of Systematic Review Methods in an Overall Strategy for Evaluating Low-Dose Toxicity from Endocrine Active Chemicals.* Washington, D.C.: National Academies Press; 2017.

[100] Id.

[101] US EPA (2020). IRIS: IRIS Assessments Database. Available: https://cfpub.epa.gov/ncea/iris_drafts/atoz.cfm?list_type=alpha

However, when querying the scoping documents, only 8 of 15 mention IRIS (table below), meaning **EPA's Draft Scoping documents fail to cite an IRIS assessment for almost half of the high priority chemicals which have completed assessments**. Second, Page 58 of the Draft Scope for Triphenyl Phosphate (TPP) lists an IRIS assessment as part of the grey literature review, however a search of the IRIS database shows that there is no such assessment for this chemical.[102] Third, the Draft Scope for Diisobutyl phthalate identifies this chemical as having potential reproductive toxicity effects, but fails to cite the NASEM Low-Dose Report which, through a systematic review, identified this chemical as a male reproductive toxicant. [103]

Chemical Name	CASRN	Existing IRIS Assessment?	IRIS Assessment Cited by Draft Scope?
Triphenyl Phosphate (TPP)	115-86-6	N	Y
Butyl benzyl phthalate (BBP)	85-68-7	Y	N
1,2-Dichlorobenzene	95-50-1	Y	N
1,4-Dichlorobenzene	106-46-7	Y	N
1,2-Dichloroethane	107-06-2	Y	N
1,2-Dichloropropane	78-87-5	Y	N
Diisobutyl phthalate (DIBP)	84-69-5	Y	N
Phthalic anhydride	85-44-9	Y	N
1,2-Dibromoethane	106-93-4	Y	Y
1,3-Butadiene	106-99-0	Y	Y
Dibutyl phthalate (DBP)	84-74-2	Y	Y
1,1-Dichloroethane	75-34-3	Y	Y
trans-1,2-Dichloroethylene	156-60-5	Y	Y
Di (2-ethylhexyl)phthalate (DEHP)	117-81-7	Y	Y
1,1,2-Trichloroethane	79-00-5	Y	Y
Formaldehyde	50-00-0	Y	Y*

*IRIS Assessment cited is not the most recent.

Throughout the process of reviewing the first 10 chemicals which have undergone draft risk evaluations, we identified various problematic inconsistencies in how EPA conducted the evaluations, such as the inconsistent number of included studies in EPA's "systematic review", to lack of cohesion between the body of draft risk evaluations and its conclusions; and this appears to be yet another inconsistency in EPA's methodology. [104,105] For these issues to appear in the Draft Scopes (foundational parts of EPA's risk evaluation assessment process) is deeply concerning and may indicate a failure to show significant methodological improvement despite recommendations from experts as well as EPA's own SACC on how to improve the transparency and consistency of EPAs risk evaluation methods under TSCA .

[102] US EPA (2020). Phosphoric acid, triphenyl ester (TPP); TSCA Review. DRAFT Scope of the Risk Evaluation for Phosphoric acid, Triphenyl Ester (TPP) (CASRN-115-86-6). Pp 58. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2018-0458-0021

[103] Id.

[104] US EPA. (2020). Toxic Substances Control Act (TSCA) Science Advisory Committee on Chemicals Review of Risk Evaluation for Carbon Tetrachloride. Comment submitted by Swati Rayasam, Science Associate, Program on Reproductive Health and the Environment, Department of Obstetrics, Gynecology and Reproductive Sciences, University of California, San Francisco et al. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0499-0041

[105] US EPA. (2020). Trichloroethylene; Draft Toxic Substances Control Act (TSCA) Risk Evaluation and TSCA Science Advisory Committee on Chemicals (SACC) Meetings; Notice of Availability, Public Meetings, and Request for Comment. Comment submitted by Swati Rayasam et al., Science Associate, Program on Reproductive Health and the Environment, Department of Obstetrics, Gynecology and Reproductive Sciences, University of California, San Francisco (UCSF PRHE). Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0500-0106

Finally, in EPA's scoping document for formaldehyde, the Agency cites an IRIS summary as part of its grey literature review, likely from the 1989 IRIS assessment, although the citation lacks a year to corroborate this claim.[106] Despite previously stating that the recent formaldehyde IRIS assessment will inform the process, the Agency fails to reference the stalled IRIS assessment even once; this is similar to EPA's actions during the prioritization process[107] even though the NASEM's most recent review of the IRIS program's implementation of systematic review by the NASEM found it to be robust.[108] Therefore, EPA must **immediately release** the recently updated IRIS assessment for public comment and NASEM review so that the Office of Pollution Prevention and Toxics (OPPT) can directly utilize the extensive work already done by NASEM and EPA IRIS scientists. A 2019 report from the Government Accountability Office also raised concerns about potential political interference through EPA leadership's leading to an unexplained directive to halt the formaldehyde assessment.[109]

7. EPA should use a cumulative approach, and at a minimum, assess all common adverse health outcomes for the risk evaluations of phthalates and chlorinated solvents.

Phthalates

The National Research Council (NRC) specifically recommended that "…a cumulative risk assessment be conducted for phthalates and that the assessment include other antiandrogens," [110] this is because the NRC found that as people are exposed simultaneously to multiple phthalates, and phthalates can contribute to common adverse health outcomes, the scientifically appropriate approach is a cumulative risk assessment.[111]

There are 7 phthalates total listed in EPA's next 20 chemicals which are moving forward to the risk evaluation process: 2 manufacturer-requested (DIDP, DINP) and 5 designated as high priority (DIBP, DCHP, DEHP, BBP, and DBP). These chemicals share many common human health hazards such as

[106] US EPA (2020). Formaldehyde; TSCA Review. Draft Scope of the Risk Evaluation for Formaldehyde (CASRN 50-00-0). Pp 76. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2018-0438-0029

[107] US EPA (2019). Prioritization of Chemicals under TSCA; First Set of Candidate Chemical Substance. Comment submitted by Swati Rayasam, Science Associate, Program on Reproductive Health and the Environment, Department of Obstetrics, Gynecology and Reproductive Sciences, University of California, San Francisco (UCSF PRHE) et al. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0131-0020

[108] National Academies of Sciences, Engineering, and Medicine. 2018. *Progress Toward Transforming the Integrated Risk Information System (IRIS) Program: A 2018 Evaluation*. Washington, DC: The National Academies Press. https://doi.org/10.17226/25086.

