December 14, 2023

Comments from Scientists, Academics, and Clinicians on Revisions to EPA's Risk Evaluation Framework Rule

Submitted online via Regulations.gov to docket EPA-HQ-OPPT-2023-0496

These comments are submitted on behalf of the undersigned scientists, academics, and clinicians. We declare collectively that we have no direct or indirect financial or fiduciary interest in the subject of these comments. The co-signers' institutional affiliations are included for identification purposes only and do not imply institutional endorsement or support unless indicated otherwise. We appreciate the opportunity to provide comment on EPA's proposed rule on Procedures for Chemical Risk Evaluation Under the Toxic Substances Control Act ("Proposed Rule").[1]

The 2016 updates to the Toxic Substances Control Act ("TSCA") via the Frank Lautenberg Chemical Safety for the 21st Century Act ("Amended TSCA") require EPA to conduct risk evaluations for chemicals in commerce that must consider risks to "potentially exposed or susceptible subpopulations" (PESS), and determine if a chemical poses an "unreasonable risk" without consideration of cost. Amended TSCA also requires EPA to regulate any existing chemical determined to pose an unreasonable risk "to the extent necessary so that the chemical substance no longer presents such risk."[2] Finally, it requires EPA to "use scientific information, technical procedures, measures, methods, protocols, methodologies, or models, employed in a manner consistent with the best available science."[3]

In June 2017, EPA issued the original Procedures for Chemical Risk Evaluation Under the Amended Toxic Substances Control Act, also referred to as the Risk Evaluation Framework Rule, to establish procedures for EPA to follow in preparing risk evaluations. The Proposed Rule presents revisions to the original 2017 Risk Evaluation Framework Rule, providing an important opportunity to establish improved procedures and approaches for ongoing and future TSCA risk evaluations.

The proposed revisions include important improvements in several key areas, including consideration of all conditions of use and exposure pathways for each chemical assessed, occupational exposure assumptions, identification of potentially exposed or susceptible subpopulations, consideration of aggregate exposure, and procedures for manufacturer-requested risk evaluations.

However, EPA's proposed revisions to the framework rule concerning use of systematic review in conducting risk evaluations are not acceptable and not consistent with the best available science. In addition, further critical improvements need to be made to the Proposed Rule concerning identification of potentially exposed or susceptible populations and estimating risk to those groups, conducting aggregate exposure assessment and cumulative risk assessment, and adopting improved methods for dose-response assessment of non-cancer health effects.

[1] US EPA, Proposed Rule: Procedures for Chemical Risk Evaluation Under the Toxic Substances Control Act (TSCA), 88 Fed. Reg. 74,292 (Oct. 30, 2023).
[2] Toxic Substances Control Act (TSCA). In Vol. 15 U.S.C. ch. 53 subch. I §§ 2601–2629.
[3] 15 U.S.C. § 2625(h).

EPA's implementation of Amended TSCA, and the scientific requirements underpinning it, has resulted in risk evaluations that are vulnerable to political interference and scientific integrity concerns.[4] Based on our review of the existing Risk Evaluation Framework Rule and the Proposed Rule, and considering the implementation challenges that the TSCA Program has faced since enactment of the Lautenberg Act, we recommend a series of revisions that will strengthen the Proposed Rule to ensure that the risk evaluations use the "best available science" and methodologies, and protect public health. We urge EPA to move expeditiously with finalizing the Proposed Rule while incorporating the priority revisions discussed below.

Our comments on the Proposed Rule revisions address the following main issues:

1. **EPA's Proposed Rule weakens the provisions regarding systematic review. EPA should instead strengthen its commitment to systematic review in the Proposed Rule.**
2. **EPA should further expand its definition of potentially exposed or susceptible subpopulations (PESS), and add language to the Proposed Rule concerning the identification of PESS and estimation of risks to PESS in risk evaluations.**
3. **The Proposed Rule should require consideration of aggregate exposure and cumulative risk in each risk evaluation, beginning with the scope document.**
4. **The Proposed Rule should require risk evaluations to use best available science to calculate risks of non-cancer effects at exposure levels commonly experienced by workers, consumers and the general public, including PESS.**
5. **The Proposed Rule requirements for manufacturer-requested risk evaluations should be expanded to better specify the information that must be provided with each request.**

For each issue, the attached detailed comments first outline the various limitations and deficiencies of the existing Risk Evaluation Framework Rule and EPA's approach to TSCA risk evaluation to date, followed by specific revisions to the Proposed Rule that should be made to address these limitations and deficiencies.

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

Sincerely,

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[4] Rayasam, S. D. G.; Koman, P. D.; Axelrad, D. A.; Woodruff, T. J.; Chartres, N., Toxic Substances Control Act (TSCA) Implementation: How the Amended Law Has Failed to Protect Vulnerable Populations from Toxic Chemicals in the United States. *Environ Sci Technol* 2022, *56*, (17), 11969-11982,https://www.ncbi.nlm.nih.gov/pubmed/35980084.

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DETAILED COMMENTS

1. **EPA's Proposed Rule weakens the provisions regarding systematic review. EPA should instead strengthen its commitment to systematic review in the Proposed Rule.**

TSCA requires that EPA use systematic review methods when conducting chemical risk evaluations. However, the systematic review methods used to date have been insufficient to meet Amended TSCA's requirements to use the "best available science."[5]

The Institute of Medicine (IOM) report *Finding What Works in Health Care: Standards for Systematic Review* identified 21 standards that, if adhered to, result in a scientifically valid, transparent, and reproducible systematic review.[6] EPA's approach to TSCA systematic review has incorporated flawed approaches that are inconsistent with the IOM standards, including a failure to publish chemical-specific systematic review protocols, inappropriate methods for assessing study quality, and a failure to include all relevant evidence.

In 2021, the National Academies of Sciences, Engineering, and Medicine (NASEM) found that the 2018 version of EPA's systematic review approach ("TSCA Method") "does not meet the criteria of 'comprehensive, workable, objective, and transparent' systematic review method" and found it "to be lacking objectivity at each step, from not using a defined approach to documenting how the problem formulation and protocol are developed. Further examples include inclusion and exclusion criteria that are too broad to identify the evidence, inherent subjectivity within the metrics that make up the evaluation score for study quality."[7] The NASEM also found the TSCA Method resulted in "reduced confidence in the findings" of EPA's risk evaluations.[8]

Following the release of the NASEM report in February 2021, EPA announced it would no longer use the 2018 TSCA method.[9,10] A draft document representing EPA's revised approach to TSCA systematic review was released in December 2021, but the draft failed to address many NASEM recommendations.[11] In July 2022, EPA's Scientific Advisory Committee on Chemicals (SACC) issued over 200 recommendations for EPA to improve its December 2021 method and identified numerous NASEM recommendations from February 2021 that were not addressed by EPA.[12] An important example from among these many recommendations concerns the practice of excluding studies from a risk evaluation

[5] 15 U.S.C. § 2625(h).
[6] Institute of Medicine, Finding What Works in Health Care: Standards for Systematic Reviews, 2011. https://www.nap.edu/catalog/13059/finding-what-works-in-health-care-standards-for-systematic-reviews.
[7] National Academies of Sciences, Engineering, and Medicine, *The Use of Systematic Review in EPA's Toxic Substances Control Act Risk Evaluations*; Washington, DC, 2021. https://www.nap.edu/catalog/25952/the-use-of-systematic-review-in-epas-toxic-substances-control-act-risk-evaluations.
[8] National Academies of Sciences Engineering and Medicine, *The Use of Systematic Review in EPA's Toxic Substances Control Act Risk Evaluations*; Washington, DC, 2021. https://www.nap.edu/catalog/25952/the-use-of-systematic-review-in-epas-toxic-substances-control-act-risk-evaluations.
[9] US Environmental Protection Agency, EPA Commits to Strengthening Science Used in Chemical Risk Evaluations In 2021. https://www.epa.gov/newsreleases/epa-commits-strengthening-science-used-chemical-risk-evaluations.
[10] Rizzuto, P., EPA Dumps Trump-Era Chemical Analysis Approach After Rebuke. *Bloomberg Law,* 2021, https://news.bloomberglaw.com/environment-and-energy/criticism-spurs-epa-to-dump-trump-era-chemical-analysis-approach,(July 1, 2022).
[11] US Environmental Protection Agency, Draft Systematic Review Protocol Supporting TSCA Risk Evaluations for Chemical Substances In 2021. https://www.regulations.gov/document/EPA-HQ-OPPT-2021-0414-0005.
[12]US Environmental Protection Agency, Transmittal of Meeting Minutes and Final Report for the Science Advisory Committee on Chemicals Virtual Meeting "Draft Systematic Review Protocol Supporting TSCA Risk Evaluations for Chemical Substances Version 1.0" held on April 19-21, 2022. 2022, https://www.regulations.gov/document/EPA-HQ-OPPT-2021-0414-0044.

based on study quality evaluation. The NASEM recommended "Do not exclude studies based on risk of bias, study quality, or reporting quality,"[13] and the SACC reiterated "As recommended by NASEM…the results of study evaluation should not be used as exclusionary criteria,"[14] but EPA continues this practice that is inconsistent with best practices in systematic review.

