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Comments on Manufacturer Request for Risk Evaluation Under the Toxic Substances Control Act (TSCA), Chemical Category for Octahydro-Tetramethyl-Naphthalenyl-Ethanone (OTNE)

Submitted online via Regulations.gov to docket EPA-HQ-OPPT-2020-0738

These comments are submitted on behalf of the undersigned scientists. 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 unless indicated otherwise.

We appreciate the opportunity to provide written comments on the manufacturer request for a risk evaluation through the OTNE Consortium[1] under the Toxic Substances Control Act (TSCA), as amended by the Frank R. Lautenberg Chemical Safety for the 21st Century Act ("amended TSCA") for Octahydro-Tetramethyl-Naphthalenyl-Ethanone or OTNE.[2] OTNE is a fragrance ingredient found in a broad range of commercial and consumer products including, cleaning products, personal care products, furnishing care products, air freshening products, soaps, and candles. According to the OTNE Consortium, every year, the National Aggregate Production Volume is between 10 million and 50 million pounds of OTNE produced or imported into the United States. [3]

EPA has previously identified two of the four OTNE chemicals, Ethanone, 1-(1,2,3,4,5,6,7,8-octahydro-2,3,5,5-tetramethyl-2-naphthalenyl) and Ethanone, 1-(1,2,3,4,5,6,7,8-octahydro-2,3,8,8-tetramethyl-2-naphthalenyl) in the 2014 TSCA Work Plan as toxic to aquatic organisms, with moderate environmental persistence and high bioaccumulation potential, [4] and therefore meeting the statutory definition of persistent, bio-accumulative, and toxic ("PBT"). The OTNE Consortium's manufacturer request for a risk evaluation, including EPA's solicitation for comments has failed to highlight this critical characteristic.

Due to its high production volume, widespread use and PBT properties, OTNE presents a significant threat to workers, consumers, and the environment,[5] underscoring the need for EPA to consider all available exposure data during the risk evaluation process, including workplace monitoring data. In the risk evaluation request, the OTNE Consortium did not provide any workplace monitoring data. EPA must fully and accurately evaluate those risks under TSCA.

[1] The request was made by International Flavors and Fragrances, Inc. (IFF), Privi Organics USA Corporation (Privi), and DRT America, Inc. (DRT) through the OTNE Consortium.

[2] OTNE chemicals include: ethanone, 1-(1,2,3,4,5,6,7,8-octahydro-2,3,5,5-tetramethyl-2-naphthalenyl); ethanone, 1-(1,2,3,4,5,6,7,8-octahydro-2,3,8,8-tetramethyl-2-naphthalenyl); ethanone, 1-(1,2,3,4,6,7,8,8a-octahydro-2,3,8,8-tetramethyl-2-naphthalenyl); and ethanone, 1-(1,2,3,5,6,7,8,8a-octahydro-2,3,8,8-tetramethyl-2-naphthalenyl).

[3] US EPA (2021) OTNE Risk Evaluation Request, Appendix III; Available: https://www.epa.gov/sites/production/files/2020-12/documents/otne_mrre.pdf

[4] EPA, TSCA Work Plan for Chemical Assessments: 2014 Update at 13 (Oct. 2014), https://www.epa.gov/sites/production/files/2015-01/documents/tsca_work_plan_chemicals_2014_update-final.pdf.

5 EPA, Proposed Rule: Regulation of Persistent, Bioaccumulative, and Toxic Chemicals Under TSCA Section 6(h), 84 Fed. Reg. 36728, 36734 (July 29, 2019)

We have previously commented on EPA's inadequate scientific methods that have been implemented in the completed draft risk evaluations. [6,7,8, 9,10,11, 12,13] Critical scientific flaws in EPA's risk evaluation approach have led to an underestimation of risk for all the first ten chemicals EPA has evaluated under amended TSCA. The OTNE Consortium's manufacturer request for a risk evaluation fails to include the necessary information for EPA to conduct the risk evaluation that TSCA requires. Most notably, the Consortium's manufacturer request fails to comprehensively include all intended and reasonably foreseen conditions of use, does not adequately consider OTNE's health effects on humans or the environment or all potentially exposed or susceptible subpopulations (PESS). It is highly likely that additional consumer and industrial uses pose unreasonable risks, and that other populations, including susceptible sub-populations, face unreasonable risks from OTNE.

EPA's risk evaluations have been and will continue to be inadequate until the methodological, scientific and technical problems we and many other commenters identified are addressed consistent with current and best scientific principles for risk evaluations and for systematic reviews. The law requires EPA to make decisions about chemical risks based on the "best available science, "adequate information" and "weight of the scientific evidence,"[14] which EPA regulation defined as "…a systematic review method, applied in a manner suited to the nature of the evidence or decision, that uses a pre-established protocol to comprehensively, objectively, transparently, and consistently identify and evaluate each stream of evidence, including strengths, limitations, and relevance of each study and to integrate evidence as necessary and appropriate based upon strengths, limitations, and relevance.''[15]

[6] 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

[7] 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

[8] 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

[9] US EPA. (2019). Draft Toxic Substances Control Act Risk Evaluations: Color Index Pigment Violet 29. Comment submitted by Veena Singla, 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-2018-0604-0014

[10] US EPA. (2020). Draft Toxic Substances Control Act Risk Evaluations: N-Methyl-2-pyrrolidone (NMP). 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-2019-0236-0048

[11] US EPA. (2020). Draft Toxic Substances Control Act Risk Evaluations: Carbon Tetrachloride. 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-2019-0499-0041

[12] US EPA. (2020). Trichloroethylene (CASRN 79-01-6); Draft Toxic Substances Control Act (TSCA) Risk Evaluation. Available: https://www.epa.gov/sites/production/files/2020-02/documents/1_draft_risk_evaluation_for_trichloroethylene_tce_public.pdf

[13] US EPA. (2020). Draft Toxic Substances Control Act Risk Evaluations. Asbestos; Comment submitted by Nicholas Chartres et al., Associate Director, Science and Policy, Program on Reproductive Health and the Environment, Department of Obstetrics, Gynecology and Reproductive Sciences, University of California, San Francisco. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0501-0087

[14] 15 USC §2625 (h)-(i) and 15 USC §2601 (b)(1)

[15] 40 CFR 702.33

Our comments on the manufacturer request for OTNE draft risk evaluation address the following main issues:

1. **EPA must consider and appropriately regulate OTNE based on its persistent, bio-accumulative, and toxic (PBT) properties.**
2. **EPA's risk evaluations must include all conditions of use and all exposure pathways in all risk evaluations.**
    a. **In the OTNE Manufacturer Requests for Risk Evaluation EPA must consider all conditions of use and all exposure pathways in aggregate, not just those identified by the OTNE Consortium.**
    b. **EPA should include all conditions of use and all exposure pathways in all risk evaluations, including those for which scope documents have already been issued.**
    c. **EPA must consider aggregate exposure within and across all exposed populations in order to make an adequate assessment of risk to meet the statutory requirements.**
3. **EPA's risk evaluations must evaluate risks to all potentially exposed and susceptible subpopulations (PESS).**
    a. **The OTNE Manufacturer Requests for Risk Evaluation fails to identify all PESS.**
    b. **EPA must follow recommendations from the National Academy of Sciences (NAS) to identify PESS under TSCA based on established extrinsic and intrinsic factors that increase vulnerability and fully assess the risks to these PESS.**
4. **EPA's risk evaluations must account for all chemical effects on human health and the environment.**
    a. **To make a risk determination, EPA must have adequate data. However, the OTNE Manufacturer Requests for Risk Evaluation fails to provide sufficient data to assess OTNE's health effects.**
    b. **EPA should require data on health hazards that are sufficiently comprehensive and sensitive to understand hazard and prevent or mitigate harmful health effects of chemicals.**
5. **EPA must address other flawed approaches that have been implemented in previous TSCA risk evaluations.**
    a. **EPA must not assume the use of personal protective equipment (PPE) in TSCA risk evaluations.**
    b. **EPA must follow recommendations from the NAS and implement a systematic review method for TSCA risk evaluations that is compatible with the National Academy of Medicine's definition of a systematic review, including the National Toxicology Program's OHAT method and the Navigation Guide developed by the University of California, San Francisco (UCSF).**
6. **TSCA risk evaluations should provide additional information to help ensure that TSCA regulations "appropriately benefit and do not inappropriately burden disadvantaged, vulnerable, or marginalized communities".**

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

Sincerely,

Nicholas Chartres, PhD
Associate Director, Program on Reproductive Health and the Environment
Department of Obstetrics, Gynecology and Reproductive Sciences
University of California, San Francisco

Patricia D. Koman, PhD, MPP
Investigator, School of Public Health
Environmental Health Sciences Department
University of Michigan

Tracey Woodruff, PhD, MPH
Professor and Director, Program on Reproductive Health and the Environment
Department of Obstetrics, Gynecology and Reproductive Sciences
University of California, San Francisco

Max Aung, PhD, MPH
Research Scientist, Program on Reproductive Health and the Environment
Department of Obstetrics, Gynecology and Reproductive Sciences
University of California, San Francisco