[109] US GAO (2019) Chemical Assessments: Status of EPA's Efforts to Produce Assessments and Implement the Toxic Substances Control Act. Available: https://www.gao.gov/assets/700/697212.pdf

[110] National Research Council (U.S.), & Committee on the Health Risks of Phthalates. (2008). *Phthalates and cumulative risk assessment: the task ahead*. Pg 7. Retrieved from http://site.ebrary.com/id/10274055

[111] Id.

reproductive toxicity, developmental toxicity, and systemic toxicity.[112] As outlined in our previous comments, these seven phthalates should be considered in a cumulative assessment. [113,114,115]

For its evaluations, EPA should draw on relevant reviews and publications, such as the Consumer Product Safety Commission's Chronic Hazard Advisory Panel (CHAP) on phthalates.[116] Previous cumulative assessments of phthalates by the NRC and the CHAP focused on one particular health outcome- effects on the development of the male reproductive system due to anti-androgenicity- but the NRC cautioned that while this is the most extensively studied endpoint, "The committee's suggestions should not be interpreted to imply that other health effects are not important or that nonchemical stressors should be ignored."[117] Likewise, the CHAP acknowledged concerns for other health effects, including cancer and neurodevelopmental toxicity, but did not quantify cumulative risks for these endpoints due to lack of data.[118]

Therefore, the NRC and CHAP risk findings on particular phthalates are not comprehensive; no cumulative assessment was conducted for other relevant health endpoints. In particular, since the NRC and CHAP reports, additional evidence on phthalates' neurodevelopmental toxicity has emerged indicating that prenatal and early life exposures are associated with a variety of adverse outcomes including lower IQ and problems with attention, hyperactivity and poorer social communication. [119]

Regarding what health endpoints should be included in a cumulative assessment, the NRC committee found "…that the focus in cumulative risk assessment should be on the health outcomes and not on the pathways that lead to them, whether defined as mechanisms of action or as modes of action. Multiple pathways can lead to a common outcome, and a focus on only a specific pathway can lead to too narrow an approach in conducting a cumulative risk assessment. **Accordingly, the chemicals that should be considered for cumulative risk assessment should be ones that cause the same health outcomes or the same types of health outcomes…**"[120](emphasis ours) This indicates that any phthalates that can contribute to an adverse health outcome (such as neurodevelopmental toxicity) should be grouped together.

To identify the relevant health endpoints for cumulative assessment, EPA should conduct a systematic literature review using an established, peer-reviewed method such as NTP's the National Toxicology

[112] 84 FR 44300

[113] US EPA (2019). Prioritization of Chemicals under TSCA; First Set of Candidate Chemical Substance. Comment submitted by Swati Rayasam, Science Associate, Program on Reproductive Health and the Environment, Department of Obstetrics, Gynecology and Reproductive Sciences, University of California, San Francisco (UCSF PRHE) et al. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0131-0020

[114] US EPA. (2019). Di-isodecyl Phthalate (DIDP); Manufacturer Request for Risk Evaluation Under the Toxic Substances Control Act (TSCA); Comment submitted by Veena Singla et al., Department of Obstetrics, Gynecology and Reproductive Sciences, University of California, San Francisco (UCSF). Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2018-0435-0008

[115] US EPA. (2019). Di-isononyl Phthalate (DINP); Manufacturer Request for Risk Evaluation Under the Toxic Substances Control Act (TSCA); Comment submitted by Veena Singla et al., Department of Obstetrics, Gynecology and Reproductive Sciences, University of California, San Francisco (UCSF). Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2018-0436-0009

[116] Gennings, C., Hauser, R., Koch, H. M., Kortenkamp, A., Lioy, P. J., Mirkes, P. E., & Schwetz, B. A. (2014). *Report to the U.S. Consumer Product Safety Commission by the Chronic Hazard Advisory Panel on Phthalates and Phthalate Alternatives*. Retrieved from U.S. Consumer Product Safety Commission website: http://www.cpsc.gov/PageFiles/169902/CHAP-REPORT-With-Appendices.pdf

[117] National Research Council (U.S.), & Committee on the Health Risks of Phthalates. (2008). *Phthalates and cumulative risk assessment: the task ahead*. Retrieved from http://site.ebrary.com/id/10274055. Pg. 4

[118] Gennings, C., Hauser, R., Koch, H. M., Kortenkamp, A., Lioy, P. J., Mirkes, P. E., & Schwetz, B. A. (2014). *Report to the U.S. Consumer Product Safety Commission by the Chronic Hazard Advisory Panel on Phthalates and Phthalate Alternatives*. Retrieved from U.S. Consumer Product Safety Commission website: http://www.cpsc.gov/PageFiles/169902/CHAP-REPORT-With-Appendices.pdf pg. 13; pg. 29-33

[119] Id.

[120] National Research Council (U.S.), & Committee on the Health Risks of Phthalates. (2008). *Phthalates and cumulative risk assessment: the task ahead*. Retrieved from http://site.ebrary.com/id/10274055. Pg. 4

Program's OHAT or the Navigation Guide. [121,122] The TSCA systematic review method should not be used, as it is not peer-reviewed or validated, and EPA's SACC has raised serious concerns about it.[123,124, 125,126]

At a minimum the health endpoints in the cumulative evaluation should include those already identified by the NRC and the CHAP, those raising concern in recent studies, as well as those which are common outcomes in the Draft Scopes:

- Reproductive toxicity;
- Male reproductive system;
- Developmental toxicity;
- Neurodevelopmental toxicity;
- Other developmental toxicity (ie, skeletal malformations,[127] immune toxicity, fertility);
- Cancer;
- Genetic toxicity; and
- Toxicokinetic/Systemic toxicity (ie, liver, kidney effects)[128]

TSCA requires EPA to determine whether "the manufacture, processing, distribution in commerce, use, or disposal of a chemical substance or mixture, or that any combination of such activities, presents an unreasonable risk of injury to health or the environment," including to potentially exposed or susceptible sub-populations.[129]

To meet this mandate, the law requires that EPA comprehensively assess all intended, known or reasonably foreseen conditions of use for phthalates, and the associated exposures. This scope is necessary both for chemicals selected for risk evaluations based on manufacturer requests and those designated high priority by the Agency. Otherwise, risk will be underestimated, including for potentially exposed and susceptible subpopulations as outlined in the points below. For example, the CHAP found that "DINP had the maximum potential for exposure to infants, toddlers, and older children…exposures were primarily from food, but also from mouthing teethers and toys, and from dermal contact with child care articles and home furnishings."[130] If EPA does not include these known exposures in its assessment, it will be missing the majority of DINP exposures for children.

