

August 30, 2019

Comments from Academics, Scientists and Clinicians on the Draft Risk Evaluations for 1,4-Dioxane and Cyclic Aliphatic Bromide Cluster (HBCD)

Submitted online via *Regulations.gov* to dockets EPA-HQ-OPPT-2019-0238 and EPA-HQ-OPPT-2019-0237

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

We appreciate the opportunity to provide written comments on the draft risk evaluations for 1,4-dioxane and cyclic aliphatic bromide cluster (HBCD), issued under EPA's Toxic Substances Control Act (TSCA), as amended by the Frank R. Lautenberg Chemical Safety for the 21st Century Act ("amended TSCA").^{1,2} The law requires EPA to make decisions about chemical risks based on the "best available science, "adequate information" and "weight of the scientific evidence,"³ 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."⁴

We detailed the scientific flaws in EPA's systematic review method developed under TSCA ("TSCA method") in August 2018 and published a peer-reviewed analysis in the *American Journal of Public Health*.^{5,6,7} But EPA has now used an entirely new approach in the 1,4-dioxane and HBCD draft risk evaluations relying on "key and supporting/ influential information." As we detail below, this approach was not previously published nor peer reviewed, has not gone through a public comment period, does not meet the requirements of EPA's regulation, and raises serious concerns about bias in the evidence base of these evaluations. These methodological problems are significant enough that EPA's risk conclusions are highly likely to be biased.

¹ US EPA (2019) 1,4-Dioxane Draft Risk Evaluation 06-27-2019. Available:

<https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0238-0011>

² US EPA (2019) HBCD Draft Risk Evaluation for Cyclic Aliphatic Bromide Cluster. Available:

<https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0237-0002>

³ 15 USC §2625 (h)-(i) and 15 USC §2601 (b)(1)

⁴ 40 CFR 702.33

⁵ EPA (2018) Application of Systematic Review in TSCA Risk Evaluations.

⁶ UCSF PRHE, et al. (2018) Comments from Academics, Scientists and Clinicians on: The Application of Systematic Review in TSCA Risk Evaluations. Available:

https://prhe.ucsf.edu/sites/g/files/tkssra341/f/wysiwyg/2018%2008%2016%20Systematic%20Review%20TSCA%20evaluations%20UCSF%20PRHE%20comments%20EPA_0.pdf

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

Further, we commented in September 2017 and August 2018 that EPA's failure to consider scientifically established factors that contribute to susceptibility, combined with inaccurate exposure assessments that exclude known sources of exposures, will lead to underestimates of risk.^{8,9} We have recently published our analysis in a peer-reviewed commentary in *PLoS Biology* (attached as Appendix A to these comments).¹⁰ Unfortunately, these deficiencies remain in the draft risk evaluations, resulting in EPA significantly underestimating the true risks that HBCD and 1,4-dioxane pose, forming a poor scientific basis for its risk determinations. EPA's risk determination is inadequate until the methodological, scientific and technical problems we and many other commenters identified are corrected to be consistent with current scientific principles for systematic reviews, population susceptibility, and exposure assessment. It is critical that EPA's risk determination adhere to the best scientific principles, as EPA's decisions affect the public's exposure to these chemicals – and thus their health. EPA should not compromise the health of the public for expediency or incomplete science.

Our comments address the following main issues:

- 1. EPA's methodology for identifying and evaluating the evidence for 1,4-dioxane and HBCD has serious scientific flaws; the following methodological changes are not evidence-based, lack transparency, and are likely to have resulted in a biased evidence base for the draft risk evaluations:**
 - a. EPA's new approach relying on "key/ supporting/ influential information," which has not been previously described or subject to comment ;
 - b. EPA's new approach using the "hierarchy of preferences" to exclude relevant studies rather than considering all the relevant science; and
 - c. EPA's revised criteria for evaluating the quality of epidemiological studies, making it more likely that relevant epidemiological studies will be excluded.
- 2. EPA should use a peer-reviewed, validated systematic review method for chemical evaluations instead of "Application of systematic review in TSCA risk evaluations."**
- 3. EPA's risk determinations are not protective of potentially exposed or susceptible subpopulations.**
 - a. EPA does not account for biological factors that can increase susceptibility to chemical toxicity.
 - b. Due to excluding known exposures, not aggregating exposures, and other problems with the exposure assessment, EPA is underestimating exposures.
 - c. EPA leaves unreasonable risks for workers unaddressed, as its assumptions about personal protective equipment (PPE) are not scientifically supported.