Swati Rayasam, MSc
Science Associate, Program on Reproductive Health and the Environment
Department of Obstetrics, Gynecology and Reproductive Sciences
University of California, San Francisco

Daniel Axelrad, MPP
Independent Consultant

Phil Brown, PhD
University Distinguished Professor of Sociology and Health Sciences
Northeastern University

Courtney Cooper, BS
Research Coordinator, Program on Reproductive Health and the Environment
Department of Obstetrics, Gynecology and Reproductive Sciences
University of California, San Francisco

Mary Martin Gant, MS
Policy Analyst (retired)
National Institute of Environmental Health Sciences

Robert M. Gould, MD
Associate Adjunct Professor, Department of Obstetrics, Gynecology and Reproductive Sciences, University of California, San Francisco
President, San Francisco Bay Physicians for Social Responsibility

Jerrold J. Heindel, PhD
Co-director
Healthy Environment and Endocrine Disruptor Strategies

Taisen Iguchi, PhD
Professor, Graduate School of Nanobioscience
Yoohama City University

Juleen Lam, PhD, MHS, MS
Assistant Professor
California State University, East Bay

Heather Patisaul, PhD
Professor and Associate Dean for Research, College of Sciences
NC State University

Ted Schettler, MD, MPH
Science Director
Science and Environmental Health Network

Ana M. Soto, MD
Professor, School of Medicine
Tufts University

Patrice Sutton, MPH
Research Scientist, Program on Reproductive Health and the Environment
Department of Obstetrics, Gynecology and Reproductive Sciences
University of California, San Francisco

Marya Zlatnik, MD
Professor, Department of Obstetrics, Gynecology and Reproductive Sciences
University of California, San Francisco

DETAILED COMMENTS

1. **EPA must consider and appropriately regulate OTNE based on its persistent, bio-accumulative, and toxic (PBT) properties.**

PBTs (also known as persistent organic pollutants, or POPs) are called the 'worst of the worst' chemicals because of their inherent nature - they have a high resistance to degradation, will build up in people and wildlife, and are toxic (harmful to life). In amended TSCA, Congress recognized that any production or use of PBT chemicals will present unreasonable risks to health and/or the environment and created a separate mandate for PBT chemicals, requiring expedited action by EPA with no risk evaluation. PBT chemicals are thus presumed to present unreasonable risks and EPA does not need to quantify specific risks per the law. Instead, the law states that once EPA determines exposure is likely:

> "the Administrator shall address the risks of injury to health or the environment that the Administrator determines are presented by the chemical substance and **shall reduce exposure to the substance to the extent practicable**." [16,17] (emphasis added)

EPA has previously identified, Ethanone, 1-(1,2,3,4,5,6,7,8-octahydro-2,3,5,5-tetramethyl-2-naphthalenyl)- and Ethanone, 1-(1,2,3,4,5,6,7,8-octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)- in the 2014 TSCA Work Plan as toxic to aquatic organisms, with moderate environmental persistence and high bioaccumulation potential, [18] and therefore, meeting the statutory definition of *persistent, bio-accumulative, and toxic (PBT).*

Currently, rules for five of the seven PBT chemicals identified in EPA's 2014 Work Plan have been finalized, with the two OTNE chemicals being excluded from those rules due to the manufacturers request for risk evaluation. The law requires that EPA remove exposures to these harmful PBT chemicals to the extent practicable, including for potentially exposed and susceptible sub-populations. To do this EPA's rule must address all phases of the chemical life-cycle (manufacturing, processing, use, recycling and disposal of these chemicals and products containing them) and all pathways of exposure and release. It is therefore critical EPA considers all available exposure data during the risk evaluation process, including workplace monitoring data and environmental release data and to acquire more data to fill any exposure data gaps. EPA must apply its authorities under sections 4 and 8 of amended TSCA to do this, which we discuss in detail below in point #4.

2. **EPA's risk evaluations must include all conditions of use and all exposure pathways in all risk evaluations.**

[16] US EPA (June 2018) Exposure and use assessment of five persistent, bioaccumulative and toxic chemicals.
[17] 15 U.S.C. § 2605(h)(4)
[18] EPA, TSCA Work Plan for Chemical Assessments: 2014 Update at 13 (Oct. 2014), https://www.epa.gov/sites/production/files/2015-01/documents/tsca_work_plan_chemicals_2014_update-final.pdf.

a. In the OTNE Manufacturer Requests for Risk Evaluation EPA must consider all conditions of use and all exposure pathways in aggregate, not just those identified by the OTNE Consortium.

Many of the uses of OTNE are designed for human inhalation and dermal contact; specifically, the conditions of use such as a fragrance, scented sheets and bedding, scented paper, and scented soap. As EPA acknowledges, there are multiple conditions of use through which people may be exposed to OTNE. Multiple exposures may occur simultaneously—such as by dermal and inhalation exposures to OTNE in the same product—or by exposure to two or more of the multitude of products containing OTNE. In EPA's documentation of the additional conditions of use for the OTNE category, OTNE chemicals are used in dozens of types of commercial and consumer products, including cleaning and furnishing care products, laundry and dishwashing products, and air freshening products. These products may all be used by the same individual in the same day—in an occupational setting, a home setting, or both. People are exposed to OTNE in a vast array of consumer and commercial products and thus the combined (aggregated) exposures from all pathways is necessary to avoid underestimation of risk and to utilize the best available scientific process.

EPA should also consider cumulative risk assessment to fully assess the human health and environmental factors that should be acknowledged and incorporated in the OTNE risk evaluation. OTNE is frequently in products mixed with other chemicals. In order to adequately assess any potential amplification of risk to potentially exposed or susceptible populations as a result of co-exposures and to use the best available science in the risk evaluation, EPA can evaluate the potential risk associated with co-exposure to OTNE and other chemicals commonly found in products that contain OTNE in its risk evaluation.

We identify several criteria that should be applied when determining when a cumulative assessment would be appropriate: 1) concomitant exposure attendant to a category or subcategory of conditions of use; 2) close chemical structural similarities, that is, members of the same chemical class; 3) shared metabolic pathways and byproducts of metabolism; 4) similar toxicity profiles; 5) similar modes/mechanisms of action of shared toxicity endpoints or shared key events, 6) environmental justice concerns by vulnerable populations such as communities near manufacturing, use or disposal sites.

Furthermore, the current administration has called on Agencies to "take into account the distributional consequences of regulations" [19] and to "develop programs, policies, and activities to address the disproportionately high and adverse human health, environmental, climate-related and other cumulative impacts on disadvantaged communities." [20] These environmental justice policies are consistent with EPA's obligation to protect potentially exposed or susceptible subpopulations under TSCA, and they should be included in EPA's analysis of potential risk management options under Section 6(c)(2). These policies further support the need for aggregate and cumulative risk assessments.

[19] Presidential Memorandum, *Modernizing Regulatory Review*, § 2(b)(i) (Jan. 20, 2021).
[20] *Executive Order on Tackling the Climate Crisis at Home and Abroad* § 219 (Jan. 27, 2021).

b. EPA must include all conditions of use and all exposure pathways in all risk evaluations, including those for which scope documents have already been issued

EPA has incorrectly asserted broad discretion to exclude conditions of use and exposure pathways from its TSCA risk evaluations, contrary to the intent of the 2016 amendments to TSCA. EPA has put forward these assertions of broad discretion in the 2017 final risk evaluation framework rule and in the scope documents it has issued for the completed and initiated risk evaluations (e.g., the 2020 scope documents for 20 high-priority chemicals).[21]

The proposed rule evaluation framework rule addressed the scope question appropriately by stating that "all" conditions of use would be considered in each risk evaluation:

> *"EPA will identify those uses that constitute the conditions of use that will be assessed during the risk evaluation. Those uses shall be all circumstances under which the Agency determines that the chemical substance is intended, known, or reasonably foreseen to be manufactured, processed, distributed in commerce, used, or disposed of."*[22]

The final risk evaluation framework rule substantially revised the language concerning the scope of TSCA risk evaluations, stating that the scope will include:

> *"The condition(s) of use, as determined by the Administrator, that the EPA plans to consider in the risk evaluation."*[23]

The preamble to the final rule explained the Agency's position that it has discretion in determining the conditions of use *"for each chemical substance on a case-by-case basis" and "As EPA interprets the statute, the Agency is to exercise that discretion consistent with the objective of conducting a technically sound, manageable evaluation*." The preamble also identified several particular circumstances to which this discretion may be applied:[24]

- *"in order to focus its analytical efforts on those exposures that are likely to present the greatest concern"* (includes exclusion of uses that *"would present only* 'de minimis' *exposures"*)
- *"a condition of use that has been adequately assessed by another regulatory agency, particularly where the other agency has effectively managed the risks"*
- *"intentional misuses"*
- *"legacy uses"* and *"associated disposal"*
- *"circumstances where the chemical substance subject to scoping is unintentionally present as an impurity in another chemical substance."*

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[21] US EPA Final Scope Documents for High-Priority Chemicals Undergoing Risk Evaluation. Available: https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/final-scope-documents-high-priority-chemicals-undergoing).