[121] National Toxicology Program (2015) Handbook for Conducting a Literature-Based Health Assessment Using OHAT Approach for Systematic Review and Evidence Integration. In: U.S. Department of Health and Human Services, editor.: Office of Health Assessment and Translation, Division of National Toxicology Program, National Institute of Environmental Health Sciences.

[122] Woodruff TJ, Sutton P (2014) The Navigation Guide sytematic review methodology: a rigorous and transparent method for translating environmental health science into better health outcomes. Environmental Health Perspectives. 122(10):A283.

[123] SACC (2019) A Set of Scientific Issues Being Considered by the Environmental Protection Agency Regarding: Peer Review for EPA Draft Risk Evaluation of C.I. Pigment Violet 29

[124] US EPA. (2019). Toxic Substances Control Act (TSCA) Science Advisory Committee on Chemicals Review of Risk Evaluation for 1-Bromopropane. 1-BP TSCA SACC Meeting Minutes Final Report. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0235-0061

[125] US EPA. (2019). Toxic Substances Control Act (TSCA) Science Advisory Committee on Chemicals Review of Risk Evaluation for 1, 4 Dioxane and Cyclic Aliphatic Bromide Cluster (HBCD); SACC July 2019 Meeting Minutes and Final Report Docket. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0238-0063

[126] US EPA. (2019). Toxic Substances Control Act (TSCA) Science Advisory Committee on Chemicals Review of Risk Evaluation for Methylene Chloride; MeCl Meeting Minutes Final Report 03/02/2020. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0437-0080

[127] Gennings, C., Hauser, R., Koch, H. M., Kortenkamp, A., Lioy, P. J., Mirkes, P. E., & Schwetz, B. A. (2014). *Report to the U.S. Consumer Product Safety Commission by the Chronic Hazard Advisory Panel on Phthalates and Phthalate Alternatives*. pg. 8. Retrieved from U.S. Consumer Product Safety Commission website: http://www.cpsc.gov/PageFiles/169902/CHAP-REPORT-With-Appendices.pdf

[128] Id. pg. 8

[129] 15 USC §2605(b)

[130] Gennings, C., Hauser, R., Koch, H. M., Kortenkamp, A., Lioy, P. J., Mirkes, P. E., & Schwetz, B. A. (2014). *Report to the U.S. Consumer Product Safety Commission by the Chronic Hazard Advisory Panel on Phthalates and Phthalate Alternatives*. Retrieved from U.S. Consumer Product Safety Commission website: http://www.cpsc.gov/PageFiles/169902/CHAP-REPORT-With-Appendices.pdf pg. 3

Chlorinated Solvents

Similarly, for chlorinated solvents, EPA designates 7 as high-priority. As stated for phthalates above, EPA should conduct a cumulative evaluation of these 7 chemicals, as they share many common human health hazard outcomes such as:

- Acute and repeated dose toxicity;
- Irritation;
- Neurotoxicity;
- Genetic toxicity;
- Carcinogenicity; and
- Systemic toxicity

The NASEM defines cumulative risk broadly to mean the risk posed by multiple chemicals and other stressors that cause varied health effects and to which people are exposed by multiple pathways and exposure routes and for varied durations.[131] Cumulative risk is critical for susceptible and more highly exposed sub-populations, who face greater chemical exposures (more chemicals, higher levels, and higher frequency) as well as non-chemical stressors.[132] The NASEM found that "Where single-chemical risk assessments might yield the verdict 'absence of risk,' dose addition might yield the opposite conclusion."[133] Additionally, effects of toxic chemicals can be compounded by non-chemical stressors such as socio-economic status.

Therefore, moving forward EPA should conduct a cumulative risk assessment for phthalates, chlorinated solvents and, for all chemicals where such an assessment is possible. It is also critical that EPA incorporate information on non-chemical stressors in its cumulative assessment to ensure that the most vulnerable populations are accounted for in the evaluation of risk.

8. EPA must consider aggregate exposure within and across populations; otherwise it will underestimate risk. Aggregate exposure should include legacy uses, uses where a chemical is present as a contaminant/by-product, and uses already assessed.

In general, EPA is proposing to consider three populations for exposure assessment: 1) Occupational users and non-users; 2) consumers and bystanders; and 3) general population. We strongly recommend that EPA consider the aggregate exposures within and across these populations, or risk will be underestimated due to inaccurate assessment of real-world exposures. Exposures within a population must be aggregated (rather than considered in isolation) in order to sufficiently estimate actual population exposure to the chemical—for example, through exposures from food, water and air.

Further, as shown in Figure 1 below, exposures must also be aggregated **across** populations. Consumers and workers are part of the general population. As workers and consumers also eat food and drink water, it is reasonable to assume that they will have the same exposures as the general population, in addition to the anticipated exposures on-the-job or from consumer products. Some workers will also be

[131] National Research Council (U.S.), & Committee on the Health Risks of Phthalates. (2008). *Phthalates and cumulative risk assessment: the task ahead*. Pg. 4 Retrieved from http://site.ebrary.com/id/10274055

[132] Solomon, G. M., Morello-Frosch, R., Zeise, L., & Faust, J. B. (2016). Cumulative Environmental Impacts: Science and Policy to Protect Communities. *Annual Review of Public Health*, *37*(1), 83–96. https://doi.org/10.1146/annurev-publhealth-032315-021807

[133] National Research Council (U.S.), & Committee on the Health Risks of Phthalates. (2008). *Phthalates and cumulative risk assessment: the task ahead*. Pg. 8 Retrieved from http://site.ebrary.com/id/10274055

consumer product users, so they have the potential to face general, consumer product, and on-the-job exposures.