The 2017 Risk Evaluation Framework Rule includes use of "a pre-established protocol" as part of the definition of "weight of scientific evidence." EPA has not complied with its own rule, as it has not published a chemical-specific protocol for any of its completed or ongoing risk evaluations. EPA's 2021 draft "protocol" document for the ongoing risk evaluations was, as pointed out by the SACC, a handbook of general practices to apply across risk evaluations and not a protocol detailing the approach to be applied in each individual risk evaluation. EPA has not released any modification to that 2021 draft document or any chemical-specific protocols for risk evaluations it is now conducting.

EPA is now proposing to delete the definition of "weight of scientific evidence" from the Proposed Rule. A notable consequence of this deletion is the removal of any mention of systematic review protocols from the regulatory language.

The preamble to the Proposed Rule repeatedly makes mention of "systematic approaches" (or "systemic approach") as substitutes for systematic review, without describing what these systematic approaches consist of or how they would be consistent with TSCA requirements to use the "best available science" and base decisions on the "weight of scientific evidence." The reference to undefined "systematic approaches" is also found in the Proposed Rule text:

> EPA will apply systematic review and/or systematic approaches to reviewing reasonably available information that are objective, unbiased, and transparent. § 702.37(b)(2)

This is the only mention of systematic review in the Proposed Rule language. Although systematic review protocols are discussed in the preamble, the Proposed Rule does not include any requirement for, or any mention or, systematic review protocols. The Proposed Rule language concerning systematic review also fails to mention key attributes of systematic review, including "comprehensive" and "consistent," which are critical elements of systematic review that are also included in the definition of "weight of scientific evidence" that EPA is proposing to delete from the Proposed Rule. It therefore appears that the Proposed Rule represents a significant retreat from systematic review principles, and thus will result in risk evaluations that are not consistent with the "best available science."

In the Proposed Rule preamble, EPA argues that including a definition of "weight of scientific evidence" will limit the Agency's flexibility to incorporate changing methods and approaches over time. However, the Proposed Rule's definition of "weight of scientific evidence" does not pose any obstacle to adoption of new methods, models or approaches, as it is an articulation of general principles such as pre-established methods, consistency, and transparency rather than a specification of particular methods,

[13] National Academies of Sciences Engineering and Medicine, *The Use of Systematic Review in EPA's Toxic Substances Control Act Risk Evaluations*; Washington, DC, 2021, page 40. https://www.nap.edu/catalog/25952/the-use-of-systematic-review-in-epas-toxic-substances-control-act-risk-evaluations.

[14] US Environmental Protection Agency, Transmittal of Meeting Minutes and Final Report for the Science Advisory Committee on Chemicals Virtual Meeting "Draft Systematic Review Protocol Supporting TSCA Risk Evaluations for Chemical Substances Version 1.0" held on April 19-21, 2022. 2022. Page 98. https://www.regulations.gov/document/EPA-HQ-OPPT-2021-0414-0044.

approaches or tools. A larger issue with the preamble's discussion of EPA's understanding of the term "weight of evidence" is that it does not address the concerns of the National Academies:

> the phrase weight of evidence has become far too vague as used in practice today and thus is of little scientific use… its use in the literature and by scientific agencies, including EPA, is vague and varied.[15]

More than seven years after enactment of the Amended TSCA, EPA still does not have a systematic review method that incorporates critical NASEM recommendations and satisfies the statutory requirement for a systematic review with a pre-established protocol publicly available before a risk evaluation is started. To ensure that its systematic review methods incorporate the best available science, as required by TSCA, and are applied consistently across TSCA risk evaluations, EPA should revise the Proposed Rule to restore and/or incorporate basic principles of systematic review.

Proposed Rule recommendations – Systematic review

Recommendation 1.1: By deleting the definition of "weight of scientific evidence" from the regulatory text, EPA has removed several cornerstones of contemporary risk assessment, including use of a "pre-established protocol" to "comprehensively" and "consistently" identify and evaluate evidence. The terms "pre-established protocol," "comprehensively" and "consistently" were also all key elements of the text on systematic review in legislative history of Amended TSCA.[16] EPA should restore these key terms to the framework rule by revising the Proposed Rule's language regarding systematic review (quoted above), found at § 702.37(b)(2), to the following (suggested insertions are underlined):

> EPA will use systematic review <u>methods outlined in a pre-established chemical-specific protocol to identify, evaluate and integrate all</u> reasonably available <u>relevant</u> information <u>based on the strengths and limitations of the evidence in a manner that is comprehensive</u>, objective, unbiased, transparent <u>and consistent</u>.

Recommendation 1.2: To correct EPA's practice of omitting or excluding relevant studies, the Proposed Rule should be revised to state that "all relevant evidence" is to be considered in conducting a risk evaluation. This should be incorporated into the § 702.37 "evaluation requirements" and "considerations" for conducting a risk evaluation.

Recommendation 1.3: EPA should add language to the Proposed Rule to clarify that "a pre-established protocol" means a document specific to each risk evaluation outlining the methods to be used in conducting systematic review for that risk evaluation, including a PECO statement, literature search and screening methods, study quality evaluation methods, data extraction plans, data analysis methods, and methods for evidence synthesis and integration. The Proposed Rule should also require that the evaluation-specific protocol is made publicly available before the risk evaluation is conducted.

[15] National Research Council (2014). Review of EPA's Integrated Risk Information System (IRIS) Process, p. 86.
[16] Congressional Record – Senate, S3518, June 7, 2016.

2. EPA should further expand its definition of potentially exposed or susceptible subpopulations (PESS), and add language to the Proposed Rule concerning the identification of PESS and estimation of risks to PESS in risk evaluations.

EPA's approach to evaluating risks to PESS in TSCA risk evaluations has consistently underestimated exposures and risks and failed to sufficiently account for the factors that enhance susceptibility to harm from the chemicals subject to risk evaluation. The Proposed Rule should incorporate improved approaches to identify PESS and evaluate risks to PESS.

The mandate for EPA to identify unreasonable risks to PESS is one of the critical improvements of the Amended TSCA. The 2017 Risk Evaluation Framework Rule incorporates the statutory definition of PESS:

> a group of individuals within the general population identified by the Administrator who, due to either greater susceptibility or greater exposure, may be at greater risk than the general population of adverse health effects from exposure to a chemical substance or mixture, such as infants, children, pregnant women, workers, or the elderly.[17]

However, EPA has yet to adequately identify relevant PESS and quantify risk to these groups in its TSCA risk evalutaions. EPA's approach to identifying PESS varied considerably in the first 10 TSCA risk evaluations. For example, there are significant differences in whether health conditions related to a chemical's hazards were considered in these four risk evaluations:

> 1,4-dioxane: People with liver disease were identified as PESS, but people with kidney, neurological or respiratory conditions (all identified hazards in the risk evaluation) were not identified as PESS.
> 1-Bromopropane: No PESS were identified based on health conditions related to the hazards of the chemical, such as liver toxicity, kidney toxicity and neurotoxicity.
> Hexabromocyclododecane (HBCD): People with pre-existing health conditions were mentioned as PESS, but no specific health conditions were named in connection with identifying PESS. Thyroid and liver effects were identified as hazards in the risk evaluation, but people with thyroid or liver conditions were not identified as PESS. The SACC review of the draft risk evaluation stated that there was a "need to…add consideration of several preexisting health conditions that result in higher fat content in the liver."[18] The final risk evaluation did not address this SACC recommendation.
> C.I. Pigment Violet 29: EPA did not identify any PESS based on susceptibility to health effects, concluding that "there is no evidence of increased susceptibility for any single group relative to the general population"[19] based on a scientifically inappropriate rationale.