[22] Procedures for Chemical Risk Evaluation under the Amended Toxic Substances Control Act, Proposed Rule. Federal Register, January 19, 2017 82 FR 7562. § 702.39(c)(1)

[23] Procedures for Chemical Risk Evaluation Under the Amended Toxic Substances Control Act, Final Rule. Federal Register, July 20, 2017, 82 FR 33726. § 702.41(c)(1)

[24] Procedures for Chemical Risk Evaluation Under the Amended Toxic Substances Control Act, Final Rule. Federal Register, July 20, 2017, 82 FR 33726.

A court ruling has nullified the Agency's claim of discretion regarding legacy uses and associated disposal, but the remaining circumstances for which the Agency asserted broad discretion are still in place.

In addition to the statements regarding the scope of risk evaluations in the final framework rule, TSCA risk evaluation scope documents have asserted that EPA may exclude from TSCA risk evaluations any exposure pathways that may be addressed by other statutes administered by EPA:

> "*EPA's careful consideration of whether other EPA-administered authorities are available, and more appropriate, for addressing certain exposures and risks is consistent with Congress' intent to maintain existing federal requirements and the state actions adopted to locally and more specifically implement those federal requirements, and to carry out TSCA in a reasonable and prudent manner. EPA believes it is both reasonable and prudent to tailor TSCA risk evaluations, rather than attempt to evaluate and regulate potential exposures and risks from those media under TSCA."* [25]

This language constitutes a further assertion of overbroad Agency discretion in selecting conditions of use to include in a risk evaluation. It also confuses the important distinction between the scope of a risk evaluation and how EPA may choose to address any unreasonable risks. It may be "reasonable and prudent" for EPA to address certain unreasonable risks under statutory authorities other than TSCA, but that is an entirely different issue than the question of whether certain conditions of use and exposure pathways should be assessed in a risk evaluation that is intended to consider all conditions of use of a chemical. Exclusion of uses and pathways from a risk evaluation will result in underestimation of risks. Further, there may be numerous scenarios in which exposures addressed by other statutes can be better addressed under TSCA. For example, it may be more effective and less costly to use TSCA to prevent releases of certain chemicals (such as 1,4-dioxane) to water, rather than allowing water to become contaminated and then try to remediate the contamination using the Safe Drinking Water Act (SDWA) and the Clean Water Act (CWA).

EPA's original judgment on this issue, as explained in the preamble to the proposed framework rule, was the correct and most defensible reading of the statute:

> *EPA interprets the amended TSCA as requiring that risk evaluations encompass all manufacture, processing, distribution in commerce, use, and disposal activities that constitute the conditions of use within the meaning of TSCA section 3. That is to say, a risk evaluation must encompass all known, intended, and reasonably foreseen activities associated with the subject chemical substance.* [26]

[25] US EPA (2020). Draft Scope of the Risk Evaluation for Formaldehyde (CASRN 50-00-0). Pp 54 Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2018-0438-0029

[26] Procedures for Chemical Risk Evaluation under the Amended Toxic Substances Control Act, Proposed Rule. Federal Register, January 19, 2017 82 FR 7562. § 702.39(c)(1)

EPA's decisions to exercise discretion in narrowing the scope of its TSCA risk evaluations from all circumstances of use may have a substantial impact on the Agency's ability "to ensure that regulatory initiatives appropriately benefit and do not inappropriately burden disadvantaged, vulnerable, or marginalized communities".[27] Conditions of use and exposure pathways that have been excluded from risk evaluations by EPA may be those that are likely to pose disproportionate risks to disadvantaged, vulnerable and marginalized communities. For example, communities near chemical manufacturing facilities and contaminated sites are often those with lower incomes, poor health status, and with a majority of residents who are people of color. The exclusion from TSCA risk evaluations of exposure pathways that may be within the scope of other EPA statutory authorities (e.g., hazardous air pollutant emissions and releases to drinking water) are the exposure pathways that frequently result in disproportionate exposures to fenceline communities.

EPA should issue a revised risk evaluation framework rule that restores the language regarding inclusion of all conditions of use from the proposed rule, § 702.39(c)(1). Until that revised rule is issued, EPA should not exercise the discretion claimed in the 2017 framework rule and should not exclude exposure pathways addressed under other EPA authorities. Any such exclusions stated in existing risk evaluation scope documents should be reversed in revised scope documents. This means no exclusions of these conditions of use and pathways in any ongoing risk evaluations:

- Legacy uses and associated disposal
- Conditions of use and exposure pathways already covered under TSCA (e.g., composite wood products regulated under the Formaldehyde Emission Standards for Composite Wood Products final rule)
- Exposure pathways covered by other statutes administered by EPA, including the CWA, SDWA, the Clean Air Act (CAA), the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA), and the Resource Conservation and Recovery Act (RCRA)
- Any condition of use assessed by another federal regulatory agency (other than those excluded by TSCA, such food and drug uses and pesticide uses)
- Conditions of use where the chemical is unintentionally present as an impurity.

[27] Presidential Memorandum, *Modernizing Regulatory Review*, § 2(b)(i) (Jan. 21, 2021).

c. EPA must consider aggregate exposure within and across all exposed populations in order to make an adequate assessment of risk to meet the statutory requirements.

TSCA requires EPA to eliminate the unreasonable risk posed by a chemical substance if EPA determines:

> "that 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."[28] (emphasis added)

This language assumes that EPA will evaluate the risks posed by combinations of uses. Without considering the multiple pathways and sources of exposures to a chemical, and the aggregated and cumulative effect that these exposures may have, EPA will underestimate the risks of a chemical substance. As highlighted above in point #2b. in its previous first 10 chemical risk evaluations, EPA mistakenly excluded known sources of chemical exposure including air, water, and soil. The Agency also failed to account for the combination of multiple routes of exposure known to occur simultaneously during a specific condition of use, including oral, inhalation and dermal. Therefore, EPA has not conducted adequate aggregate assessments based upon combined (aggregate) exposures as required under TSCA.

3. EPA's risk evaluations must evaluate risks to all potentially exposed and susceptible subpopulations (PESS).

a. The OTNE Manufacturer Requests for Risk Evaluation fails to identify all PESS.

The manufacturer is proposing that EPA consider 5 populations for exposure assessment.[29] Accordingly, PESS identified by the OTNE Consortium are expected to include 1) infants, 2) children, 3) pregnant women, 4) workers, and 5) the elderly, given the potential for use of OTNE as a fragrance in consumer products such as bath and shower products, personal care products, and laundry products such as fabric softeners and detergents. We agree with these categories; however, this evaluation is missing 1) the general public; 2) consumers and bystanders; 3) people who live or work near manufacturing, processing, distribution, use or disposal sites; 4) people with chemical sensitivities[30]; and 5) those with chronic conditions such as people with asthma. Importantly, when conducting or assessing risk evaluations, EPA must account for combined exposures and risks from multiple roles related to the conditions of use (e.g., janitor who also uses consumer products, has asthma and lives near a near manufacturing, processing, distribution, use or disposal site for OTNE).[31]

[28] 15 U.S.C. § 2605(a) (emphasis added).

[29] See OTNE Risk Evaluation Request. https://www.epa.gov/sites/production/files/2020-12/documents/otne_mrre.pdf

30 Steinemann, A. International prevalence of chemical sensitivity, co-prevalences with asthma and autism, and effects from fragranced consumer products. Air Qual Atmos Health 12, 519–527 (2019). https://doi.org/10.1007/s11869-019-00672-1

31 National Research Council (US) Committee on Improving Risk Analysis Approaches Used by the U.S. EPA. Science and Decisions: Advancing Risk Assessment. Washington (DC): National Academies Press (US); 2009. PMID: 25009905.

The general public should be evaluated due to the ubiquitous conditions of use in commercial and consumer products as well as the potential for environmental exposures from disposal as OTNE has been detected in wastewater discharges from sewage treatment plants.[32] Likewise, consumers and bystanders can be exposed to air emissions from these products.[33] Commercial consumers such as cleaning contractors, domestic workers, janitors, and hospitality workers are likely to experience greater exposures to cleaning products containing OTNE than general consumers. Moreover, many of those workers are also exposed to products containing OTNE at home, including cleaning products, personal care products, textiles, candles, and more. It is reasonable to anticipate people who use products containing OTNE will be exposed, and they will be exposed to OTNE from more than one product or one condition of use.

For individuals with chronic respiratory conditions such as asthma, the prevalence of fragrance sensitivity is several times higher.[34] Fragrance chemicals can be both initiators and promoters of adverse health effects in both subgroups, including migraine, asthma attacks, neurological problems (e.g., dizziness, seizures), and respiratory problems (e.g., shortness of breath, asthma exacerbations). Given the ubiquitous use of OTNE in fragranced products, EPA should consider the subpopulations of asthmatic individuals as especially vulnerable for the following reasons:

- Inhalation is a known pathway and OTNE is a respiratory irritant. According to the Centers for Disease Control and Prevention (CDC), more than 25 million Americans have asthma, of which 8.4% are children.[35]
- Black children have the highest prevalence of asthma in the United States. About 13.5% of Black children have asthma, compared to about 6.4% of white children.[36] Asthmatic children in low wealth households face additional burdens that lead to worse health outcomes to which chemical exposures add.[37, 38]
- "To meet environmental justice goals under President Biden's January 20, 2021 memorandum on Modernizing Regulatory Review and Executive Order 13985."[39]

Contributing factors to heightened sensitivity includes intrinsic factors (e.g., life stage, genetics, disease status, nutrition) and extrinsic factors (e.g., additional chemical exposures and non-chemical stressors).