For example, an individual working in a tire factory where 1,3-butadiene is used or manufactured with inadequate PPE could be exposed (inhalation and dermal) to the chemical during their shift, finish their shift with their clothing and skin contaminated with 1,3-butadiene, drive home to their nearby community downwind of the factory breathing air contaminated by the 1.2 million pounds released to the environment in the US in 2018, 98% of which was released into the air. Upon arriving home, this worker could hug their family, contaminating them, and take their child to a park to play where the ground is made synthetic turf (another use for 1,3-butadiene) or be exposed to any other number of products containing 1,3-butadiene through combined dermal and inhalation pathways as a consumer and general population member. Therefore, this person could be exposed to 1,3-butadiene through multiple pathways: on-the-job, ingesting contaminated water or food, breathing contaminated outdoor and indoor air and use of any number of consumer products, and then also expose their families and communities who may also be at heightened risk. In particular, children are vulnerable to such exposures, and the timing of exposure during developmental "windows of susceptibility" plays a critical role, whether during pre-conception to a parent, in utero, or in early life.[134]

Additionally, EPA needs to account for combined dermal and inhalation exposures as these two types of exposure often occur concurrently, such as for workers; instead of EPA's proposed approach to account for dermal and inhalation separately. If exposures were properly aggregated, this would properly identify higher non-cancer and cancer risks relative to the Agency's benchmarks.

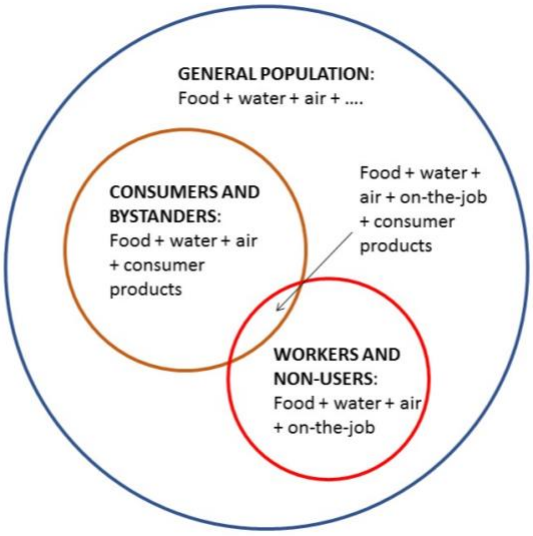


Figure 1: EPA must assess aggregate exposures within and across all the populations for accurate exposure assessment.

To accurately account for real-life exposures, EPA needs to aggregate exposures across exposure pathways. EPA has described the concept of assessing aggregate exposures as "the risk cup," where every use of a chemical contributes to filling the cup.[135] The Agency can only determine if risks exceed levels of concern, that is whether the risk cup is full or overflowing, by adding together all contributing

[134] Wild, C.P. and Kleinjans, J. (2003) Children and increased susceptibility to environmental carcinogens: evidence or empathy? *Cancer Epidemiol. Biomarkers Prev.* 12, 1389–94.

[135] US EPA (January 31, 1997) PRN 97-1: Agency Actions under the Requirements of the Food Quality Protection Act. Available: https://www.epa.gov/pesticide-registration/prn-97-1-agency-actions-under-requirements-food-quality-protection-act#risk

exposures and taking into consideration extrinsic and intrinsic factors which contribute to vulnerability as outlined below. However, if known chemical uses and exposures are ignored, the cup levels will be an underestimate of the true risk posed, suggesting that risks are below levels of concern when in reality the cup might be full or overflowing. This is compounded by the fact that the population is not only exposed to a single chemical through multiple pathways, but that they are exposed to mixtures of *multiple* chemicals (disclosed or undisclosed due to CBI) through *multiple* pathways. These chemicals may present human health hazards both individually and compounding health hazards synergistically. We have previously submitted detailed comments to EPA on this topic.[136]

Finally, in the introduction section of the chemical scope documents for the first 10 chemicals, EPA stated that it "may consider background exposures from legacy use, associated disposal, and legacy disposal as part of an assessment of aggregate exposure or as a tool to evaluate the risk of exposures resulting from non-legacy uses."[137] It subsequently chose to exclude them, and we commented previously that this language fell short of the analysis required under Lautenberg TSCA. [138] Our assertion was reaffirmed by a U.S. Court of Appeals for the Ninth Circuit which ruled on challenges to the risk evaluation rule in November 2019 that EPA's exclusion of legacy activities was a violation of the plain language of TSCA, finding its rationale for the exclusion "without merit." [139] Further the court outlined on page 53 of the decision that "These legacy activities must also be addressed in the upcoming risk evaluations for the 20 high-priority substances." [140]

However, in the Draft Scopes for the next 20 chemicals, none of the documents reference legacy uses, associated disposal, and legacy disposal as being considered a part of the scope of the assessment. Therefore, while EPA is not explicitly and actively excluding legacy uses (which would be a violation of the 9th Circuit decision), it is simply omitting them, thus excluding them passively. EPA must consider legacy uses and bring its approach, and these Draft Scopes for the next 20 chemicals, into compliance the Court's ruling and account for chemicals' uses and exposures per the court's decision and in order to sufficiently protect the public's health.

It is critical that EPA consider ongoing exposures from legacy uses and disposal and include these as part of the aggregate exposure assessment, especially considering that many of these 20 chemical substances are contaminants found at Superfund Sites across the country. Additionally, when a chemical is present in products or media as a contaminant/by-product, EPA needs to include and assess these exposures. We strongly recommend against ignoring or discounting these potential exposures routes as it will lead EPA to underestimate risk. When analyzing aggregate exposures, "sentinel exposure" may be considered simultaneously, where appropriate. However, these are not mutually exclusive, and EPA should **not** incorporate sentinel to the exclusion of aggregate.

[136] US EPA. (2016). Asbestos; TSCA Review and Risk Evaluation. Comment submitted by Veena Singla, PhD, Associate Director, Science and Policy, Program on Reproductive Health and the Environment, University of California, San Francisco et al. https://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0736-0479

[137] See, for example, US EPA (2017). Scope of the Risk Evaluation for Cyclic Aliphatic Bromides Cluster. Pg. 12

[138] US EPA. (2019). Toxic Substances Control Act (TSCA) Science Advisory Committee on Chemicals Review of Risk Evaluation for 1-Bromopropane. Comment submitted by Swati Rayasam, Science Associate, Program on Reproductive Health and the Environment, Department of Obstetrics, Gynecology and Reproductive Sciences, University of California, San Francisco et al. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0235-0053