⁸ UCSF PRHE, et al. (2017) Comments from Academics, Scientists and Clinicians on the Risk Evaluation Scoping Efforts Under TSCA for Ten Chemical Substances. Available: <https://prhe.ucsf.edu/sites/g/files/tkssra341/f/wysiwyg/01%20Risk%20Evaluation%20Scoping%20Efforts%20Under%20TSCA%20for%20Ten%20Chemical%20Substances.pdf>

⁹ UCSF PRHE, et al. (2018) Comments from Academics, Scientists and Clinicians on Problem Formulations for the Risk Evaluations to Be Conducted Under the Toxic Substances Control Act (TSCA). Available: <https://prhe.ucsf.edu/sites/g/files/tkssra341/f/wysiwyg/2018%2008%2016%20Problem%20formulations%20UCSF-PRHE%20comments%20EPA.pdf>

¹⁰ Koman, P.D., Singla, V. I., Lam, J., & Woodruff, T. J. (2019). Population susceptibility: A vital consideration in chemical risk evaluation under the Lautenberg Toxic Substances Control Act. *PLoS Biology*. <https://doi.org/10.1371/journal.pbio.3000372>

- 4. EPA should use a unified linear approach for dose response analysis and risk calculations for all carcinogens and non-carcinogens as recommended by the NAS and EPA should not use the MOE approach.**
- 5. EPA must include HBCD byproducts generated during the conditions of use in the evaluation of risk for HBCD.**

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

Sincerely,

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

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

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

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

John Froines, PhD
Professor Emeritus, Fielding School of Public Health
University of California, Los Angeles

Elinor Fujimoto, MPH
Project Coordinator, Family Resiliency Center
University of Illinois Urbana-Champaign

Mary 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, Physicians for Social Responsibility, San Francisco Bay Area Chapter

Patricia D. Koman, MPP, PhD
Senior Health Scientist and President
Green Barn Research Associates

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

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

DETAILED COMMENTS

- 1. EPA's methodology for identifying and evaluating the evidence for 1,4-dioxane and HBCD has serious scientific flaws; the following methodological changes are not evidence-based, lack transparency, and are likely to have resulted in a biased evidence base for the draft risk evaluations.**

EPA states that its literature search, screening strategy, inclusion and exclusion criteria were previously described, and that EPA used the *Application of Systematic Review in TSCA Risk Evaluations* for the 1,4-dioxane and HBCD draft risk evaluations.^{11,12} But in fact, in the HBCD and 1,4-dioxane draft risk evaluations, EPA has significantly changed its approach for identifying and evaluating the information relied on in the draft evaluation, and these changes have not been previously described, available for public comment, or peer-reviewed.

EPA says this is a "pragmatic approach" but pragmatism is not what EPA's regulation requires. EPA is required to perform a comprehensive, objective, transparent, and consistent evaluation of the body of evidence,¹³ for the underlying reason that such an evaluation will result in better, scientifically based decisions--and these new approaches do not meet these requirements. Specifically, with regard to 1,4-dioxane, if EPA is trying to take a pragmatic approach to the draft risk evaluation, it should utilize its own in-house resources and begin with IRIS assessment rather than developing an entirely new process.¹⁴

1a. EPA's new approach relying on "key/ supporting/ influential information," which has not been previously described or subject to comment.

In the draft risk evaluations, EPA states:

"Although EPA conducted a comprehensive search and screening process as described above, EPA generally used previous chemical assessments to identify key and supporting information that would be influential in the risk evaluation, in other words, information supporting key analyses, arguments, and/or conclusions in the risk evaluation... EPA made the decision to leverage the literature published in previous assessments when identifying relevant key and supporting data and information for developing the HBCD risk evaluation. This is discussed in the *Strategy for Conducting Literature Searches for Cyclic Aliphatic Bromine Cluster (HBCD): Supplemental Document to the TSCA Scope Document*."^{15,16}

¹¹ US EPA (2019) HBCD Draft Risk Evaluation for Cyclic Aliphatic Bromide Cluster, pg. 50-51. Available: <https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0237-0002>

¹² US EPA (2019) 1,4-Dioxane Draft Risk Evaluation 06-27-2019, pg. 36-38. Available: <https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0238-0011>

¹³ 40 CFR 702.33

¹⁴ US EPA (2013) IRIS Assessments: 1,4-Dioxane. Available: https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?&substance_nmbr=326

¹⁵ US EPA (2019) HBCD Draft Risk Evaluation for Cyclic Aliphatic Bromide Cluster, pg. 50-51. Available: <https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0237-0002>

¹⁶ US EPA (2019) 1,4-Dioxane Draft Risk Evaluation 06-27-2019, pg. 36-38. Available: <https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0238-0011> [Similar Statements]

Though EPA references the *Strategy for Conducting Literature Searches for Cyclic Aliphatic Bromine Cluster (HBCD): Supplemental Document to the TSCA Scope Document* as discussing the approach of utilizing key/ supporting/ influential information from previous assessments, the phrases “key and supporting information,” “key and supporting data” and the word “influential” do not appear in this document. Further, this approach is not described in the scopes or problem formulations for HBCD or 1,4-dioxane, the *Application of Systematic Review in TSCA Risk Evaluations*, or any other supplementary documents.