32 Kathleen McDonough et al., Probabilistic determination of the ecological risk from OTNE in aquatic and terrestrial compartments based on US-wide monitoring data, 167 Chemosphere 255-261 (2017), https://doi.org/10.1016/j.chemosphere.2016.10.006

[33] Zota AR, Shamasunder B. The environmental injustice of beauty: framing chemical exposures from beauty products as a health disparities concern. American Journal of Obstetrics and Gynecology. 2017;217:418.e1-418.e6.

[34] Steinemann, A. International prevalence of chemical sensitivity, co-prevalences with asthma and autism, and effects from fragranced consumer products. Air Qual Atmos Health 12, 519–527 (2019). https://doi.org/10.1007/s11869-019-00672-1

35 CDC.gov. (2021). CDC - Asthma. [online] Available at: https://www.cdc.gov/asthma/default.htm

[36]CDC.gov. (2019). CDC - Asthma - Most Recent Asthma Data. [online] Available at: https://www.cdc.gov/asthma/most_recent_national_asthma_data.htm

[37] Beck AF, Huang B, Simmons JM, Moncrief T, Sauers HS, Chen C, et al. Role of financial and social hardships in asthma racial disparities. Pediatrics. 2014;133:431–9.

[38] Hughes HK, Matsui EC, Tschudy MM, Pollack CE, Keet CA. Pediatric Asthma Health Disparities: Race, Hardship, Housing, and Asthma in a National Survey. Acad Pediatr. 2017;17:127–34

[39] Presidential Memorandum, *Modernizing Regulatory Review*, § 2(b)(i) (Jan. 20, 2021).

Extrinsic factors – social stressors – like lack of access to health care facilities, [40, 41, 42] healthy food, [43, 44] and information and adequate formal education opportunities for health literacy [45] can compound the negative effects of environmental exposures among these subpopulations. Environmental exposures at multiple critical periods of development can modify response to each other, leading to greater adverse consequences.[46]

Physiological parameters specific to life stage may make individuals more or less susceptible to environmental exposures.[47, 48] Young infants (less than three months old) have lower lipid content with respect to adults (reducing their relative retention of lipophilic chemicals) while older infants have higher lipid content with respect to adults (increasing their relative retention of lipophilic chemicals). Likewise, elderly populations may have greater sensitivity to chemicals including pharmaceuticals due to decreased metabolic capacity and ability to respond and repair physiological damage with older age.[49] EPA risk evaluations should directly account for exposure to multiple related stressors (e.g., considering chemical classes and mixtures rather than a chemical-by-chemical approach and evaluating cumulative exposure to non-chemical stressors). However, risk evaluations can improve human variability adjustment factors to reflect that other chemical and non-chemical exposures contribute to the variability in response to a given chemical. Risk evaluations should also account for additivity to background chemical exposure in selecting methods for low-dose in extrapolation (e.g., probabilistic methods rather than derivation of a "safe" or threshold level). The 2004 National Environmental Justice Advisory Council (NEJAC) report on cumulative risk assessment emphasized that incorporating the full range of stressors to which populations are exposed is key to understanding community risk and community health.[50] This is consistent with recommendations of the National Academy of Sciences

[40] 2018 National Healthcare Quality and Disparities Report | Agency for Health Research and Quality [Internet]. [cited 2020 Aug 8]. Available from: https://www.ahrq.gov/research/findings/nhqrdr/nhqdr18/index.html

[41] Medicine I of. Unequal Treatment: Confronting Racial and Ethnic Disparities in Health Care [Internet]. 2002 [cited 2020 Aug 2]. Available from: https://www.nap.edu/catalog/12875/unequal-treatment-confronting-racial-and-ethnic-disparities-in-health-care

[42] Shi L, Chen C-C, Nie X, Zhu J, Hu R. Racial and Socioeconomic Disparities in Access to Primary Care Among People with Chronic Conditions. J Am Board Fam Med. American Board of Family Medicine; 2014;27:189–98.

[43] Hilmers A, Hilmers DC, Dave J. Neighborhood Disparities in Access to Healthy Foods and Their Effects on Environmental Justice. Am J Public Health. 2012;102:1644–54.

[44] Walker RE, Keane CR, Burke JG. Disparities and access to healthy food in the United States: A review of food deserts literature. Health & Place. 2010;16:876–84.

[45] National Academies of Sciences E. Monitoring Educational Equity [Internet]. 2019 [cited 2020 Aug 2]. Available from: https://www.nap.edu/catalog/25389/monitoring-educational-equity

[46] Balbus JM, Barouki R, Birnbaum LS, Etzel RA, Gluckman PD, Grandjean P, et al. Early-life prevention of non-communicable diseases. The Lancet. Elsevier; 2013;381:3–4.

[47] Axelrad DA, Setzer RW, Bateson TF, DeVito M, Dzubow RC, Fitzpatrick JW, et al. Methods for evaluating variability in human health dose–response characterization. Human and Ecological Risk Assessment: An International Journal. 2019;0:1–24.

[48] Hines RN, Sargent D, Autrup H, Birnbaum LS, Brent RL, Doerrer NG, et al. Approaches for assessing risks to sensitive populations: lessons learned from evaluating risks in the pediatric population. Toxicol Sci. 2010;113:4–26.

[49] OEHHA (Office of Environmental Health Hazard Assessment), Air Toxicology and Epidemiology Branch, California Environmental Protection Agency. Air Toxics Hot Spots Risk Assessment Guidelines: Technical Support Document For the Derivation of Noncancer Reference Exposure Levels [Internet]. 2008. Available from: https://oehha.ca.gov/media/downloads/crnr/noncancertsdfinal.pdf

[50] US EPA O. Ensuring Risk Reduction in Communities with Multiple Stressors: Environmental Justice and Cumulative Risks/Impacts [Internet]. Prepared by the National Environmental Justice Advisory Council Cumulative Risks/Impacts Work Group; 2004 Dec. Available from: https://www.epa.gov/environmentaljustice/ensuring-risk-reduction- stressors-environmental-justice / https://www.epa.gov/sites/production/files/2015-02/documents/nejac-cum-risk-rpt-122104.pdf

[50] National Research Council. Toxicity Testing in the 21st Century: A Vision and a Strategy [Internet]. Washington, D.C.: The National Academies Press; 2007. Available from: https://www.nap.edu/download/11970#

[50] National Research Council. Phthalates and Cumulative Risk Assessment: The Task Ahead [Internet]. Washington, D.C.: The National Academies Press; 2008 [cited 2011 Oct 15]. Available from: https://doi.org/10.17226/12528

(NAS) [51] [52] [53] and scientific articles [54] [55] which report that default approaches to treatment of human variability in risk assessments need to be updated to better incorporate current knowledge regarding human variability and vulnerability factors.

b. EPA must follow recommendations from the National Academy of Sciences (NAS) to identify PESS under TSCA based on established extrinsic and intrinsic factors that increase vulnerability and fully assess the risks to these PESS.

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 PESS.

To meet this mandate, the law requires that EPA comprehensively assess all intended, known or reasonably foreseen conditions of use for the chemical (or class of chemicals) under consideration, and the associated exposures. Otherwise, risk will be underestimated, including the risk to PESS.

In the first 10 risk evaluations conducted under the 2016 TSCA Lautenberg Amendments, EPA did not adequately evaluate risks to PESS, as described above. Specifically, EPA systematically understated risks to workers by improperly assuming the use of personal protective equipment (PPE); omitted general population exposures from air inhalation and other pathways; failed to evaluate risks to the communities surrounding the facilities that use and release the chemicals; and did not consider the cumulative effects of known or foreseen combinations of chemicals exposures.[56]

A critical element of the accuracy and usefulness of chemical risk assessment is accounting for the full range of individual and population variability in response to environmental chemical exposures. This ensures the protection of everyone, including those most susceptible (increased sensitivity due to

[50] National Research Council. Science and Decisions: Advancing Risk Assessment [Internet]. Washington, D.C.: The National Academies Press; 2009 [cited 2011 Oct 15]. Available from: http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=202175

[50] Chiu WA, Rusyn I. Advancing chemical risk assessment decision-making with population variability data: challenges and opportunities. Mamm Genome. 2018;29:182–9.

[50] Bhat VS, Meek ME (Bette), Valcke M, English C, Boobis A, Brown R. Evolution of chemical-specific adjustment factors (CSAF) based on recent international experience; increasing utility and facilitating regulatory acceptance. Critical Reviews in Toxicology. 2017;47:733–53.