[17] US EPA. (2017). Procedures for Chemical Risk Evaluation under the Amended Toxic Substances Control Act (Final); Vol. 40 CFR 702, Available: https://www.federalregister.gov/documents/2017/07/20/2017-14337/procedures-for-chemical-risk-evaluation-under-the-amended-toxic-substances-control-act.
[18] TSCA Science Advisory Committee on Chemicals. 2019. Peer Review for EPA Draft Risk Evaluations for 1,4-Dioxane and Cyclic Aliphatic Bromide Cluster (HBCD). Meeting Minutes and Final Report. https://www.regulations.gov/document/EPA-HQ-OPPT-2019-0238-0063
[19] US EPA. (2020). Revised Draft Risk Evaluation for C.I. Pigment Violet 29 Public. Available: https://www.regulations.gov/document/EPA-HQ-OPPT-2018-0604-0100.

Whether fenceline communities were identified as PESS is another example of inconsistency across the first 10 risk evaluations. The risk evaluation for HBCD considered "People living close to a facility with HBCD releases" as PESS,[20] but the risk evaluations for 1,4-dioxane, 1-bromopropane, and C.I. Pigment Violet 29 made no mention of fenceline communities as PESS.

Pollution exposure disparities have been repeatedly identified by EPA in other contexts, and communities of color disproportionately bear the burden of adverse health impacts from chemical exposures.[21,22,23,24] Compared to White non-Hispanic children, Black children are more likely to be diagnosed with asthma (12.3% v. 5.6%); and Black women are more likely to experience pre-term birth compared to White non-Hispanic women (14.2% v. 9.3%).[25] Compared to White non-Hispanic children, Mexican-American children are more likely to be diagnosed with obesity (24% v. 14%).[26] These and other health outcomes observed disproportionately in communities of color are associated with chemical exposures, and the levels of chemical exposures are disproportionate among these communities.[27,28,29] Additionally, communities near manufacturing facilities and contaminated sites are often those with lower wealth, poorer health, and with a majority of residents who are people of color.[30,31, 32,33, 34] EPA did not consistently incorporate these considerations in identifying PESS in the risk evaluations completed to date, and none of the 10 completed TSCA risk evaluations have assessed differences in chemical exposures or risks along the parameters of race/ethnicity or income.

Additionally, EPA's language regarding identification of PESS in the first 10 risk evaluations was often vague, in some cases discussing general factors that may increase susceptibility (e.g., alcohol consumption, nutrition, genetic differences) without clearly identifying groups as PESS. In several

[20] US EPA (2020). Risk Evaluation for Cyclic Aliphatic Bromide Cluster (HBCD).
[21] Rayasam, S. D. G.; Koman, P. D.; Axelrad, D. A.; Woodruff, T. J.; Chartres, N., Toxic Substances Control Act (TSCA) Implementation: How the Amended Law Has Failed to Protect Vulnerable Populations from Toxic Chemicals in the United States. Environmental Science & Technology 2022, 56, (17), 11969-11982,https://doi.org/10.1021/acs.est.2c02079.
[22] Mikati, I.; Benson, A. F.; Luben, T. J.; Sacks, J. D.; Richmond-Bryant, J., Disparities in Distribution of Particulate Matter Emission Sources by Race and Poverty Status. American Journal of Public Health 2018, 108, (4), 480-485,https://doi.org/10.2105/AJPH.2017.304297.
[23] US Environmental Protection Agency. (2022). Cumulative Impacts Research – Recommendations for EPA's Office of Research and Development. Available: https://www.epa.gov/healthresearch/cumulative-impacts-research.
[24] U.S. Environmental Protection Agency, EJScreen: Environmental Justice Screening and Mapping Tool, https://www.epa.gov/ejscreen (December 22,2022).
[25] US Environmental Protection Agency, America's Children and the Environment. https://www.epa.gov/ace, (accessed November 17, 2023).
[26] US Environmental Protection Agency, America's Children and the Environment. https://www.epa.gov/ace, (accessed November 17, 2023).
[27] Tyrrell, Jessica, David Melzer, William Henley, Tamara S. Galloway, and Nicholas J. Osborne. 2013. "Associations between Socioeconomic Status and Environmental Toxicant Concentrations in Adults in the USA: NHANES 2001-2010." Environment International 59 (September): 328–35. https://doi.org/10.1016/j.envint.2013.06.017.
[28] Nguyen, Vy Kim, Adam Kahana, Julien Heidt, Katelyn Polemi, Jacob Kvasnicka, Olivier Jolliet, and Justin A. Colacino. 2020. "A Comprehensive Analysis of Racial Disparities in Chemical Biomarker Concentrations in United States Women, 1999–2014." Environment International 137 (April): 105496. https://doi.org/10.1016/j.envint.2020.105496.
[29] Cunningham TJ, Croft JB, Liu Y, Lu H, Eke PI, Giles WH. Vital Signs: Racial Disparities in Age-Specific Mortality Among Blacks or African Americans - United States, 1999-2015. MMWR Morb Mortal Wkly Rep 2017;66:444–56. https://doi.org/10.15585/mmwr.mm6617e1.
[30] Mohai, P.; Lantz, P. M.; Morenoff, J.; House, J. S.; Mero, R. P., Racial and socioeconomic disparities in residential proximity to polluting industrial facilities: evidence from the Americans' Changing Lives Study. Am J Public Health 2009, 99 Suppl 3, S649-56, https://www.ncbi.nlm.nih.gov/pubmed/19890171.
[31] Houston, D.; Li, W.; Wu, J., Disparities in exposure to automobile and truck traffic and vehicle emissions near the Los Angeles-Long Beach port complex. Am J Public Health 2014, 104, (1), 156-64,https://www.ncbi.nlm.nih.gov/pubmed/23678919.
[32] US EPA. (2022). Draft TSCA Screening Level Approach for Assessing Ambient Air and Water Exposures to Fenceline Communities Version 1.0. In Office of Chemical Safety and Pollution Prevention U.S. Environmental Protection Agency, Ed.
[33] Johnston J, Cushing L. Chemical Exposures, Health, and Environmental Justice in Communities Living on the Fenceline of Industry. Curr Environ Health Rep. 2020 Mar;7(1):48-57. doi: 10.1007/s40572-020-00263-8. PMID: 31970715; PMCID: PMC7035204.
[34] Cushing, L.; Morello-Frosch, R.; Wander, M.; Pastor, M., The Haves, the Have-Nots, and the Health of Everyone: The Relationship Between Social Inequality and Environmental Quality. Annual Review of Public Health 2015, 36, (1), 193-209,https://doi.org/10.1146/annurev-publhealth-031914-122646.

instances, groups named as PESS in the statute were not identified in the risk evaluations; for example, pregnant and aging populations were not considered PESS for 1,4-dioxane and Pigment Violet 29.

Deficiencies in identification of PESS continued with the scope documents for the 23 ongoing risk evaluations. EPA did not consider the broader set of intrinsic and extrinsic factors that may contribute to susceptibility and did not consider chemical-specific information when identifying PESS. Most of the 23 scope documents identified only children, women of reproductive age, workers and consumers as PESS; the sole exception is the scope for D4, which additionally identified populations with elevated fish ingestion as PESS.

EPA's approach to analyzing risks to groups identified as PESS in the first 10 TSCA risk evaluations was also inadequate. TSCA requires a thorough consideration of how risks to susceptible populations differ from the general public, as it explicitly mandates consideration of risks to PESS in the determination of unreasonable risk:

> The Administrator shall conduct risk evaluations pursuant to this paragraph to determine whether a chemical substance presents an unreasonable risk of injury to health or the environment, without consideration of costs or other nonrisk factors, **including an unreasonable risk to a potentially exposed or susceptible subpopulation** identified as relevant to the risk evaluation by the Administrator, under the conditions of use.[35] (emphasis added)

EPA did not incorporate PESS-specific risk calculations for groups identified as having elevated susceptibility in its TSCA risk evaluations, saying it lacked "sufficient quantitative information about these potential sources of susceptibility."[36] Instead, EPA applied the customary 10-fold adjustment factor to account for human variability, noting uncertainty around whether this adjustment factor was sufficient to capture differences in risk due to enhanced susceptibility. EPA should give greater consideration to the quantification of elevated risks to PESS beyond rote application of the traditional 10-fold adjustment factor, as this value 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 and frequently results in underestimation of risk.[37,38,39,40,41] For example, the WHO recommends at least a 42-fold adjustment factor to capture human variability in response to chemical exposures for a risk level of 1% (1-in-100).[42] EPA has also failed to sufficiently account for early-life vulnerability to carcinogens. California EPA guidance incorporates more recent science on increased prenatal and childhood