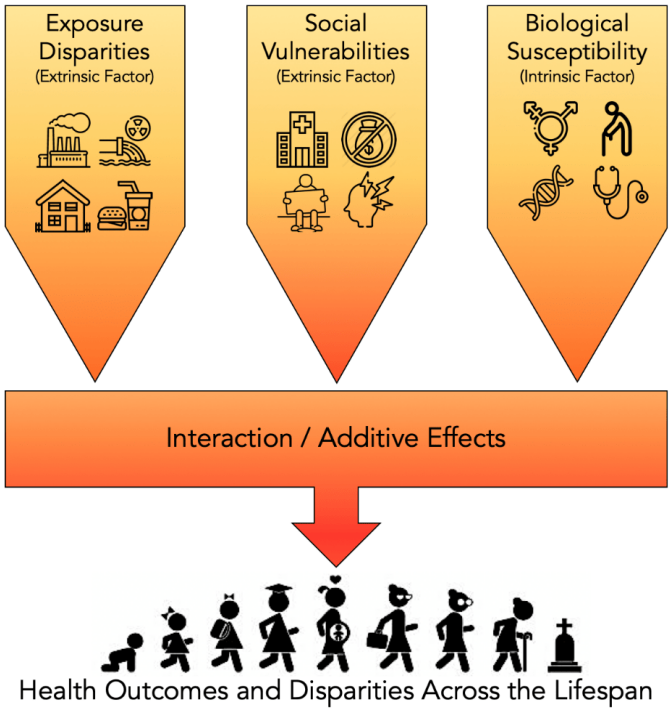
[139] *Safer Chemicals, Healthy Families v USEPA* (2019). No. 17-72260 (9th Cir. Nov. 14, 2019). Pg. 53. *"EPA's contention that TSCA can reasonably be read to refer to the future use of a product, and disposals associated with such use, only when the product will also be manufactured in the future for that use—and not when the product is no longer manufactured for the relevant use—is without merit. TSCA's "conditions of use" definition plainly addresses conditions of use of chemical substances that will be used or disposed of in the future, regardless of whether the substances are still manufactured for the particular use."*

[140] *Id.*

In summary, EPA needs to account for all the sources of exposure, or it will underestimate risk for all of the next 20 chemicals similar to what happened for the first 10 chemicals.

9. EPA should follow recommendations from the National Academies of Sciences (NAS) to identify susceptible sub-populations based on established extrinsic and intrinsic factors that increase vulnerability.

As stated above, EPA is proposing to consider three populations for exposure assessment: 1) Occupational users and non-users; 2) consumers and bystanders; and 3) general population. In particular, EPA has appropriately identified people who live or work near manufacturing, processing, distribution, use or disposal sites as facing greater exposures in multiple scopes. Across a population, typically the highest chemical exposures are to workers and communities near industrial facilities/contaminated sites. Such communities are often low income and/ or people of color, exposed to a disproportionate share of pollution, environmental hazards, social and economic stressors, as shown in Figure 2.[141]



Exposure disparities (such as from proximity to polluting industries or use of consumer products), social vulnerabilities (such as lack of access to health care) and biological susceptibilities (such as age or pre-existing disease) create differences in how chemicals affect a person's health, contributing to adverse health outcomes and disparities for vulnerable populations throughout the lifespan. To protect susceptible groups as required by law, EPA's risk evaluations must be aligned with evidence-based principles to protect public health.

[141] Mohai, P., & Saha, R. (2015). Which came first, people or pollution? Assessing the disparate siting and post-siting demographic change hypotheses of environmental injustice. *Environmental Research Letters*, *10*(11), 115008. doi: 10.1088/1748-9326/10/11/115008

Multiple exposures to chemical and non-chemical stressors collectively increase the risk of harm, combined with synergistic effects with other health stressors in their daily lives such as limited access to quality health care.[142,143] EPA's risk evaluation process, both the finalization of the first 10 and the scoping of the next 20, needs to fully account for the reality of cumulative exposures, as recommended by the NASEM in their Phthalates and Cumulative Risk report.[144]

All of the draft scopes contain some variation of the phrase, "Releases of *[chemical]* from certain conditions of use, such as manufacturing, disposal, or waste treatment activities, may result in general population exposures." However, in addition to that, in the scoping documents for six chemicals (1,3-Butadiene [145] 1,1-Dichloroethane [146], 1,2-Dichloroethane [147], 1,2-Dichloropropane [148], Ethylene Dibromide [149], and o-Dichlorobenzene [150]) EPA also outlines that there are portions of the general population which may have higher exposure. For example, in the draft scope for *o*-Dichlorobenzene, EPA says:

"Several groups within the general population have potentially higher exposures (higher than background levels) to o-dichlorobenzene. These populations include individuals living near sites where o-dichlorobenzene is produced or used in manufacturing and disposal sites. Individuals living in proximity to hazardous waste sites may also be exposed to o-dichlorobenzene by contaminated groundwater."[151]

And the draft scope for 1,2- dichloroethane says:
"Populations living near industrial waste sites may have a higher likelihood of exposure to 1,2-dichloroethane."[152]

TSCA §3(12) states that "the term 'potentially exposed or susceptible subpopulation' means a group of individuals within the general population…who, due to either greater susceptibility or greater exposure, may be at greater risk than the general population for adverse health effects from exposure to a chemical substance or mixture, such as infants, children, pregnant women, workers, or the elderly."

Therefore, EPA is acknowledging these populations have a higher likelihood of exposure due to their geography but failing to categorize most of them as eligible for consideration as a potentially exposed or susceptible subpopulation (PESS). Exposures which occur as a result of proximity to industrial facilities

[142] Morello-Frosch R, Zuk M, Jerrett M, Shamasunder B, Kyle AD. Understanding the cumulative impacts of inequalities in environmental health: Implications for policy. Health Aff. 2011;30(5):879–87.
[143] Vesterinen HM, Morello-Frosch R, Sen S, Zeise L, Woodruff TJ. Cumulative effects of prenatal-exposure to exogenous chemicals and psychosocial stress on fetal growth: Systematic-review of the human and animal evidence. Meliker J, editor. PLoS One. 2017 Jul 12;12(7):e0176331.
[144] National Research Council. Committee on the Health Risks of Phthalates, Board on Environmental Studies and Toxicology, Division on Earth and Life Studies. 2008. Phthalates and cumulative risk assessment: the task ahead. Washington, D.C.: National Academies Press.
[145] US EPA (2020). Draft Scope of the Risk Evaluation for 1,3-Butadiene (CASRN 106-99-0). Pg 27. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2018-0451-0023
[146] US EPA (2020). Draft Scope of the Risk Evaluation for 1,1-Dichloroethane (CASRN 75-34-3). Pg 27. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2018-0426-0015
[147] US EPA (2020). Draft Scope of the Risk Evaluation for 1,2-Dichloroethane (CASRN 107-06-2). Pg 29. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2018-0427-0029
[148] US EPA (2020). Draft Scope of the Risk Evaluation for 1,2-Dichloropropane (CASRN 78-87-5). Pg 30. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2018-0428-0020
[149] US EPA (2020). Draft Scope of the Risk Evaluation for Ethylene Dibromide (CASRN 106-93-4). Pg 28. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2018-0488-0024
[150] US EPA (2020). Draft Scope of the Risk Evaluation for o-Dichlorobenzene (CASRN 95-50-1). Pg 31. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2018-0444-0019
[151] US EPA (2020). Draft Scope of the Risk Evaluation for o-Dichlorobenzene (CASRN 95-50-1). Pg 31. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2018-0444-0019
[152] US EPA (2020). Draft Scope of the Risk Evaluation for 1,1-Dichloroethane (CASRN 75-34-3). Pg 29. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2018-0426-0015