[50] Koman PD, Singla V, Lam J, Woodruff TJ. Population susceptibility: A vital consideration in chemical risk evaluation under the Lautenberg Toxic Substances Control Act. PLoS Biol [Internet]. 2019 [cited 2020 Apr 30];17. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6715167/

communities-multiple-stressors-environmental-justice / https://www.epa.gov/sites/production/files/2015-02/documents/nejac-cum-risk-rpt-122104.pdf

[51] National Research Council. Toxicity Testing in the 21st Century: A Vision and a Strategy [Internet]. Washington, D.C.: The National Academies Press; 2007. Available from: https://www.nap.edu/download/11970#

[52] National Research Council. Phthalates and Cumulative Risk Assessment: The Task Ahead [Internet]. Washington, D.C.: The National Academies Press; 2008 [cited 2011 Oct 15]. Available from: https://doi.org/10.17226/12528

[53] National Research Council. Science and Decisions: Advancing Risk Assessment [Internet]. Washington, D.C.: The National Academies Press; 2009 [cited 2011 Oct 15]. Available from: http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=202175

[54] Chiu WA, Rusyn I. Advancing chemical risk assessment decision-making with population variability data: challenges and opportunities. Mamm Genome. 2018;29:182–9.

[55] Bhat VS, Meek ME (Bette), Valcke M, English C, Boobis A, Brown R. Evolution of chemical-specific adjustment factors (CSAF) based on recent international experience; increasing utility and facilitating regulatory acceptance. Critical Reviews in Toxicology. 2017;47:733–53.

[56] Koman PD, Singla V, Lam J, Woodruff TJ. Population susceptibility: A vital consideration in chemical risk evaluation under the Lautenberg Toxic Substances Control Act. PLoS Biol [Internet]. 2019 [cited 2020 Apr 30];17. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6715167/

biological sensitivity) and/or vulnerable (increased sensitivity due to external factors like cumulative exposure to multiple chemical and non-chemical stressors, or they have fewer resources to access healthcare or mitigate the effects of the exposure(s).[57] Many intrinsic and extrinsic factors, including genetics, age/life stage of development, socioeconomic status, and/or underlying health status can affect population variability in response to chemical exposures.[58, 59]

The current regulatory implementation of the statutory definition of PESS in the risk evaluation framework rule does not limit the subpopulations that EPA may evaluate.[60] Nevertheless, we recommend that EPA correct its definition of PESS, similar to the definition EPA proposed in its 2017 TSCA proposed risk evaluation framework rule. Current scientific understanding indicates that intrinsic factors (such as age, pre-existing diseases, reproductive status, gender, genetic traits) and extrinsic factors (such as stress due to food insecurity and/or poverty, geographic, socioeconomic, cultural, and workplace factors) can increase susceptibility to environmental chemical exposure risks. [61]We recommend the EPA apply scientific and risk assessment principles to consider aggregate exposures from all exposure pathways, as recommended by the National Academies of Sciences.[62]

Under TSCA, EPA must consider impacts of chemical exposures on potentially susceptible subpopulations; however, EPA's current definition in the TSCA framework rules[63] and subsequent risk evaluations do not capture the reality of susceptibility. Naming the factors to be considered for susceptible populations is an important step to ensure consideration of these factors in hazard and risk evaluation and subsequent risk management. We recommend a modified version (explicitly identifying racism and other acquired factors, and the role of communities) of the definition found in EPA's January 2017 proposed TSCA risk evaluation framework rule, which focused on identifying intrinsic and extrinsic factors of vulnerability Preferred 2017 EPA proposed definition:[64]

> *"Potentially susceptible subpopulation means a group of individuals or communities within the general population who, due to greater susceptibility, 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 women, workers, or the elderly. Susceptibility can be due to both intrinsic (e.g., life stage, reproductive status, age, gender, genetic traits) and*

[57] Schulz AJ, Kannan S, Dvonch JT, Israel BA, Allen A, James SA, et al. Social and physical environments and disparities in risk for cardiovascular disease: the healthy environments partnership conceptual model. Environ Health Perspect. 2005;113:1817–25.

[58] Schulz AJ, Mentz GB, Sampson N, Ward M, Anderson R, de Majo R, et al. Race and the distribution of social and physical environmental risk: a case example from the Detroit metropolitan area. Du Bois Rev. 2016;13:285–304.

[59] Morello-Frosch R Zuk, M, Jerrett, M, Shamasunder, B, Kyle, AD. Racial & Ethnic Disparities: Understanding The Cumulative Impacts Of Inequalities In Environmental Health: Implications For Policy. Health Affairs. 2011;30:5879–87.

[60] 82 Federal Register 33726 (July 20, 2017)

[61] Institute of Medicine. 1999. Toward Environmental Justice. Washington, D.C.: National Academies Press.
[Online]. http://www.nap.edu/catalog/6034. Accessed November 3, 2016. https://www.nap.edu/catalog/6034/toward-environmental-justice-research-education-and-health-policy-needs

[62] National Research Council (US) Committee on Improving Risk Analysis Approaches Used by the U.S. EPA. Science and Decisions: Advancing Risk Assessment. Washington (DC): National Academies Press (US); 2009. PMID: 25009905.

[63] Procedures for Chemical Risk Evaluation Under the Amended Toxic Substances Control Act, Final Rule. Federal Register, July 20, 2017, 82 FR 33726. § 702.41(c)(1)

[64] 82 Federal Register 7562 (January 19, 2017) [FRL-9957-75] https://www.federalregister.gov/documents/2017/01/19/2017-01224/procedures-for-chemical-risk-evaluation-under-the-amended-toxic-substances-control-act

acquired (e.g., pre-existing disease, geography, socioeconomic, racism/discrimination, cultural, workplace) factors when identifying this population."

Making this modification would clarify that the partial list in the final rule was never intended as a deliberate exclusion of other subpopulations.

EPA must ensure that PESS are identified and that sufficient evidence for adequately evaluating risks to PESS are presented in manufacturers' requests.

4. **EPA's risk evaluations must account for all chemical effects on human health and the environment.**
    a. **To make a risk determination, EPA must have adequate data. However, the OTNE Manufacturer Requests for Risk Evaluation fails to provide sufficient data to assess OTNE's health effects.**

TSCA statute[65] and regulation[66] require that EPA has adequate data on chemicals to inform its risk evaluations. Regulation also requires the evaluation of "relevant" potential human and environmental hazards.[67]

Certain health hazards are specifically designated in TSCA, indicating that Congress expressly recognized these types of health effects could present an unreasonable risk, and envisioned that EPA should assess them: "cancer/ carcinogenesis, mutagenesis/ gene mutation, teratogenesis, behavioral disorders, and birth defects."[68] To assess the sufficiency/ adequacy of the data on OTNE for assessment, EPA should compare the completeness of the database on each chemical to existing lists of traits deemed important to assess for chemical safety. Additionally, EPA must assess the completeness of the database regarding information needed to conduct a cumulative assessment. Currently the OTNE Consortium Request does not provide any studies whatsoever for critical health endpoints, including carcinogenicity and chronic toxicity.

For the existing list of traits deemed important to assess for chemical safety, we recommend as a starting point the health hazard dataset needed for EPA's Design for the Environment (DfE) (known now as the Safer Choice program) to conduct an alternatives assessment, which is similar to the widely used chemical assessment protocol GreenScreen. [69,70] The dataset includes the following health endpoints:

1. Acute mammalian toxicity
    a. Oral
    b. Dermal

[65] 15 USC §2601 (b)(1)
[66] 40 CFR § 702.41 (b)
[67] 40 CFR § 702.41 (d)(3)
[68] 15 USC §2603 (b)(2)(A); 15 USC §2603 (e); 15 USC §2605 (b)(2)(D)
[69] US EPA (2011) Design for the Environment Alternatives Assessment Criteria for Hazard Evaluation. Available: https://www.epa.gov/sites/production/files/2014-01/documents/aa_criteria_v2.pdf
[70] Clean Production Action (2018) GreenScreen for Safer Chemicals. Available: https://www.greenscreenchemicals.org/images/ee_images/uploads/resources/GS_TwoPager_July2018.pdf

    c. Inhalation
2. Respiratory sensitization
3. Skin sensitization
4. Eye irritation/ corrosivity
5. Skin irritation/ corrosivity
6. Carcinogenicity
7. Mutagenicity/ genotoxicity
8. Reproductive and developmental toxicity
9. Developmental neurotoxicity
10. Neurotoxicity
11. Repeated dose toxicity
12. Endocrine activity

If EPA proceeds, it should describe the key areas (hazard and exposure) where data are lacking for the chemical and for mixtures, and use its information gathering authorities pursuant to TSCA to fill the data gaps we have highlighted. Under TSCA section 4, EPA can use its authority to generate and obtain information about chemical substances by ordering further testing from the chemical manufacturers and importers in order to conduct a lawful risk evaluation and impose reporting obligations on parties "likely to have [relevant] information" under TSCA section 8. Additionally, under section 10, EPA can conduct or fund research, in coordination with other federal agencies, to generate such information. Section 4 test orders should be focused on the most relevant test models, exposure pathways, health outcomes, and target populations (including any vulnerable or sensitive populations) anticipated to support the generation of high-quality and relevant evidence to support timely decision-making on OTNE.

EPA should also make the data developed or submitted under these rules or orders publicly available. TSCA section 14 clearly states that health and safety studies are not confidential business information (CBI) and thus are not protected from disclosure. EPA should also provide a public summary characterizing the data and its completeness for each chemical and relevant mixtures.