[35] Toxic Substances Control Act (TSCA). In Vol. 15 USC ch. 53 subch. §2605(b)(4)(A)
[36] US EPA. (2020). Final Risk Evaluation for 1,4-Dioxane. Available: https://www.epa.gov/sites/default/files/2020-12/documents/1._risk_evaluation_for_14-dioxane_casrn_123-91-1.pdf.
[37] National Research Council. Science and Decisions: Advancing Risk Assessment. Washington, DC: National Academies Press; 2009.
[38] World Health Organization, International Programme on Chemical Safety (2017). Guidance document on evaluating and expressing uncertainty in hazard characterization, 2nd edition. https://www.who.int/publications/i/item/9789241513548
[39] Varshavsky JR, Rayasam SDG, Sass JB, Axelrad DA, Cranor CF, Hattis D, Hauser R, Koman PD, Marquez EC, Morello-Frosch R, Oksas C, Patton S, Robinson JF, Sathyanarayana S, Shepard PM, Woodruff TJ. Current practice and recommendations for advancing how human variability and susceptibility are considered in chemical risk assessment. *Environmental Health* 21 (Suppl 1), 133 (2023). doi:10.1186/s12940-022-00940-1
[40] California Environmental Protection Agency, Office of Environmental Health Hazard Assessment. Technical Support Document For the Derivation of Noncancer Reference Exposure Levels. 2008. http://oehha.ca.gov/media/downloads/crnr/noncancertsdfinal.pdf
[41] 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
[42] World Health Organization, International Programme on Chemical Safety (2017). Guidance document on evaluating and expressing uncertainty in hazard characterization, 2nd edition, Table 4.5.

susceptibility for non-mutagenic carcinogens, as well as mutagenic chemicals, and provides appropriate life-stage adjustment factors.[43,44]

In addition, EPA frequently applied uncited and unrealistic assumptions in its risk evaluation for PESS. For example, in the 1-bromopropane risk evaluation, EPA "did not calculate risk for children associated with acute exposure at dry cleaners because the acute health domains (developmental effects) are not applicable to children," and did not calculate risks for chronic exposure for children at dry cleaners because "EPA believes exposure to children at workplaces are unlikely to be chronic in nature."[45] EPA's risk evaluation assumes exposures to children happen only in a four-hour period after school, likely underestimating exposures and risks for school-age children and younger children who may spend the majority of their time in family-owned dry-cleaning facilities.

Another deficiency in the first 10 risk evaluations was the frequent omission of exposures to fenceline communities, due to EPA's decision to exclude exposure pathways within the jurisdiction of other EPA-administered statutes, such as the Clean Air Act and Safe Drinking Water Act.[46] EPA released a draft Fenceline Screening Methodology outlining approaches to assessing some of the omitted exposures pathways in early 2022, which had numerous critical deficiencies.[47,48 49] It remains unclear whether EPA will incorporate methodologies that appropriately and thoroughly account for exposures to fenceline communities in its TSCA risk evaluations.

Finally, fully accounting for risks to PESS requires utilizing methodologies to account for aggregate exposure and cumulative risk (see item 3 below for further discussion).

President Biden's Executive Order on Revitalizing Our Nation's Commitment to Environmental Justice for All directs each federal agency to

> identify, analyze, and address historical inequities, systemic barriers, or actions related to any Federal regulation, policy, or practice that impair the ability of communities with environmental justice concerns to achieve or maintain a healthy and sustainable environment
>
> identify, analyze, and address barriers related to Federal activities that impair the ability of communities with environmental justice concerns to receive equitable access to human health or environmental benefits.[50]

[43] OEHHA. In Utero and Early Life Susceptibility to Carcinogens: [Internet]. 2009. Available from: https://oehha.ca.gov/media/downloads/crnr/appendixjearly.pdf.
[44] California 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.
[45] US EPA. (2020). Risk Evaluation for 1-Bromopropane (n-Propyl Bromide).
[46] Rayasam, S. D. G.; Koman, P. D.; Axelrad, D. A.; Woodruff, T. J.; Chartres, N., Toxic Substances Control Act (TSCA) Implementation: How the Amended Law Has Failed to Protect Vulnerable Populations from Toxic Chemicals in the United States. Environmental Science & Technology 2022, 56, (17), 11969-11982,https://doi.org/10.1021/acs.est.2c02079.
[47] US EPA. (2022). The TSCA Science Advisory Committee on Chemicals (SACC) - Fenceline Analysis Approach for Risk Evaluation. SACC Meeting Minutes and Final Report. Available: https://www.regulations.gov/document/EPA-HQ-OPPT-2021-0415-0095
[48] US EPA. (2022). The TSCA Science Advisory Committee on Chemicals (SACC) - Fenceline Analysis Approach for Risk Evaluation. Comment submitted by University of California San Francisco (UCSF) et al. Available: https://www.regulations.gov/comment/EPA-HQ-OPPT-2021-0415-0064
[49] US EPA. (2022). The TSCA Science Advisory Committee on Chemicals (SACC) - Fenceline Analysis Approach for Risk Evaluation. Comment submitted by University of California, San Francisco's Program on Reproductive Health and the Environment (UCSF PRHE). Available: https://www.regulations.gov/comment/EPA-HQ-OPPT-2021-0415-0088
[50] Executive Order 14096, April 21, 2023.

EPA's Proposed Rule incorporates an improvement to the definition of PESS by adding "overburdened communities" to the listed examples of groups considered to be PESS. This is an important change, but further steps are necessary. The preamble to the Proposed Rule mentions that non-chemical stressors are important to identification of PESS:

> TSCA also explicitly requires EPA's risk evaluations to consider unreasonable risk to "potentially exposed or susceptible subpopulations," and the statute provides authority to consider non-chemical as well as chemical stressors when identifying these subpopulations. Non-chemical stressors are factors found in the built, natural, and social environments including physical factors (e.g., geographic location) and psychosocial factors (e.g., poor nutrition).

EPA has therefore acknowledged the importance of non-chemical stressors to enhanced susceptibility, but consideration of non-chemical stressors is not incorporated in the PESS definition or other elements of the Proposed Rule. EPA's updated definition of PESS should make use of the definition of human biological variability recently published by the National Academies that incorporates intrinsic and acquired (or extrinsic) factors:

> Biological variability is defined as the true differences in attributes due to heterogeneity or diversity...For humans this would correspond to differences in outcomes across the population due to differences in intrinsic factors (e.g., life stage, reproductive status, age, gender, genetic traits) and acquired factors (e.g., previous or ongoing exposure to multiple chemicals, pre-existing disease, geography, socioeconomic status, racism/discrimination, cultural, workplace).[51]

EPA should expand its definition of PESS in the Proposed Rule and establish that scope documents and risk evaluations must specify how PESS were identified for each risk evaluation and how differential risks to PESS were quantified in the risk evaluation. Revising the Proposed Rule to expand the definition of PESS, and to ensure more thorough identification of PESS and estimation of risks to PESS should lead to improved rigor and consistency in EPA's TSCA risk evaluations. We emphasize, however, that EPA must implement more robust consideration of PESS in its risk evaluations to satisfy the requirements of TSCA regarding PESS and "best available science," regardless of whether or not it makes these recommended revisions to the Proposed Rule.

In addition to the following recommended revisions to the risk evaluation framework rule, we also strongly recommend that EPA prepare a guidance document presenting a comprehensive methodology for identifying PESS and incorporating community input on this topic, as well a separate guidance document on quantifying risks to susceptible subpopulations identified as PESS. Such guidance is necessary to ensure robust and consistent approaches to assessing PESS in TSCA risk evaluations and to ensure constructive engagement with affected populations and communities. One potential model for guidance on identification of PESS is CalEnviroscreen, which used a collaborative process to define a set of indicators to effectively identify PESS.[52]

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[51] National Academies of Sciences, Engineering, and Medicine (2023). Building Confidence in New Evidence Streams for Human Health Risk Assessment: Lessons Learned from Laboratory Mammalian Toxicity Tests, p. 31. https://doi.org/10.17226/26906.

[52] California Office of Environmental Health Hazard Assessment. (2022). CalEnviroScreen 4.0. Available: https://oehha.ca.gov/calenviroscreen/report/calenviroscreen-40.

Proposed Rule recommendations - Definition of PESS

Recommendation 2.1: EPA has proposed to add "overburdened communities" to the definition of PESS, which is an important improvement that should be included in the final rule. EPA should further expand the definition to reflect additional considerations that influence susceptibility to risks, including factors and conditions that are not necessarily driven by residential location. For example, EPA mentions "socio-economic stressors" in the preamble to the Proposed Rule, which are important to consider in identifying overburdened communities but may also impact subpopulations that are at increased risks due to these factors but do not live in overburdened communities defined by geography.