EPA is introducing this approach of selecting key/ supporting/ influential information for the first time in the draft risk evaluations. The first problem is that EPA has published no protocols for its review to date, so the public and peer reviewers cannot see and evaluate what methodological changes EPA has made. Established standard practice for a systematic review is to publish a protocol prior to commencing the review, then update the protocol as needed, with all versions of the protocol publicly available. Protocol changes are described along with rationales for the changes. A pre-established protocol is critical to minimize bias in the review, so EPA’s continued lack of a protocol for its review, in combination with a fluid methodological approach that has shifted significantly over time with little rationale or explanation, raises serious concerns about the potential for bias in the review and transparency. In addition, the framework rules, which have been codified, require that EPA provide a protocol.¹⁷

Regarding transparency, EPA has not provided clear information on the key/ supporting/ influential information sources, including a list of what these sources are for each draft risk evaluation nor the specific criteria EPA used to identify these sources. The only definition we were able to find for key/ supporting/ influential information sources is that it “...would be influential in the risk evaluation, in other words, information supporting key analyses, arguments, and/or conclusions in the risk evaluation.”^{18,19} This definition requires knowing what the “key analyses, arguments, and/ or conclusions” are first, and then identifying the supporting information. This is extremely problematic, as in any scientific evaluation, the evidence should be identified first and then used to determine the conclusions—not the other way around.

Without further information on selection of the key/ supporting/ influential information sources, it could appear that EPA started with a conclusion, and then found evidence to support that conclusion. This is explicitly what systematic reviews are designed to address, using the conclusions in the studies to identify the literature will bias the scientific evaluation. It also is not what is required by the framework rules.

It is also difficult to identify what the key sources of data and information are, as they’re not presented in a clearly marked list in the draft risk evaluations. For example, the 1,4- dioxane draft risk evaluation identifies 14 ‘key sources’ with 2 additional sources (16 total) used for data integration for engineering releases and occupational exposure data sources.²⁰ There is a list of 16 sources in Appendix G1, Table G-

¹⁷ 40 CFR Part 702. Pg. 33727. “...the extent of independent verification or peer review of the information or of the procedures, measures, methods, protocols, methodologies, or models.”

¹⁸ US EPA (2019) HBCD Draft Risk Evaluation for Cyclic Aliphatic Bromide Cluster, pg. 50-51. Available: <https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0237-0002>

¹⁹ US EPA (2019) 1,4-Dioxane Draft Risk Evaluation 06-27-2019, pg. 36-38. Available: <https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0238-0011> [Similar Statements]

²⁰ US EPA (2019) EPA – 1,4-Dioxane Draft Risk Evaluation 06-27-2019, page 39. Available: <https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0238-0011>

1 which we assumed includes the key sources, but the Table does not identify which of these sources are “key” nor is it noted in the source HERO records.²¹ It is even more unclear in the draft risk evaluation for HBCD, as EPA identifies 11 ‘key sources’ with 15 additional sources (26 total) used for data integration for environmental releases and occupational exposure data sources.²² But the corresponding table in Appendix E7, Table E-13 contains 30 entries, with the majority being listed as excluded, so it is unclear what the 26 sources EPA used are, and which ones of these are the 11 “key” sources.²³ This is out of step with other well-established systematic review methods, which require a clear table listing of included studies, and affects the transparency of EPA’s evaluation.

Further, EPA describes that the “key/supporting data sources”:

“...allowed EPA to maximize the scientific and analytical efforts of other regulatory and non-regulatory agencies by accepting for the most part the relevant scientific knowledge gathered and analyzed by others except for influential information sources that may have an impact on the weight of the scientific evidence and ultimately the risk findings. The influential information (i.e., key/supporting) came from a smaller pool of sources subject to the rigor of the TSCA systematic review process to ensure that the risk evaluation uses the best available science and the weight of the scientific evidence.”^{24,25} (Emphasis added)

There is no additional explanation of what is meant by “accepting for the most part.” Without more information, it could appear that EPA is accepting certain conclusions for expediency based on political or other pressures, while subjecting other conclusions considered unfavorable to further scrutiny. These issues would all be mitigated if EPA published and adhered to a protocol which contained clearly defined criteria, like established systematic review methods highlighted in point 2. Investing time in a protocol will ensure that EPA’s process is replicable and transparent, and more importantly will avoid any issues with regard to assertions that EPA is ‘cherry-picking’ data.