Therefore, EPA needs to determine the completeness of the database on OTNE and exercise its full authorities to fill these data gaps under TSCA sections 4, 8 and 10, and make information public under section 14.

b. EPA should require data on health hazards that are sufficiently comprehensive and sensitive to understand hazard and prevent or mitigate harmful health effects of chemicals

An opportunity for EPA and federal government to acquire more data is by applying its authorities under sections 4 and 8 of amended TSCA.[71] While the aforementioned sections gave EPA stronger authorities to require provision of data, including enhanced authority to require new studies be conducted, EPA has not fully utilized these authorities, leading to persistent data gaps and the decision-making without critical health or toxicity information. Thus, EPA should proactively outline existing data gaps and explicitly state where data are most needed so as to make a fully informed decision with regard to chemicals under its consideration. Such proactive steps would facilitate the external development and design of studies to generate these data in a timely manner and is consistent with other programs in California and Europe.

EPA should require data on health hazards that are sufficiently comprehensive and sensitive to understand hazard and prevent or mitigate harmful health effects of chemicals. A potential approach to data gaps includes developing "completeness metrics"— a list of certain properties or hazards such as physical characteristics, health endpoints, subpopulations, etc. deemed important to assess. Once those metrics are developed, the Agency could track how many may be assessed based on available data, and provide a public summary characterizing the "completeness of the database" for each chemical. EPA has adopted similar approaches in the past, for instance using published criteria to evaluate the data adequacy in its brominated phthalates Data Needs Assessment. [72]

These metrics would consider a range of health effects (e.g., neurodevelopmental, reproductive development, cancer, and others outlined in the statute), health effects due to exposures that occur during sensitive life stages (e.g., preconception, during fetal and child development, and aging), and tests which are sufficiently robust to capture increased risk of health effects in humans (e.g., length of exposure, accounting for cumulative exposures, and periods of exposure). Additionally, advances have been made to identify and classify key characteristics of chemicals associated with various hazard endpoints including cancer, reproductive toxicity, and endocrine disruption.[73,74,75,76,77] These can be used to organize mechanistic data that may serve as early indicators of harm for chemicals, though it is

[71] 15 U.S.C. §§ 2607(a)(5), 2603(a).

[72] US Environmental Protection Agency: TSCA Work Plan Chemical Problem Formulation and Data Needs Assessment: Brominated Phthalates Cluster Flame Retardants. In.; 2015.

[73] Rider CV, McHale CM, Webster TF, Lowe L, Goodson WH, La MA, Merrill, Rice G, Zeise L, Zhang Let al: Using the Key Characteristics of Carcinogens to Develop Research on Chemical Mixtures and Cancer. Environ Health Perspect 2021, 129(3):35003.

[74] Arzuaga X, Smith MT, Gibbons CF, Skakkebæk NE, Yost EE, Beverly BEJ, Hotchkiss AK, Hauser R, Pagani RL, Schrader SMet al: Proposed Key Characteristics of Male Reproductive Toxicants as an Approach for Organizing and Evaluating Mechanistic Evidence in Human Health Hazard Assessments. Environ Health Perspect 2019, 127(6):65001.

[75] Luderer U, Eskenazi B, Hauser R, Korach KS, McHale CM, Moran F, Rieswijk L, Solomon G, Udagawa O, Zhang Let al: Proposed Key Characteristics of Female Reproductive Toxicants as an Approach for Organizing and Evaluating Mechanistic Data in Hazard Assessment. Environ Health Perspect 2019, 127(7):75001

[76] Smith MT, GuytonKZ, Gibbons CF, Fritz JM, Portier CJ, Rusyn I, DeMarini DM, Caldwell JC, Kavlock RJ, Lambert PFet al: Key Characteristics of Carcinogens as a Basis for Organizing Data on Mechanisms of Carcinogenesis. Environ Health Perspect 2016, 124(6):713-721

[77] La Merrill MA, Vandenberg LN, Smith MT, Goodson W, Browne P, Patisaul HB, Guyton KZ, Kortenkamp A, Cogliano VJ, Woodruff TJet al: Consensus on the key characteristics of endocrine-disrupting chemicals as a basis for hazard identification. Nat Rev Endocrinol 2020, 16(1):45-57.

critical to ensure that in vitro exposure data is not used as the sole evidence stream to determine whether a chemical is safe for hazard or risk identification, unless there is a strong basis to link such studies to an apical endpoint. Finally, EPA must require data around environmental and community monitoring and allow for additional testing in order to generate a robust and living data set.

Timely generation of health and toxicity data for chemicals is critical to break the cycle of placing harmful chemicals on the market without adequate testing data and instead to ensure that existing chemicals that pose a risk to human health are managed effectively and new chemicals are sufficiently regulated upon entering the market. Without adequate monitoring, modeling, and up-to-date data, exposures, hazards, and health effects will remain unknown to the public and unaddressed by the private sector, researchers, and government. EPA should proactively outline existing data gaps and explicitly state where data are most needed for chemicals so as to facilitate the external development and design of studies to generate these data in a timely manner; this is consistent with other programs such as California and European programs. EPA should proactively review the list of 100-150 chemicals that are "candidates" for high-priority listing (pre-prioritization) and risk evaluations from the 2014 TSCA Work Plan. Those on the 2014 TSCA Work Plan list that have not yet been selected for risk evaluations should be included because they have already been screened for hazard and exposure and determined to raise significant concerns. This would give EPA sufficient time to order testing.

5. **EPA must address and rectify other flawed approaches that have been implemented in previous TSCA risk evaluations.**
    a. **EPA must not assume the use of personal protective equipment (PPE) in TSCA risk evaluations**

EPA systematically underestimated the occupational risks posed by each of the first 10 risk evaluation chemicals by assuming that workers exposed to those chemicals would be provided with and protected by PPE.[78] This assumption of universal and effective PPE use is not supported by evidence, as both OSHA and NIOSH told EPA in their comments on EPA's draft risk evaluations. In contrast, OSHA and NIOSH both measure worker exposures and risks without the assumption of PPE use.[79] Under well-established occupational "hierarchy of controls" PPE is used only as a measure of last resort, after an employer has already evaluated risk without the assumption of PPE use, identified a significant risk to employers, and exhausted or ruled out all other means of addressing that risk, such as chemical elimination, substitution and engineering controls.

OSHA acknowledged that there is only a nominal possibility that respirators will be properly worn at all times, because respirators are often not provided, workers may have little leverage to obtain protections, and respirators are known to cause worker discomfort, skin irritation or heat stress, impaired body movements, difficulties in communicating and vision limitations.[80] When respirators are

78 The OTNE Risk Evaluation Request also assumes the use of PPE, asserting that "[d]ue to the use of PPE, dermal exposure is expected to be negligible." OTNE Risk Evaluation Request App'x IV. For all of the reasons stated below, EPA should reject that assumption when conducting the OTNE Risk Evalaution.

79 See 29 C.F.R. § 1910.1052(b) (defining "employee exposure" to methylene chloride as the exposure levels "which occur[] or would occur if the employee were not using respiratory protection."

80 51 Fed. Reg. 22693.

provided, workers are frequently not provided the training, fit testing and medical examinations that are required to achieve the respirator's stated level of protectiveness.[81] Finally, EPA has previously acknowledged that not all workers may be able to wear respirators. Workers with impaired lung function, such as those with asthma, emphysema, and chronic obstructive pulmonary disease or with facial hair may be inadequately protected by respirators.[82]

EPA should identify the absence of worker safeguards and PPE as "reasonably foreseen" conditions of use and assume a lack of PPE unless data are presented to the contrary.

In its TSCA New Chemicals program, EPA announced in March 2021 its intention to ensure necessary protections for workers through regulatory means.[83] Where EPA identifies a potential unreasonable risk to workers that could be addressed with appropriate PPE and hazard communication, EPA indicated it will no longer assume that workers are adequately protected under OSHA's worker protection standards and updated Safety Data Sheets. Instead, EPA stated it will identify the absence of worker safeguards as "reasonably foreseen" conditions of use, and mandate necessary protections through a TSCA section 5(e) order, as appropriate. EPA should make consistent assumptions in the existing risk evaluation and risk reduction program and seek to obtain data about PPE use.

In the specific case of OTNE, the OTNE Consortium documents assume the use of PPE and conclude dermal exposure is expected to be negligible. EPA should reject that assumption without supporting evidence to the contrary when assessing the OTNE Risk Evaluation. EPA has previously classified at least two of the four OTNE chemicals as PBTs[84] underscoring the need for EPA to consider all available exposure data during the risk evaluation process, including workplace monitoring data. In the risk evaluation request, the OTNE Consortium did not provide workplace monitoring data. EPA can mandate the production of that data under TSCA Section 8 and compel monitoring in the workplace under TSCA Section 4 or document exposures from wastewater discharges from sewage treatment plants.[85]

b. EPA must follow recommendations from the NAS and implement a systematic review method for TSCA risk evaluations that is compatible with the National Academy of Medicine's definition of a systematic review, such as the National Toxicology Program's OHAT method and the Navigation Guide developed by the University of California, San Francisco.