EPA provided a broader definition of PESS, referencing intrinsic and extrinsic factors that influence susceptibility in the January 2017 Proposed Risk Evaluation Framework Rule, but these factors were not included in the June 2017 final rule. The National Academies recently published a definition (see above) of human biological variability that also includes intrinsic and acquired (or extrinsic) factors for purposes of identifying susceptible populations. EPA should expand the definition of PESS to include intrinsic and extrinsic factors that influence susceptibility, similar to the January 2017 proposed definition. Specifically, EPA should revise the definition of PESS in § 702.33 to the following:

> Potentially exposed or susceptible subpopulation means a group of individuals or communities within the general population identified by EPA who, due to either greater susceptibility or greater exposure, may be at greater risk than the general population of adverse health effects from exposure to a chemical substance or mixture, including but not limited to infants, children, pregnant people, workers, the elderly, or overburdened communities. Susceptibility can be due to either intrinsic (e.g., life stage, pre-existing disease, reproductive status, age, sex, genetic traits) or extrinsic (e.g., food insecurity, geography, poverty, socioeconomic status, racism, discrimination, culture, workplace) factors when identifying this population.

This revised definition will help improve risk evaluations by informing risk assessors, peer reviewers and the public of the broader set of considerations that should be evaluated in the process of identifying PESS.

Proposed Rule recommendations - Identification of PESS

An improved definition of PESS is an important step toward improved identification of PESS, but further revisions should be made to the framework rule directing risk assessors to apply a more systematic approach to considering groups that are PESS for the chemical under evaluation. A requirement to assess risks to overburdened communities should be added to the Proposed Rule to prevent exclusion of the relevant exposure pathways from future risk evaluations.

Recommendation 2.2: Improved identification of PESS must begin with the Proposed Rule requirements for the scope document for each risk evaluation. The existing Risk Evaluation Framework Rule provisions regarding the scope contains only a brief mention of PESS, stating that the scope of the risk evaluation will include "The potentially exposed populations, including any potentially exposed or susceptible subpopulations as identified as relevant to the risk evaluation."[53] This language, found in §

[53] § 702.41(c)(2)

702.39(b)(2) in the current Proposed Rule, should be expanded to require an explanation of how PESS were identified for the chemical being evaluated, with reference to thorough and systematic assessment of both intrinsic and extrinsic factors, identification of specific overburdened communities, and discussion of how exposures and risks to overburdened communities will be assessed.

Recommendation 2.3: After completion of a scope document, EPA may identify additional groups as PESS as it proceeds with evidence identification, evaluation and synthesis steps of a risk evaluation. Additional PESS may be identified, for example, from review of health effects studies that were not considered during the scoping process. The Proposed Rule should be revised to require that risk evaluations include discussion of whether any additional groups were identified as PESS or considered for possible identification as PESS after completion of the scope document.

Proposed Rule recommendations - Analysis of exposure, hazard, dose-response and risk for PESS

Identification of PESS is a crucial step, but must be followed by appropriate quantification of risks to PESS. The current Proposed Rule says that "hazard information…will be evaluated" for all PESS and the "exposure assessment will consider" all PESS (§ 702.39(c)(4) and § 702.39(d)(5)) without elaboration on the nature of that evaluation or consideration, and no further details are provided in § 702.39(e) concerning risk characterization. This vague language fails to indicate what EPA considers necessary to conduct an assessment of risks to PESS.

Recommendation 2.4: The proposed § 702.39(c)(4) and § 702.39(d)(5) should be strengthened with text stating that differences in exposure, hazard and dose-response for each PESS (relative to the general population) will be identified and quantified, either through the use of chemical- or endpoint-specific evidence or, in the absence of that, health-protective adjustment factors.

Recommendation 2.5: § 702.39(e) should incorporate a requirement that the risk characterization summary of each risk evaluation will include an explanation of how estimates of human health risk account for the differences in risk to each identified PESS, and discussion of whether the data and approaches employed are sufficient to fully account for the differences in risk to PESS.

3. The Proposed Rule should require consideration of aggregate exposure and cumulative risk in each risk evaluation, beginning with the scope document.

Assessment of aggregate exposure and cumulative risk are critical for evaluating risks to PESS, including fully accounting for disproportionate exposures in environmental justice communities.

The 2017 Risk Evaluation Framework Rule defines aggregate exposure as "the combined exposures to an individual from a single chemical substance across multiple routes and across multiple pathways."[54]

[54] US EPA. (2017). Procedures for Chemical Risk Evaluation under the Amended Toxic Substances Control Act (Final); Vol. 40 CFR 702, Available: https://www.federalregister.gov/documents/2017/07/20/2017-14337/procedures-for-chemical-risk-evaluation-under-the-amended-toxic-substances-control-act.

Consideration of aggregate exposure is a necessary approach to consider the exposed individual as a "whole person" who may be routinely exposed to a given chemical in numerous ways, rather than treating exposures from work, from various consumer products, and from the ambient environment as independent events that happen to different people.

In the first 10 TSCA risk evaluations, EPA estimated aggregate exposure, to a limited extent, for NMP and HBCD, and also to a limited extent in the 2023 draft supplemental risk evaluation for 1,4-dioxane, but did not consider aggregate exposure for the remaining 7 chemicals. In these 10 risk evaluations, EPA generally assessed three exposed populations separately: workers exposed directly or indirectly; consumers exposed via products; and the general population exposed via ambient air and drinking water. However, EPA assessed inhalation and dermal exposures separately for workers, without calculating combined exposure for workers exposed via both routes. EPA also assessed consumer exposures for individual products without calculating the combined exposure for consumers using multiple products containing the same chemical. Finally, EPA did not aggregate the exposures of individuals who have occupational, consumer, and general population exposures, such as individuals exposed at both work and home. Put simply, EPA's approach to TSCA chemical exposure assessment has never considered the entirety of people's exposures or their environment, but rather subdivided exposure into separate categories and conditions of use.

To satisfy TSCA's requirements to evaluate and regulate chemicals using the "best available science"[55] and to regulate any unreasonable risks posed by "the manufacture, processing, distribution in commerce, use, or disposal of a chemical substance…or… any combination of such activities,"[56] EPA must quantify aggregate exposures in its risk evaluations. Risk characterization using aggregate exposure constitutes best available science, and failure to do so will unambiguously underestimate exposure for any individuals exposed to a chemical by multiple exposure routes, multiple exposure pathways, or from multiple conditions of use, including individuals among groups that are PESS (including residents of fenceline communities) under TSCA.

We strongly agree with the significant improvement in EPA's position regarding aggregate exposure stated in the preamble to the current Proposed Rule:

> Not only does the Agency have the authority, but in developing a comprehensive risk estimate for a chemical substance, it is the Agency's responsibility to consider the aggregation of what may be lower individual exposures from individual conditions of use and routes of exposure. EPA is committed to conducting an aggregate assessment, as supported by the science, in future TSCA risk evaluations.[57]

Consistent with this statement, EPA has proposed new language in the regulatory text concerning aggregate exposure. We urge EPA to build on this important statement with further improvements to the Proposed Rule by including provisions on conducting cumulative risk assessment, as detailed in the

[55] 15 U.S.C. § 2625(h).
[56] 15 U.S.C. § 2605(a).
[57] 88 Fed. Reg. at 74,305.

recommendations below.

More than 20 years ago, EPA established guidance for assessing risks from exposures to mixtures of chemicals,[58, 59] and has defined cumulative risk assessment as the "analysis, characterization, and possible quantification of the combined risks to health or the environment from multiple agents or stressors," considering both chemical and non-chemical stressors.[60] Non-chemical stressors include intrinsic (e.g., life stage, reproductive status, age, sex, genetic traits) and extrinsic (e.g., pre-existing disease, food insecurity, geography, poverty, socioeconomic status, racism, discrimination, culture, workplace) factors that make an individual mores susceptible to harm from chemical exposures.

In the first 10 TSCA risk evaluations, EPA failed to estimate cumulative risk. Instead, EPA evaluated risk for individual chemicals, disregarding how multiple exposures (chemical and non-chemical) may combine to produce common adverse health outcomes, ultimately resulting in underestimation of risks.