should not be categorized as a general population exposure as living near an industrial facility is not a vulnerability of the general population.[153] Therefore, geographic should be treated as an extrinsic vulnerability, which would categorize nearby populations as PESS.

With regard to exposure disparities such as geographical proximity to polluting industries, the Draft Scopes also fail to be consistent. Five of the six scopes which discuss geography, categorize it as a "General Population" exposure and the last (1,3-Butadiene) categorizes it under both General Population and PESS.

In the PESS exposure section of the draft scope for 1,3-Butadiene, EPA states that, *"…elevated ambient air concentrations of 1,3-butadiene have been measured in the vicinity of heavily trafficked areas, refineries, chemical manufacturing plants, and plastic and rubber factories (OEHHA 2013). Populations living in areas near oil refineries, chemical manufacturing plants, and plastic and rubber factories where 1,3-butadiene is manufactured or used would be expected to have higher exposures (ATSDR 2012)."* [154]

This inconsistency is again an issue that we have highlighted multiple times. EPA should consider communities near industrial facilities as a PESS under TSCA due to their heightened susceptibility, and additionally must harmonize that consideration across all scoping documents, as all of the scopes identify releases from industrial conditions of use as highlighted above.

With regard to greater susceptibility, the following are well-known factors that increase biologic sensitivity or reduce resilience to exposures,[155,156] and should be considered consistently for all 20 chemicals to identify susceptible sub-populations:

Intrinsic/ endogenous factors

- Genetic polymorphisms/ genetics/ genetic makeup;
- Pre-existing conditions/underlying health conditions;
- Pre-disposing (pre-existing or background) exposure to other chemicals;
- Nutritional deficiencies;
- Prenatal lifestage;
- Age; and
- Sex.

Extrinsic factors

- Multiple exposures/ co-exposures;
- Place-based risk factors such as geographic/regional differences (living on contaminated land);
- Exposure to neighborhood crime and/or violence;
- Exposure to systemic racism, racial profiling, and harassment by authorities;
- Lack of proper access to health care or basic health preventative services;
- Lack of social support;
- Food or job insecurity;

[153] Mohai, P., & Saha, R. (2015). Which came first, people or pollution? Assessing the disparate siting and post-siting demographic change hypotheses of environmental injustice. *Environmental Research Letters*, *10*(11), 115008. doi: 10.1088/1748-9326/10/11/115008

[154] US EPA (2020). Draft Scope of the Risk Evaluation for 1,3-Butadiene (CASRN 106-99-0). Pg 29. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2018-0451-0023

[155] Morello-Frosch R, Zuk M, Jerrett M, Shamasunder B, Kyle AD. Understanding the cumulative impacts of inequalities in environmental health: Implications for policy. Health Aff. 2011;30(5):879–87.

[156] National Research Council. Science and Decisions: Advancing Risk Assessment. Washington, D.C.: National Academies Press; 2009.

- Poverty;
- Harmful occupational exposures and low wage jobs with limited access to chemical health and safety information, or personal protective equipment, leading to disproportionate exposures to multiple toxic chemicals both at home and work; and
- other non-chemical stressors.

As discussed below in point #10, EPA can use "default values" to account for cumulative exposures. Evidence-based defaults should be used to account for these and other susceptibilities, unless there is there is chemical-specific data available to support increasing or decreasing the default. Established scientific principles for exposure assessment require that known exposures be included in the assessment, or exposure will not be accurately quantified, and risk will be underestimated.[157] This is of particular concern for potentially exposed and susceptible subpopulations, as we outlined in our peer-reviewed commentary in *PLoS Biology*.[158]

10. For risk characterization, EPA should use health protective defaults and methods that generate risk estimates.

Health-protective defaults

We strongly support the use of health protective defaults to incorporate factors that reflect the range of variability and susceptibility in the population to ensure risks are not underestimated. The importance of using protective science-based defaults was highlighted by the NASEM in 2009.[159] The default should be used for factors known to influence risk unless there is chemical-specific data that support increasing or decreasing such factors; when there is inadequate information to quantitatively assess inter- or intra-species differences for a specific chemical, the defaults should be used. For example, current methods do not account for *in utero* susceptibility to chemical exposures, despite ample scientific literature demonstrating increased sensitivity among developing fetuses and the potential for fetal origins of disease.[160,161,162] EPA's defaults should include:

- Intra-human variability, general;
- Intra-human susceptibility to carcinogens, adult;
- Intra-human susceptibility to carcinogens, early life (including prenatal);
- Intra-human susceptibility to non-carcinogens, early life (including prenatal);
- Animal findings as they are relevant to humans; and
- Findings from one route of exposure are considered representative unless data show otherwise

[157] US EPA (2018). Problem Formulations for Risk Evaluations To Be Conducted Under Toxic Substances Control Act, and General Guiding Principles To Apply Systematic Review in TSCA Risk Evaluations. Comment submitted by Veena Singla, Associate Director, Science and Policy, Program on Reproductive Health and the Environment, University of California, San Francisco et al. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2018-0210-0107

[158] Koman, P.D., Singla, V. I., Lam, J., & Woodruff, T. J. (2019). Population susceptibility: A vital consideration in chemical risk evaluation under the Lautenberg Toxic Substances Control Act. *PLoS Biology*. https://doi.org/10.1371/journal.pbio.3000372

[159] National Research Council. Science and Decisions: Advancing Risk Assessment. Washington, D.C.: National Academies Press; 2009. Ch 4-6

[160] Hoffman DJ, Reynolds RM, Hardy DB. Developmental origins of health and disease: current knowledge and potential mechanisms. Nutr Rev. 2017;75:951–70.