Historically, EPA used the *Application of Systematic Review in TSCA Risk Evaluations* to "guide the agency's selection and review of the scientific studies that are used to inform TSCA chemical risk

[81]NIOSH, Respirator Usage in Private Section Firms, 2001 at 2 (Sept. 2003), https://www.cdc.gov/niosh/docs/respsurv/pdfs/respsurv2001.pdf
82 Methylene Chloride and N-Methylpyrrolidone; Regulation of Certain Uses Under TSCA Section 6(a), 82 Fed. Reg. 7464, 7481 (Jan. 19, 2017).
83 EPA, Important Updates on EPA's TSCA New Chemicals Program (Mar. 29, 2021), https://www.epa.gov/chemicals-under-tsca/important-updates-epas-tsca-new-chemicals-program
84 EPA, Proposed Rule: Regulation of Persistent, Bioaccumulative, and Toxic Chemicals Under TSCA Section 6(h), 84 Fed. Reg. 36728, 36734 (July 29, 2019)
85 Kathleen McDonough et al., Probabilistic determination of the ecological risk from OTNE in aquatic and terrestrial compartments based on US-wide monitoring data, 167 Chemosphere 255-261 (2017), https://doi.org/10.1016/j.chemosphere.2016.10.006

evaluations."[86] This method, herein called the TSCA method, was developed by EPA as part of the implementation of TSCA, as amended by the Frank R. Lautenberg Chemical Safety for the 21st Century Act (Lautenberg TSCA). The Act requires that EPA make decisions about chemical risks based on the "best available science" and the "weight of the scientific evidence".[87] Recently, however, the NAS comprehensively reviewed the TSCA method and cited several underlying factors indicating that the TSCA method "does not meet the criteria of 'comprehensive, workable, objective, and transparent' systematic review method.[88] EPA has announced that it would no longer use that method but have not yet identified an alternative.

The NAS recommended that EPA should implement a systematic review method that is compatible with empirically based existing methods and aligns with the Institute of Medicine's (now known as the National Academy of Medicine) definition of a systematic review, including but not limited to, using explicit and pre-specified scientific methods for every step of the review:

> *Additionally, the committee would expect that all systematic reviews should meet the definition and principles from the IOM (2011) report—explicit prespecified methods to identify, select, and synthesize the evidence from studies.*[89]

The National Academy of Medicine which has 21 standards covering the entire systematic review process that, if adhered to, result in a scientifically valid, transparent, and reproducible systematic review, defines a systematic review as a "scientific investigation that focuses on a specific question and uses explicit, **pre-specified scientific methods** to identify, select, assess, and summarize the findings of similar but separate studies" (emphasis added).[90]

The NAS identified critical issues within the TSCA method that EPA must ensure it addresses when implementing a systematic review method for all future TSCA risk evaluations. These include:

The use of Protocol

<u>The NAS report highlights:</u>

> "*The committee found the OPPT approach 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…, and the lack of a consistent approach for documenting the objectives or methods for synthesis and evidence*

[86] https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/application-systematic-review-tsca-risk-evaluations
[87] 15 USC §2625 (h)-(i)
[88] National Academies of Sciences, Engineering, and Medicine 2021. The Use of Systematic Review in EPA's Toxic Substances Control Act Risk Evaluations. Washington, DC: The National Academies Press. Pp 15 https://doi.org/10.17226/25952.
[89] National Academies of Sciences, Engineering, and Medicine 2021. The Use of Systematic Review in EPA's Toxic Substances Control Act Risk Evaluations. Washington, DC: The National Academies Press. Pp 15 https://doi.org/10.17226/25952.
[90] Institute of Medicine. (2011). Finding What Works in Health Care: Standards for Systematic Reviews. Page 1. Washington, DC: The National Academies Press

integration. ***The committee found that many of these concerns were related to the absence of a protocol a priori or the combination of the traditionally discrete and distinct steps of a systematic review****.*[91] *(emphasis added)*

EPA must use a systematic review method, which includes a chemical specific protocol released to the public before the risk evaluation is conducted for each risk evaluation the Agency will undertake. Protocols developed for applying the [92] 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[93,94]

Incorporating best practices for conducting a systematic and transparent literature review.

The NAS report highlights:

"The process for searching and selecting the evidence lacked objectivity, because the inclusion and exclusion criteria were broad and thus less objective. A benefit of systematic review is that clear, predefined inclusion or exclusion criteria increase objectivity of the process for selecting the evidence.[95] *Overall, the committee found that the lack of information about the specific processes used for the identification of evidence reduced confidence in the findings and were inconsistent with systematic review practices.*[96] *In the TSCA evaluation process, eligibility criteria are not predefined in the protocols and shift during the systematic review process.*[97]

EPA must use a systematic review method that it is congruent with all of the National Academy of Medicine's best practices and explicitly predefine the eligibility criteria for the included studies before conducting any part of the systematic review process.

Using validated and best practice methods for assessing risk of bias of an individual study

The NAS report instructs the EPA to:

[91] National Academies of Sciences, Engineering, and Medicine 2021. The Use of Systematic Review in EPA's Toxic Substances Control Act Risk Evaluations. Washington, DC: The National Academies Press. Pp 6 https://doi.org/10.17226/25952.
[92] 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
[93] 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
[94] National Toxicology Program. Completed Evaluations. Available: https://ntp.niehs.nih.gov/whatwestudy/assessments/noncancer/completed/index.html
[95] National Academies of Sciences, Engineering, and Medicine 2021. The Use of Systematic Review in EPA's Toxic Substances Control Act Risk Evaluations. Washington, DC: The National Academies Press. Pp 40 https://doi.org/10.17226/25952. Pp 34
[96] National Academies of Sciences, Engineering, and Medicine 2021. The Use of Systematic Review in EPA's Toxic Substances Control Act Risk Evaluations. Washington, DC: The National Academies Press. Pp 40 https://doi.org/10.17226/25952. Pp 34
[97] National Academies of Sciences, Engineering, and Medicine 2021. The Use of Systematic Review in EPA's Toxic Substances Control Act Risk Evaluations. Washington, DC: The National Academies Press. Pp 40 https://doi.org/10.17226/25952. Pp 34

I. *"Do not use numeric scores to evaluate studies; replace them with domain-based scoring as is done in the tools used in the Navigation Guide and OHAT."* [98]

II. *"Use established tools for assessing risk of bias and study quality such as those developed for use by OHAT or the Navigation Guide, or, at a minimum, remove inappropriate appraisal criteria from the current tools."* [99]

III. *"Do not exclude studies based on risk of bias, study quality, or reporting quality."* [100]

IV. "*While there is inevitably variation in the internal validity and risk of bias across individual studies, it is standard practice to include all studies, even the studies with a high risk of bias into the evidence synthesis. The most appropriate method to exclude studies from evidence synthesis is based on predefined exclusion criteria that should preclude an irrelevant study from being evaluated."* [101]

EPA must not use a quantitative scoring method to assess quality in individual studies; it should not conflate study reporting with study quality; and it should not exclude otherwise quality research based on a single reporting or methodological limitation. Rather EPA should employ a scientifically valid method to assess risk of bias of individual studies. We recommend that the approaches of the OHAT method or the Navigation Guide be used for this step.

Using a pre-established protocol or methods for evidence integration.

<u>The NAS report instructs the EPA to:</u>

I. *"Document the synthesis methods and data requirements in the study protocol for each evidence stream. This should be done for every evidence stream whether or not a systematic review approach will be taken."* [102]

II. *"Separate evidence synthesis from evidence integration. Evidence synthesis deals with more homogeneous data within a single stream, and evidence integration deals with more heterogeneous data from multiple streams."* [103]

EPA must include a predefined method in the protocol before EPA conducts their review. EPA must use a systematic review method that predefines and transparently presents how each evidence stream will be evaluated, then integrated and how conclusions are reached in assessing human health hazards for each end point it assesses, such as the OHAT method and the Navigation Guide.

[98] National Academies of Sciences, Engineering, and Medicine 2021. The Use of Systematic Review in EPA's Toxic Substances Control Act Risk Evaluations. Washington, DC: The National Academies Press. Pp 40 https://doi.org/10.17226/25952.

[99] National Academies of Sciences, Engineering, and Medicine 2021. The Use of Systematic Review in EPA's Toxic Substances Control Act Risk Evaluations. Washington, DC: The National Academies Press. Pp 40 https://doi.org/10.17226/25952.

[100] National Academies of Sciences, Engineering, and Medicine 2021. The Use of Systematic Review in EPA's Toxic Substances Control Act Risk Evaluations. Washington, DC: The National Academies Press. Pp 40 https://doi.org/10.17226/25952.

[101] National Academies of Sciences, Engineering, and Medicine 2021. The Use of Systematic Review in EPA's Toxic Substances Control Act Risk Evaluations. Washington, DC: The National Academies Press. Pp 36 https://doi.org/10.17226/25952.

[102] National Academies of Sciences, Engineering, and Medicine 2021. The Use of Systematic Review in EPA's Toxic Substances Control Act Risk Evaluations. Washington, DC: The National Academies Press. Pp 45 https://doi.org/10.17226/25952.

[103] National Academies of Sciences, Engineering, and Medicine 2021. The Use of Systematic Review in EPA's Toxic Substances Control Act Risk Evaluations. Washington, DC: The National Academies Press. Pp 45 h5ttps://doi.org/10.17226/25952.