In February 2023, EPA released a draft plan for conducting a cumulative risk assessment for six phthalates with TSCA risk evaluations in progress, and an accompanying draft set of principles for conducting cumulative risk assessment under TSCA. These draft documents represent an important improvement in EPA's implementation of TSCA. EPA has reflected these efforts in the preamble to the current Proposed Rule, stating that:

> Because individuals are co-exposed to many chemicals in their daily lives, some of which may have the same health effects, EPA believes that in some cases the best approach to assess risk to human health may be to look at the combined risk to health from multiple chemicals…EPA recognizes that for some chemical substances undergoing risk evaluation, the best available science may indicate that the development of a cumulative risk assessment is appropriate to ensure that risk to human health and the environment is adequately characterized…EPA is committed to considering applying cumulative risk assessment approaches, as appropriate and where such analysis, based on reasonably available information, represents the best available science, for future chemicals undergoing risk evaluation.[61]

There is much to commend in EPA's statement, including the recognition that consideration of whether to conduct cumulative risk assessment in TSCA risk evaluations must take into account the TSCA requirement to use the "best available science." However, the Proposed Rule does not mention cumulative risk assessment at all, and EPA's preamble statement equivocates by saying "in some cases the best approach to assess risk to human health may be to look at the combined risk to health from exposure to multiple chemicals" and "for some chemical substances undergoing risk evaluation, the best available science may indicate that the development of a cumulative risk assessment is appropriate." EPA must acknowledge that the hazards of chemicals undergoing TSCA risk evaluation are also the hazards posed by many other chemicals and non-chemical stressors with routine exposures in the population. In other words, every chemical being evaluated under TSCA is toxicologically similar to other chemicals for at

[58] US EPA. (2000). Supplementary Guidance for Conducting Health Risk Assessment of Chemical Mixtures. EPA/630/R-00/002.
[59] US EPA. (2008). Concepts, Methods, and Data Sources For Cumulative Health Risk Assessment of Multiple Chemicals, Exposures and Effects: A Resource Document (Final Report, 2008). Available: https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=190187EP
[60] US EPA. (2003). Framework for Cumulative Risk Assessment. In Office of Research and Development Center for Public Health and Environmental Assessment (CPHEA) formerly known as the National Center for Environmental Assessment (NCEA), Ed. Washington, DC; Vol. EPA/600/P-02/001F,https://www.epa.gov/risk/framework-cumulative-risk-assessment.
[61] 88 Fed. Reg. at 74,305.

least one hazard. The NAS recommends that EPA conduct cumulative risk assessments for chemicals sharing a "common adverse outcome," [62] and this approach constitutes the "best available science," as required by TSCA.[63] The NAS has also recommended broader application of cumulative risk assessment.[64]

EPA has made a good start at incorporating cumulative risk assessment into the TSCA program with the draft plan for phthalates, and the Proposed Rule should build on this by confirming broader application of available cumulative risk assessment methods in TSCA risk evaluations. Expanded consideration of and application of cumulative risk assessment is also necessary to satisfy TSCA's mandates to identify unreasonable risks to PESS for each chemical undergoing risk evaluation. To evaluate risks to susceptible populations, EPA must consider the factors that make a group of individuals more susceptible to harm from chemical exposures. Among these factors are co-exposures to other chemicals with similar health consequences, and non-chemical stressors that can contribute to or exacerbate the health consequences of the chemical being evaluated. EPA cannot fully identify PESS and assess risks to PESS without conducting cumulative risk assessments incorporating those other chemicals and non-chemical stressors.

Consideration of non-chemical stressors is a key element of cumulative risk. As noted above, the Proposed Rule preamble recognizes such stressors in the context of identifying PESS; however the preamble has only this to say concerning the role of non-chemical stressors in cumulative risk assessment:

> EPA's Office of Research and Development has defined cumulative impacts as the totality of exposures to combinations of chemical and non-chemical stressors and their effects on health, well-being, and quality of life outcomes…and may or may not include toxicologically defined risk. EPA has not to date considered cumulative impacts in TSCA risk evaluations, but may in the future as appropriate data, methods, and guidance are available.[65]

Estimation of the combined risk resulting from exposure to multiple chemicals and non-chemical stressors such as food insecurity, pre-existing disease, poverty, or racism is necessary to comply with TSCA's mandate to use the "best available science" in TSCA risk evaluations.[66,67,68,69,70,71,72] Methods for incorporation of non-chemical stressors into cumulative risk assessment are advancing. New methods

[62] National Research Council, Phthalates and Cumulative Risk Assessment: The Tasks Ahead. 2008.
[63] 15 U.S.C. § 2625(h).
[64] National Research Council. Science and Decisions: Advancing Risk Assessment. Washington, DC: National Academies Press; 2009.
[65] 88 Fed. Reg. at 74,306.
[66] National Research Council. Science and Decisions: Advancing Risk Assessment. Washington, DC: National Academies Press; 2009.
[67] US EPA. (2022). E.O. 13985 EQUITY ACTION PLAN: U.S. ENVIRONMENTAL PROTECTION AGENCY. Available: https://www.epa.gov/environmentaljustice/equity-action-plan.
[68] Koman, P. D.; Singla, V.; Lam, J.; Woodruff, T. J., Population susceptibility: A vital consideration in chemical risk evaluation under the Lautenberg Toxic Substances Control Act. *PLoS Biol* 2019, *17*, (8), e3000372,.
[69] Pullen Fedinick, K.; Yiliqi, I.; Lam, Y.; Lennett, D.; Singla, V.; Rotkin-Ellman, M.; Sass, J., A Cumulative Framework for Identifying Overburdened Populations under the Toxic Substances Control Act: Formaldehyde Case Study. *Int J Environ Res Public Health* 2021, *18*, (11),
[70] Sexton, K.; Linder, S. H., Cumulative Risk Assessment for Combined Health Effects From Chemical and Nonchemical Stressors. *American Journal of Public Health* 2011, *101*, (S1), S81-S88.
[71] McPartland, J.; Shaffer, R. M.; Fox, M. A.; Nachman, K. E.; Burke, T. A.; Denison, R. A., Charting a Path Forward: Assessing the Science of Chemical Risk Evaluations under the Toxic Substances Control Act in the Context of Recent National Academies Recommendations. *Environmental Health Perspectives* 2022, *130*, (2).
[72] Rayasam, S. D. G.; Koman, P. D.; Axelrad, D. A.; Woodruff, T. J.; Chartres, N., Toxic Substances Control Act (TSCA) Implementation: How the Amended Law Has Failed to Protect Vulnerable Populations from Toxic Chemicals in the United States. *Environ Sci Technol* 2022, *56*, (17), 11969-11982.

have emerged from social epidemiology for assessing the combined effect of exposure to chemical and non-chemical stressors (e.g., psychosocial stress, air pollution, and asthma; and studies investigating allostatic load with exposure to lead), with advanced statistical techniques.[73] These analyses can be used to quantify variability in susceptible subgroups if the populations examined include biologically susceptible and/or socially disadvantaged subgroups.

We also note with concern that the TSCA program continues to give inappropriate examples of psychosocial stressors. The preamble's only example of psychosocial stressors is "poor nutrition." This is scientifically inappropriate as psychosocial stressors represent a broad range of extrinsic social factors that are outside an individual's control, including racism, poverty, food insecurity, and exposure to violence. EPA should not characterize psychosocial stressors in terms that can be interpreted as placing responsibility on individuals and implying that they are due to "lifestyle choices" rather than external systemic factors.

Revisions to the Proposed Rule definitions and its requirements for scope documents, exposure assessment and risk characterization are necessary to establish an expectation that TSCA risk evaluations will incorporate estimates of aggregate exposure and cumulative risk as necessary to meet the TSCA requirement to use the "best available science."

Proposed Rule recommendations – Definitions of aggregate exposure and cumulative risk

Recommendation 3.1: EPA should expand the definition of aggregate exposure provided under § 702.33. The current definition (quoted above) appropriately references multiple routes and pathways of exposure. However, the definition must be revised to better align with the context provided by TSCA, which focuses on conditions of use (COUs). The definition of aggregate exposure in the Proposed Rule should be expanded to include "all conditions of use" along with "multiple routes" and "multiple pathways" (suggested insertion is underlined):

> *Aggregate exposure* means the combined exposures from a chemical substance across multiple routes and across multiple pathways considering all conditions of use.

This revision will clarify that risk assessors should, for example, consider how consumers can be exposed to a specified chemical from multiple consumer products and also by other exposure pathways like food, drinking water and ambient air. This recommended change would also make the TSCA definition more consistent with EPA's 2003 definition of aggregate exposure, which included consideration of relevant "sources," as well as routes and pathways.[74]

***Recommendation 3.2*:** A definition of cumulative risk should be added to the Proposed Rule, as accounting for cumulative risk is necessary to produce a risk evaluation consistent with the best available science, and to fully evaluate risks to PESS. EPA has an established definition of cumulative risk (quoted

[73] Payne-Sturges DC, Scammell MK, Levy JI, Cory-Slechta DA, Symanski E, Carr Shmool JL, et al. Methods for evaluating the combined effects of chemical and nonchemical exposures for cumulative Environmental health risk assessment. Int J Environ Res Public Health Multidiscip Digit Publish Institute. 2018;15:2797.