[161] Dzubow R, Fields C, Ginsberg G, Sandy M, Mabson M, Foos B. Comparison of carcinogenic potency across life stages: implications for the assessment of transplacental cancer risk. J Toxicol Environ Health Part A. 2019;82:769–87.

[162] OEHHA. In Utero and Early Life Susceptibility to Carcinogens: [Internet]. 2009. Available from: https://oehha.ca.gov/media/downloads/crnr/appendixjearly.pdf

EPA has relied on standard default values ("uncertainty" or "safety" factors) that have been applied across the board to various chemicals and health outcomes. But newer science demonstrates that EPA's typical safety factor of 10 is insufficient to account for variability due to life stage, genetics, underlying disease status, and external stressors that may be due to poverty or other difficult life conditions. For cancer, the NASEM found that a factor of 25- to 50- may account for the variability between the median individual and those with more extreme responses.[163]

Similarly, the science describing early-life vulnerability to carcinogens has advanced. California EPA's (Cal EPA) guidance for incorporating differential susceptibilities to carcinogens and non-carcinogens incorporates more recent science on increased susceptibility during the prenatal period and age-related susceptibility for non-mutagenic carcinogenic agents. [164] Its literature review on differential susceptibility to carcinogens and non-carcinogens based on age and life stage derived age adjustment values for carcinogens which include the prenatal period[165] and increased the default intraspecies uncertainty factors for non-carcinogens to 30 and 100 for specific endpoints such as asthma or neurotoxicity. [166] The Cal EPA default factor can then be modified upwards or downwards depending on chemical specific information (*e.g.*, for benzene because of variability in metabolism and other sensitivities the non-cancer variability is 100). At a minimum, EPA should start with using Cal EPA's age adjustment values and intraspecies uncertainty factors for incorporating age/early life susceptibility. Cal EPA also developed child-specific risk values for chemicals (e.g., atrazine, lead, nickel, manganese, heptachlor) that specifically address routes of exposure and differences in susceptibility unique to children compared to adults.[167] EPA should review these additional evaluations and incorporate these values as appropriate to the baseline of 30 and 100. Furthermore, a default guidance principle should be that animal findings are relevant to humans unless there is sufficient and compelling information to support otherwise.

Risk estimates

In the draft risk evaluations for the first 10 chemicals, EPA incorrectly treated the no-observed-adverse-effect-level (NOAEL) as if it is a *no/zero* effect level. [168] However, NOAELs are not zero response concentrations; they are a concentration at which there is not an observable response in the experiment. The Benchmark Dose (BMD) or its statistical lower limit (BMDL) should be used instead of a no observed adverse effect level (NOAEL) or lowest observed adverse effect level (LOAEL), since NOAELs and LOAELs are limited by the dose groups tested, are not informed by the shape of the dose-response relationship, can be highly influenced by study design, and have been shown to represent levels of risk

[163] National Research Council. Science and Decisions: Advancing Risk Assessment. Washington, D.C.: National Academies Press; 2009. Pg. 168

[164] OEHHA. In Utero and Early Life Susceptibility to Carcinogens: [Internet]. 2009. Available from: https://oehha.ca.gov/media/downloads/crnr/appendixjearly.pdf

[165] California EPA 2009. Cal EPA 2009. California Environmental Protection Agency, Office of Environmental Health Hazard Assessment. Technical Support Document for Cancer Potency Factors: Methodologies for derivation, listing of available values, and adjustments to allow for early life stage exposures. http://oehha.ca.gov/media/downloads/crnr/tsdcancerpotency.pdf

[166] Cal EPA 2008. California Environmental Protection Agency, Office of Environmental Health Hazard Assessment. Technical Support Document For the Derivation of Noncancer Reference Exposure Levels http://oehha.ca.gov/media/downloads/crnr/noncancertsdfinal.pdf

[167] California Environmental Protection Agency. Office of Environmental Health Hazard Assessment (OEHHA). Child-Specific Reference Doses (chRDs) Finalized to Date. Available from: http://oehha.ca.gov/risk-assessment/chrd/table-all-chrds

[168] US EPA. (2019). Toxic Substances Control Act (TSCA) Science Advisory Committee on Chemicals Review of Risk Evaluation for 1-Bromopropane. Comment submitted by Swati Rayasam, Science Associate, Program on Reproductive Health and the Environment, Department of Obstetrics, Gynecology and Reproductive Sciences, University of California, San Francisco et al. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0235-0053

(e.g. NOAEL typically represents up to a 10% response).[169,170] The POD (*i.e.*, BMDL) is divided by a set of adjustment factors (AF) related to a) variability between humans and the experimental animals (inter-species variability), b) variability among humans, including more susceptible and vulnerable humans (intra-species variability), and c) study or database limitations, including use of measured/higher doses to extrapolate to unmeasured/lower doses (*i.e.*, LOAEL-to-NOAEL); use of short-term toxicity data to inform more chronic toxicity endpoints (*i.e.*, subchronic-to-chronic); and an incomplete database (*i.e.*, database uncertainty. There are multiple methodological reasons that an effect may not be observed, including low statistical power and inadequate statistical analysis. An empirical comparison of NOAELs and BMRs finds that the average NOAEL approximates the dose that represents a 1–5% Benchmark Response (BMR),[171] while some NOAELs are more similar to a 10% BMR.[172] Thus, it is more appropriate to assume that NOAELs are more similar to a 5-10% benchmark response.

EPA already recognizes the features that make BMDs superior: BMDs account for the shape of the dose–response function; are independent of study design, such as the space between dosing; and are comparable across chemicals.[173] This failure to assess a chemical's risk to the general population is of particular concern. For calculating cancer or non-cancer risks, we recommend using a point of departure (POD) of a benchmark dose (BMD) at 1%. The POD should be based on a BMD calculation, not the NOAEL/LOAEL, unless the data are insufficient to model. EPA should be calculating BMD as well as the risk-specific dose, and if it does not have sufficient data to calculate the risk levels then the Agency should state that clearly rather than relying on NOAELs which as mentioned before are subject to study design and interpretation.