Future approaches for systematic review

Collectively, the critical issues cited above underscore the need for EPA to modify their systematic review approach. The NAS highlighted that:

> *"With regard to hazard assessment for human and ecological receptors, the committee comments that OPPT should step back from the approach that it has taken and consider components of the OHAT, IRIS, and Navigation Guide methods that could be incorporate directly and specifically into hazard assessment"*

In agreement with the NAS, we recommend EPA to consider using and adapting one or more of the following methods going forward: (1) the National Toxicology Program's OHAT method; (2) UCSF's Navigation Guide method; and/or (3) EPA's Integrated Risk Information System (IRIS) method.

Both the Navigation Guide and the OHAT method have been used or recommended by the NASEM[104,105,106] and demonstrated in case studies in the peer-reviewed literature.[107,108,109,110,111, 112,113,114] The World Health Organization and International Labor Organization (WHO/ILO) are using the Navigation Guide to conduct systematic reviews of occupational exposures and disease as part of assessing the global burden of work-related injury and disease due to exposure to occupational risk

[104] 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

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

[106] 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.

[107] 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.

[108] 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.

[109] 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

[110] 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.

[111] 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.

[112] 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.

[113] 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.

[114] 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.

factors.[115] These methods are validated and could be used immediately adopted and implemented for TSCA risk evaluations.

Systematic review methods have also been adopted by the EPA's Integrated Risk Information System (IRIS) program.[116] The NAS has recommended changes to improve IRIS' approach to evaluating scientific evidence, including implementation of systematic review. In 2014 and 2018, the NAS released reports evaluating whether the IRIS program had been responsive to its past recommendations.[117,118] Both review committees were impressed with IRIS' progress, including steps to develop and implement systematic review methods and that there is "*a commitment to use systematic-review methods to conduct IRIS assessments.*"[119] We commend the EPA on the substantial progress it has made in adopting and implementing systematic review methods in conducting IRIS assessments.

The IRIS program is critically important to EPA's mission of protecting human health, and the recent release of the *ORD Staff Handbook for Developing IRIS Assessments* is an important milestone in the program's adoption of systematic review methods. [120]

There are methodological flaws, however, in the current *Handbook* that need to be addressed; these methodological flaws are not consistent with NAS recommendations from the 2014, and 2018, or with the methods that EPA has stated to the NAS it is using in the IRIS program. Further, these methods are inconsistent with a number of the recommendations made recently by the NAS in its consensus report *"The Use of Systematic Review in EPA's Toxic Substances Control Act Risk Evaluations (2021)."*[121] For example, the risk of bias method presented in the *Handbook* is not validated and excludes studies based on one "critically deficient" domain, which could significantly reduce the available evidence to identify the harms caused by the toxic substances it evaluates. As highlighted above, in the recent consensus report the NAS explicitly recommends that EPA "Do not exclude studies based on risk of bias, study quality, or reporting quality."[122]

This underscores that incorporation of approaches from the IRIS program still requires careful consideration of the limitations and areas of improvement that we have previously cited with the

[115] Mandrioli, D., Schlünssen, V., Ádám, B., Cohen, R. A., Colosio, C., Chen, W.et al. (2018). WHO/ILO work-related burden of disease and injury: Protocol for systematic reviews of occupational exposure to dusts and/or fibres and of the effect of occupational exposure to dusts and/or fibres on pneumoconiosis. Environment International, Vol. 119, Pg. 174–185. https://doi.org/10.1016/j.envint.2018.06.005

[116] 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.

[117] National Research Council. 2014. Review of EPA's Integrated Risk Information System (IRIS) Process. Washington, DC: The National Academies Press. https://doi.org/10.17226/18764.

[118] 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

[119] 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. Pp 1

[120] US EPA (2020) ORD Staff Handbook for Developing IRIS Assessments EPA/600/R-20/137. Available: https://cfpub.epa.gov/ncea/iris_drafts/recordisplay.cfm?deid=350086

[121] National Academies of Sciences, Engineering, and Medicine 2021. The Use of Systematic Review in EPA's Toxic Substances Control Act Risk Evaluations. Washington, DC: The National Academies Press. https://doi.org/10.17226/25952.

[122] National Academies of Sciences, Engineering, and Medicine 2021. The Use of Systematic Review in EPA's Toxic Substances Control Act Risk Evaluations. Washington, DC: The National Academies Press. Pp 40. https://doi.org/10.17226/25952.

existing *ORD Staff Handbook for Developing IRIS Assessments*.[123] Chiefly, we have recommended modifications in extensive detail in our recent public comments,[124] which is summarized by the following key issues with the IRIS method:

1. The Overview in the *Handbook* is a helpful outline of the key steps in conducting an IRIS assessment. It would be significantly improved with a few minor edits/insertions that would demonstrate and reinforce the use of key foundations of Systematic Review, including the Protocol and PECO statement.
2. The *Handbook* states that revisions to the initial protocol may be necessary as the assessment team develops a greater understanding of scientific/technical issues that arise during assessment development. However, some points require greater emphasis to ensure that the purpose of having a protocol is not compromised.
3. The *Handbook's* epidemiology study evaluation is incompatible with validated best practice methods already being implemented in environmental health in fundamental ways.
4. The *Handbook* is unclear on the distinction between "Synthesis" and "Integration" of evidence. The *Handbook* would be improved by merging Chapter 9 ("Analysis and Synthesis of Human and Experimental Animal Data") into Chapter 11 ("Evidence Integration"), or alternately by moving the Chapter 11 content (regarding conclusions by evidence stream) into Chapter 9.
5. The Handbook is not clear regarding important aspects of how the IRIS program derives Toxicity Values and should incorporate updated methods (Chapters 12 and 13).
6. The *Handbook* should consider financial conflicts of interest as a potential source of bias in research.

In conclusion, as EPA proceeds with modification of their systematic review methodology, we urge them to consider best practices developed in the OHAT, Navigation Guide, or IRIS methods. If EPA utilizes the IRIS methods, they must consider each of the issues we have outlined above regarding the IRIS method and ensure that their use of the IRIS method appropriately adapts the systematic review approach to account for these issues. This is necessary in order for EPA to adequately assess the "best available science" and the "weight of the scientific evidence" for OTNE and all future chemicals under TSCA. Although there are several areas needing improvement, the *Handbook* provides a strong foundation for conducting systematic review across the Agency in the years to come.

6. TSCA risk evaluations should provide additional information to help ensure that TSCA regulations "appropriately benefit and do not inappropriately burden disadvantaged, vulnerable, or marginalized communities."

President Biden's January 20, 2021 memorandum on "Modernizing Regulatory Review" indicates an interest in promoting *"social welfare, racial justice…and the interests of future generations"* and the intention to develop *"procedures that take into account the distributional consequences of regulations,*

[123] US EPA (2020) ORD Staff Handbook for Developing IRIS Assessments EPA/600/R-20/137. Available: https://cfpub.epa.gov/ncea/iris_drafts/recordisplay.cfm?deid=350086
[124] Regulations.gov docket EPA-HQ-ORD-2018-0654

including as part of any quantitative or qualitative analysis of the costs and benefits of regulations, to ensure that regulatory initiatives appropriately benefit and do not inappropriately burden disadvantaged, vulnerable, or marginalized communities." [125] President Biden's Executive Order 13985, "On Advancing Racial Equity and Support for Underserved Communities Through the Federal Government," observes that:

> *"By advancing equity across the Federal Government, we can create opportunities for the improvement of communities that have been historically underserved, which benefits everyone…The Federal Government's goal in advancing equity is to provide everyone with the opportunity to reach their full potential. Consistent with these aims, each agency must assess whether, and to what extent, its programs and policies perpetuate systemic barriers to opportunities and benefits for people of color and other underserved groups. Such assessments will better equip agencies to develop policies and programs that deliver resources and benefits equitably to all."*

Disproportionate chemical exposures, by contributing to disproportionate health outcomes, are an important factor that affects the well-being of disadvantaged and vulnerable communities and can pose systemic barriers to opportunities for people of color. EPA's implementation of TSCA can play a significant role in advancing the President's objectives of equity and opportunity for all, and TSCA risk evaluations are critical to achieving this objective.

TSCA risk evaluations to date have generally not provided analyses to inform assessment of the distributional consequences of TSCA risk management regulations, but they could do so. The demographic characteristics of exposed populations should be reported to the extent possible in each risk evaluation. Demographic characteristics of exposed populations that should be reported include race/ethnicity, income group, and life stage. As a first step, census data for populations living in proximity to particular facilities that may be associated with exposure (any point of release, such as a manufacturing or processing facility, or location of chemical storage near a drinking water source) should be reported in each risk evaluation. OPPT should also develop a strategy for gathering data on demographic characteristics of exposed populations for exposure pathways that cannot be represented with census data. This strategy could be coupled with data-gathering efforts to make other critical improvements to exposure assessment in TSCA risk evaluations, such as consumer surveys regarding usage of various consumer products. The demographic information provided in the risk evaluations can then be used for analysis of how risk management alternatives will benefit disadvantaged, vulnerable, or marginalized communities.

[125] Presidential Memorandum, *Modernizing Regulatory Review*, § 2(b)(i) (Jan. 20, 2021).