[74] US EPA. (2003). Framework for Cumulative Risk Assessment. In Office of Research and Development Center for Public Health and Environmental Assessment (CPHEA) formerly known as the National Center for Environmental Assessment (NCEA), Ed. Washington, DC; Vol. EPA/600/P-02/001F, Available: https://www.epa.gov/risk/framework-cumulative-risk-assessment.

above, and discussed in the preamble to the Proposed Rule) from the 2003 Framework for Cumulative Risk Assessment that should be incorporated into the framework rule regulatory text.

Proposed Rule recommendations – Addressing aggregate exposures and cumulative risk in the scope document

The Proposed Rule language should be revised to incorporate specific requirements for consideration of aggregate exposure and cumulative risk in the scope document for each risk evaluation. EPA's decision regarding whether or not to estimate aggregate exposure, with a justification for that decision, should be presented in the scope document for each risk evaluation. Further, the scope document should specify the exposures that are to be aggregated. EPA should adopt a policy of estimating aggregate exposure in all circumstances, across all exposure routes and pathways and all conditions of use, unless there is a strong rationale for not doing so. Similarly, EPA should identify stressors that share common adverse outcomes with the chemical under evaluation in the scope document, and discuss how the risk evaluation will account for cumulative risk.

Recommendation 3.3: The Proposed Rule at § 702.39(b)(7) regarding the scope document analysis plan should be expanded to require the consideration of aggregate exposure, for example by describing how individuals may be exposed to the chemical in question by multiple exposure routes, pathways and conditions of use, and describing how the exposures will be aggregated in the risk evaluation.

Recommendation 3.4: The Proposed Rule at § 702.39(b)(7) regarding the scope document analysis plan should be expanded to require the consideration of cumulative risk by identifying other chemicals and non-chemical stressors that may contribute to common adverse outcomes with the chemical subject to risk evaluation, and describing how the cumulative risk resulting from co-exposures to these stressors will be accounted for in the risk evaluation.

Proposed Rule recommendations – Addressing aggregate exposure in exposure assessment and risk characterization

The Proposed Rule's requirements for "exposure assessment" incorporate several important improvements over the existing Risk Evaluation Framework Rule, including these additions regarding aggregate exposure and assessment of all exposure routes and pathways:

> EPA will consider aggregate exposures to the chemical substance, and, when supported by reasonably available information, consistent with the best available science and based on the weight of scientific evidence, include an aggregate exposure assessment in the risk evaluation, or will otherwise explain in the risk evaluation the basis for not including such an assessment. § 702.39(d)(8)
>
> EPA will assess all exposure routes and pathways relevant to the chemical substance under the conditions of use, including those that are regulated under other federal statutes. § 702.39(d)(9)

Recommendation 3.5: The Proposed Rule at § 702.39(d)(8) concerning aggregate exposure assessment should be strengthened to indicate that a full aggregate exposure assessment requires considering combinations of all conditions of use and exposure routes and pathways, in contrast to the subsets of combined exposures that have been previously considered in EPA's risk evaluations. We recommend expanding the Proposed Rule regulatory text as follows (suggested insertion is underlined):

> EPA will consider aggregate exposures to the chemical substance, and, when supported by reasonably available information, consistent with the best available science and based on the weight of scientific evidence, include an aggregate exposure assessment <u>considering all combinations of multiple routes of exposure, multiple pathways of exposure and multiple conditions of use that may contribute to total exposure of an individual or a subpopulation</u> in the risk evaluation, or will otherwise explain in the risk evaluation the basis for not including such an assessment.

Recommendation 3.6: The Proposed Rule at § 702.37(a)(5) under "Evaluation requirements" regarding unreasonable risk determinations should be expanded to incorporate aggregate exposure considerations (suggested insertions are underlined):

> EPA will determine whether a chemical substance does or does not present an unreasonable risk after considering the risks posed under all of the conditions of use <u>including combinations of conditions of use</u> and, where EPA makes a determination of unreasonable risk, EPA intends to identify the conditions of use <u>or combinations of such conditions</u> that significantly contribute to such determination.

4. The Proposed Rule should require risk evaluations to use best available science to calculate risks of non-cancer effects at exposure levels commonly experienced by workers, consumers and the general public, including PESS.

Methods used to date for evaluation of non-cancer risks in TSCA risk evaluations have been insufficient to meet Amended TSCA's requirements to use the "best available science" and to ensure protection of PESS. In particular, use of the "Margin of Exposure" ("MOE") for risk characterization, which relies only on a point of departure ("POD") with no extrapolation to lower doses, is a simplistic approach that does not estimate the proportion of the exposed population projected to experience a specified health endpoint or the number of individuals affected. The National Academy of Sciences ("NAS")[75] and World Health Organization[76] have outlined superior methods for risk estimation that have been demonstrated in

[75] National Research Council. Science and Decisions: Advancing Risk Assessment. Washington, DC: National Academies Press; 2009. Ch 5.
[76] World Health Organization, International Programme on Chemical Safety (2017). Guidance document on evaluating and expressing uncertainty in hazard characterization, 2nd edition. https://www.who.int/publications/i/item/9789241513548.

published case studies.[77,78,79,80] Application of these methods to TSCA assessments has been demonstrated in public comments submitted to EPA.[81]

In *Science and Decisions,* the NAS said:

> Noncancer effects do not necessarily have a threshold, or low-dose nonlinearity…Background exposures and underlying disease processes contribute to population background risk and can lead to linearity at the population doses of concern.[82]
>
> 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.[83]
>
> Quantification of risk (along with the attendant uncertainty)...along the dose continuum is an important advance for risk benefit analysis.[84]

In testing the feasibility and implications of replacing traditional reference doses with probabilistic estimates of risk for non-cancer effects, 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."[85] In addition, EPA has recently used dose-response functions from epidemiological studies for estimating risk of non-cancer effects in support of the Lead and Copper Rule Improvements,[86] the proposed drinking water standard for six per- and polyfluoroalkyl substances (PFAS),[87] and in the draft *IRIS Toxicological Review of Inorganic Arsenic*.[88] Probabilistic methods, such as the WHO methodology, and epidemiologic dose-response functions are a significant upgrade in methods over EPA's MOE approach and represent the best available science. These approaches should be incorporated

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[77] Blessinger T, Davis A, Chiu WA, et al. Application of a unified probabilistic framework to the dose-response assessment of acrolein. *Environment international.* 2020;143:105953. doi: 10.1016/j.envint.2020.105953.

[78] 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. Environmental Health Perspectives, 2018 June;126(6):067009. doi: 10.1289/EHP3368.

[79] Ginsberg GL. Cadmium risk assessment in relation to background risk of chronic kidney disease. Toxicol Environ Health A. 2012;75(7):374-90. doi: 10.1080/15287394.2012.670895.

[80] Nielsen GH, Heiger-Bernays WJ, Levy JI, White RF, Axelrad DA, Lam J, Chartres N, Abrahamsson DP, Rayasam SDG, Shaffer RM, Zeise L, Woodruff TJ, Ginsberg GL. Application of probabilistic methods to address variability and uncertainty in estimating risks for non-cancer health effects. *Environmental Health* 21 (Suppl 1), 129 (2023). doi:10.1186/s12940-022-00918-z.

[81] US EPA. (2023). Methylene Chloride; Rulemaking under TSCA section 6(a). Comment submitted by Program on Reproductive Health and the Environment, University of California, San Francisco et al. Available: https://www.regulations.gov/comment/EPA-HQ-OPPT-2020-0465-0282; US EPA. (2023). Perchloroethylene (PCE); Rulemaking under TSCA Section 6(a). Comment submitted by University of California, San Francisco Program on Reproductive Health and the Environment (UCSF PRHE) et al. Available: https://www.regulations.gov/comment/EPA-HQ-OPPT-2020-0720-0283; US EPA. (2023). Carbon Tetrachloride; Rulemaking under TSCA Section 6(a). Comment submitted by University of California, San Francisco Program on Reproductive Health and the Environment (UCSF PRHE) et al. Available: https://www.regulations.gov/comment/EPA-HQ-OPPT-2020-0592-0136; US EPA. (2023). Science Advisory Committee on Chemicals (SACC) Peer Review of 2023 Draft Supplement to the 1,4-Dioxane Risk Evaluation. Comment submitted by University of California, San Francisco Program on Reproductive Health and the Environment (UCSF PRHE) et al. Available: https://www.regulations.gov/comment/EPA-HQ-OPPT-2022-0905-0058.