Additionally, we have previously stated our concerns with how EPA is using factors to adjust for scientific uncertainties in the risk (referred to by EPA as uncertainty factors). The first issue is that the term uncertainty factor does not reflect the variability and adjustment elements that the factor represents. This issue is discussed by the NASEM report *Science and Decisions* on page 132:

> *"Another problem posed by the current noncancer framework is that the term uncertainty factors is applied to the adjustments made to calculate the RfD to address species differences, human variability, data gaps, study duration, and other issues.* ***The term engenders misunderstanding: groups unfamiliar with the underlying logic and science of RfD derivation can take it to mean that the factors are simply added on for safety or because of a lack of knowledge or confidence in the process.*** *That may lead some to think that the true behavior of the phenomenon being described may be best reflected in the unadjusted value and that these factors create an RfD that is highly conservative. But the factors are used to adjust for differences in individual human sensitivities, for humans' generally greater sensitivity than test animals' on a milligrams-per-kilogram basis, for the fact that chemicals typically induce harm at lower doses with longer exposures, and so on. At times, the factors have been termed safety*

[169] Wignall JA, Shapiro AJ, Wright FA, Woodruff TJ, Chiu WA, Guyton KZ, Rusyn I. 2014. Standardizing benchmark dose calculations to improve science-based decisions in human health assessments. Environmental health perspectives. 122(5).

[170] Despite extensive literature documenting the inadequacy of using the NOAEL/LOAEL approach in chemical risk assessment, NOAELs and LOAELs have been traditionally used and are the only values available in certain cases (*e.g.*, when lack of model fit precludes BMD estimation). Thus, NOAELs and LOAELs are commonly used in risk assessment documents.

[171] Allen BC, Kavlock RJ, Kimmel CA, Faustman EM. 1994. Dose–response assessment for developmental toxicity. II. Comparison of generic benchmark dose estimates with no observed adverse effect levels. Fundam Appl Toxicol. 23:487–495.

[172] Wignall JA, Shapiro AJ, Wright FA, Woodruff TJ, Chiu WA, Guyton KZ, et al.2014. Standardizing benchmark dose calculations to improve science-based decisions in human health assessments. Environ Health Perspect 122(5):499–505.

[173] Wignall JA, Shapiro AJ, Wright FA, Woodruff TJ, Chiu WA, Guyton KZ, Rusyn I. 2014. Standardizing benchmark dose calculations to improve science-based decisions in human health assessments. Environmental health perspectives. 122(5).

factors, which is especially problematic given that they cover variability and uncertainty and are not meant as a guarantee of safety." [174] *(emphasis ours)*

"Uncertainty factors" are generally used to make adjustments to the dose-response. Therefore, rather than uncertainty factors, these should really be thought of as uncertainty **and** adjustment factors, as per their function within a dose-response assessment.

Second, EPA has been setting its Margin of Exposure (MOE) at 100 and calculating it as shown for example in the 1-bromopropane draft risk evaluation. We have previously detailed why MOE is not an appropriate approach for risk characterization. [175]

$(UF_S=1) \times (UF_A=10) \times (UF_H=10) \times (UF_L=1)^3 = 100$
Total UF=Benchmark MOE=100

UF_S - Subchronic to chronic "uncertainty factor"
UF_A - Interspecies "uncertainty factor"
UF_H - Intraspecies "uncertainty factor"
UF_L - LOAEL to NOAEL "uncertainty factor"

Based on the above calculation, EPA is only adjusting for animal and human variability (Inter- and Intraspecies), and by setting the UF_L and UF_s at 1, the Agency indicates that there is no need to adjust from either less chronic NOAELs to chronic NOAELs or from LOAELs to NOAELs. Reiterating the above issue, EPA is treating NOAEL as if it represents *no effect*, rather than *no observed effect,* even though Wignall et al. demonstrated that NOAEL can represent upwards of 10% of the BMR. Thus, any application of uncertainty factors to assess risks should include at least a combined value of greater than 1,000.

Third, while *Science and Decisions* acknowledged single-value "uncertainty factors" may sometimes be preferable either out of necessity or reflecting science-policy choices, a 2007 Science Advisory Board recommended that EPA "incrementally replace the current system of single-point uncertainty factors with a set of distributions, using probabilistic methods." [176] In *Science and Decisions,* NAS stated "Use of default distributions for adjustments in extrapolations, rather than default point-estimate uncertainty factors, provides an improved representation of variability and uncertainty and offers an opportunity for further refinements and incentives to gather and analyze existing information and to generate new data targeted to specific extrapolation needs." [177] In testing the feasibility and implications of replacing traditional reference doses with probabilistic estimates (as recommended by NAS), Chiu et al. found that in comparison to traditional methods, these estimates provided a more consistent, scientifically rigorous, and transparent basis for risk management decisions.[178] These methods can also

[174] National Research Council. (2009). *Science and Decisions: Advancing Risk Assessment*. Pp 132. Retrieved from https://www.nap.edu/catalog/12209/science-and-decisions-advancing-risk-assessment

[175] US EPA (2019). Draft Toxic Substances Control Act (TSCA) Risk Evaluations and TSCA Science Advisory Committee on Chemicals (SACC) Meetings; Cyclic Aliphatic Bromide Cluster (HBCD) and 1,4-Dioxane; Notice of Availability and Public Meetings. Comment submitted by Swati Rayasam, Science Associate, Program on Reproductive Health and the Environment, Department of Obstetrics, Gynecology and Reproductive Sciences, University of California, San Francisco et al. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0237-0059 and https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0238-0056

[176] National Research Council. (2009). *Science and Decisions: Advancing Risk Assessment*. Pp 294. Retrieved from https://www.nap.edu/catalog/12209/science-and-decisions-advancing-risk-assessment

[177] Id. Pp 174.

[178] Chiu WA, Axelrad DA, Dalaijamts C, Dockins C, Shao K, Shapiro AJ, Paoli G. Beyond the RfD: broad application of a probabilistic approach to improve chemical dose-response assessment for non-cancer effects. Environ Health Perspect. doi:10.1289/EHP3368.

be applied to a multitude of decision-making contexts such as benefit-cost analysis, and life-cycle impact analysis. We recommend that EPA not use the MOE or RfD/RfC due to it does not reflect a risk based valued that was recommended by the NAS and has been demonstrated in use as described above. Moving forward, EPA should employ such probabilistic methods in the final first 10 draft risk evaluations and incorporate such methods into the draft risk evaluations for the next 20, in place of these single-point “uncertainty factors” and MOE.