[82] National Research Council. Science and Decisions: Advancing Risk Assessment. Washington, DC: National Academies Press; 2009. Page 8.

[83] National Research Council. Science and Decisions: Advancing Risk Assessment. Washington, DC: National Academies Press; 2009. Page 174.

[84] National Research Council. Science and Decisions: Advancing Risk Assessment. Washington, DC: National Academies Press; 2009. Page 178.

[85] 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.

[86] U.S. EPA. National Primary Drinking Water Regulations for Lead and Copper: Improvements (LCRI), Proposed rule, December 26, 2023. 88 FR 84878.

[87] U.S. EPA. PFAS National Primary Drinking Water Regulation Rulemaking, Proposed rule, March 29, 2023. 88 FR 18638

[88] U.S. EPA. *IRIS Toxicological Review of Inorganic Arsenic,* External Review Draft, October 2023

in TSCA risk evaluations and can also be applied to a multitude of decision-making contexts following risk evaluation, such as benefit-cost analysis and life-cycle impact analysis.

To promote the application of dose-response and risk characterization alternatives that make better use of the existing science, EPA should revise the Proposed Rule to require explanation of how its analytic methods and assumptions constitute the best available science and ensure that risks to PESS are not underestimated. We emphasize, however, that EPA must justify its choices of methods as best available science and must implement improved approaches to dose-response analysis of non-cancer effects in it risk evaluations regardless of whether or not it makes these revisions to the Proposed Rule.

Proposed Rule recommendations – analytic methods

Recommendation 4.1: The Proposed Rule should be modified to recognize recommendations of the NAS, including those in *Science and Decisions*, as representing the best available science. The current proposal language at § 702.37(a)(1) should be amended to include NAS reports concerning risk assessment methods along with EPA guidance.

Recommendation 4.2: The Proposed Rule language concerning dose-response assessment at § 702.39(c)(5) of the current proposal should be amended to require that risk evaluations include a rationale justifying the selection of data for dose-response analysis, justifying the selection of the approach to dose-response assessment as the best available science, discussing how risks of non-cancer effects are calculated at commonly-experienced exposure levels, and discussing how differential risk to PESS is quantitatively accounted for in dose-response assessment.

Recommendation 4.3: The Proposed Rule text regarding the "Summary of considerations" at § 702.39(e)(2) of the current proposal should be amended to require that risk evaluations include explanation of the extent to which selected approaches, models and assumptions for dose-response assessment avoid underestimation of risk, including risks to each group identified as PESS. This should include explanation of how a risk evaluation has quantitatively accounted for aggregate exposure and cumulative risk, including effects of non-chemical stressors.

5. The Proposed Rule requirements for manufacturer-requested risk evaluations should be expanded to better specify the information that must be provided with each request.

The current Risk Evaluation Framework Rule specifies procedures and requirements for chemical manufacturer requests that EPA conduct a TSCA risk evaluation for a selected chemical. The manufacturer requests submitted to date have all had significant flaws that have hindered the Agency's ability to meet its deadlines or acquire the necessary high-quality, timely data it needs to conduct

comprehensive and impactful evaluations.[89,90] TSCA mandates that EPA must use the "best available science" to inform its decisions on chemicals, and that EPA apply the same standards to manufacturer-requested risk evaluations. However, the existing process and requirements for manufacturer-requested risk evaluations under Amended TSCA create administrative challenges for EPA and are overly narrow in the data submitters are required to provide. EPA should revise the Proposed Rule to clarify that submitters of a manufacturer-requested risk evaluation (MRRE) must provide all reasonably available information concerning the chemical that is the subject of the request. The Proposed Rule should also be revised to remove requirements for manufacturer requests to include items outside of industry expertise, such as identifying PESS, as manufacturers have an incentive to understate such issues and the submitter's opinion does not help EPA conduct the risk evaluation.

The current Risk Evaluation Framework Rule appropriately indicates, at § 702.37(e)(3), that the identification of conditions of use (COUs) to be considered in an MRRE will be no different from the identification of COUs for a risk evaluation conducted on a high-priority chemical, as designated by EPA. Given this context, the language at § 702.37(b)(3) requiring submitters to identify the particular COUs for which they are requesting a risk evaluation is not useful, and potentially creates a misunderstanding that the scope of an MRRE may be limited to selected COUs.

The Proposed Rule has significantly improved the provisions regarding MRREs. We strongly agree with EPA's statement that "the requesting manufacturer(s) should bear the primary burden of providing EPA with all information necessary to conduct a risk evaluation on the chemical substance." Consistent with this position, the Proposed Rule includes the following provisions:

> it is the burden of the requesting manufacturer to provide EPA with the information necessary to carry out the risk evaluation. § 702.45(a)(3)
>
> EPA may identify data needs at any time during the process described in this section, and, by submitting a request for risk evaluation under this section, the requesting manufacturer agrees to provide, or develop and provide, EPA with information EPA deems necessary to carry out the risk evaluation § 702.45(a)(5)
>
> Requests must include all of the following information:… A description of the circumstances under which the chemical substance is intended, known, or reasonably foreseen to be manufactured, processed, distributed in commerce, used, or disposed of, and all information known to or reasonably ascertainable by the requesting manufacturer that supports the identification of the circumstances described in this paragraph. § 702.45(c)(4)
>
> All information known to or reasonably ascertainable by the requesting manufacturer on the health and environmental hazard(s) of the chemical substance, human and environmental exposure(s), and exposed population(s). § 702.45(c)(5)

[89] US EPA. (2020). Manufacturer Request for Risk Evaluation under the Toxic Substances Control Act: Octamethylcyclotetra-siloxane (D4). 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). Available: https://www.regulations.gov/comment/EPA-HQ-OPPT-2018-0443-0013

[90] US EPA. (2021). Chemical Category for OctahydroTetramethyl-Naphthalenyl-Ethanone (OTNE); Manufacturer Request for Risk Evaluation Under the Toxic Substances Control Act (TSCA); Notice of Availability and Request for Comments. Comment submitted by University of California, San Francisco Program on Reproductive Health and the Environment (UCSF PRHE). Available: https://www.regulations.gov/comment/EPA-HQ-OPPT-2020-0738-0010

Importantly, the proposed § 702.45(a)(3) and § 702.45(a)(5) clarify that submitters have a responsibility to provide EPA with the data needed to conduct a risk evaluation, and the proposed § 702.45(c)(4) would require submitters to identify all conditions of use, in place of the previous allowance for submitters to identify only selected conditions of use that they are interested in.

These changes should be retained in the final rule, and further improvements should be incorporated, as detailed below.

Proposed Rule recommendations – Manufacturer-requested risk evaluations

Recommendation 5.1: The Proposed Rule's list of items at § 702.45(c)(5) that must be submitted in a request for an MRRE allows submitters to exercise their own judgment regarding the relevance of existing information that may be important to EPA in conducting the risk evaluation. This list should be revised to better articulate the information that the manufacturer must submit:

- Modify § 702.45(c)(5)(ii), which currently says: "The chemical substance's hazard potential, including all potential environmental and human health hazards." This phrasing may allow the submitter to exercise judgment regarding the hazards relevant to the chemical in question, possibly providing an opportunity to withhold relevant evidence. Instead, the submitter should be required to provide *all* evidence regarding potential hazards, including toxicology studies, epidemiological studies, worker case studies, etc., and any existing reviews of the health hazards evidence from the published journal literature, government agencies or other authoritative bodies.
- Delete § 702.45(c)(5)(v), as the submitter's belief regarding relevant PESS has no utility in the risk evaluation process.
- Revise § 702.45(c)(5)(vii)to indicate that the submitter must identify all known locations where the chemical is stored – not just those locations that the submitter judges to be near significant sources of drinking water.
- Add items to the list indicating that the submitter must identify all known industrial and commercial locations at which the chemical is used, and all known consumer products containing the chemical.

These proposed changes would help EPA obtain critical information from manufacturers to support a comprehensive risk evaluation while still allowing for independent assessment by the Agency with regard to hazards, PESS, conditions of use, and exposure pathways.

Recommendation 5.2: EPA should finalize § 702.45(e)(7) of the Proposed Rule concerning Identification of information needs and § 702.45(e)(8) concerning unfulfilled information needs. These provisions implement the policy that submitters are responsible for providing any information that EPA identifies, after receiving the manufacturers' submission, as necessary to conduct a risk evaluation.