As it stands, without a protocol to ensure consistent identification and evaluation of evidence, EPA’s approach using key/ supporting/ influential information sources is very likely to have created a biased evidence base for the 1,4-dioxane and HBCD draft risk evaluations. Further there is a significant lack of clarity and transparency about the key/ supporting/ influential information.

1b. EPA’s new approach using the “hierarchy of preferences” to exclude relevant studies rather than considering all the relevant science.

EPA has also changed how it is conducting its systematic review and is not applying its own method consistently. In these two risk evaluations, EPA has introduced a new “hierarchy of preferences” to exclude data for occupational exposures which are rated ‘acceptable’ by its TSCA method. This is not described in *Application of Systematic Review in TSCA Evaluations*; the *Strategy for Conducting Literature Searches for 1,4-Dioxane/ HBCD*; the *Bibliography: Supplemental File for the TSCA Scope*

²¹ Id. Pg. 226.1

²² US EPA (2019) EPA – HBCD Draft Risk Evaluation for Cyclic Aliphatic Bromide Cluster, page 54. Available: <https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0237-0002>

²³ Id. Pg. 490

²⁴ US EPA (2019) EPA – 1,4-Dioxane Draft Risk Evaluation 06-27-2019, page 37. Available: <https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0238-0011>

²⁵ US EPA (2019) EPA – HBCD Draft Risk Evaluation for Cyclic Aliphatic Bromide Cluster, page 51. Available: <https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0237-0002>

Document; the *Scope of the Risk Evaluation*; nor the *Problem Formulation*; therefore, this appears to be a new process EPA is using to exclude data in the draft risk evaluations, and it has not been subject to public comment or peer review.^{26,27,28}

For sources excluded based on the hierarchy of preferences, EPA states that “The quality of these sources...were acceptable for risk assessment purposes, but they were ultimately excluded from further consideration based on EPA’s integration approach for environmental release and occupational exposure data/ information. EPA’s approach uses a hierarchy of preferences that guide decisions about what types of data are included for further analysis...”²⁹ EPA describes the hierarchy as preferring monitoring data over modeling approaches or occupational exposure limits;³⁰ however, there is no protocol describing how EPA applied this hierarchy to select sources to exclude. Further, EPA does not provide an empirical basis or rationale for why it ‘preferred’ certain data.

Specifically, in the 1,4- dioxane draft risk assessment, EPA states that 44 sources rated ‘acceptable’ for engineering releases and occupational exposure data were eliminated due to the hierarchy of preferences.³¹ Looking at the Data Quality Evaluation Environmental Release and Occupational Exposure supplement, there are 87 sources rated ‘acceptable’ that EPA may have eliminated, but there is no clear list of which were excluded, and in the absence of a protocol, it is not possible to replicate the process and determine what sources EPA excluded based on the hierarchy.³² Based on our best attempts, it appears that EPA may have eliminated both OSHA and NIOSH references (some with EPA’s highest rating of 1.0) in exchange for (among other ‘key sources’) industry emails and factsheets from contracting websites. EPA also eliminated 70 high rated studies in exchange for a few medium rated studies in their key sources without adequate justification, and similar to our previous critiques, has left no reproducible protocol nor justification for their elimination process. Adhering to a systematic review with a protocol would have added the appropriate transparency to this process that is currently lacking and thus is highly likely to bias the final risk assessment.

Compared to the 1,4-dioxane evaluation, the HBCD evaluation is even more unclear as there was no clear list of key sources, EPA stated that there were 42 sources rated as unacceptable, however within EPA’s supplemental rating sheets we found 47 sources (based on unique Hero ID) or 74 individual entries were rated as unacceptable. This lack of alignment and clear protocol made it impossible to

²⁶ US EPA (2017) Strategy for Conducting Literature Searches for Cyclic Aliphatic Bromine Cluster (HBCD): Supplemental Document to the TSCA Scope Document. Available: https://www.epa.gov/sites/production/files/2017-06/documents/hbcd_lit_search_strategy_053017.pdf

²⁷ US EPA (2017) Bibliography: Supplemental File for the TSCA Scope Document. Available: https://www.epa.gov/sites/production/files/2017-06/documents/hbcd_comp_bib.pdf

²⁸ US EPA (2018) Problem Formulation for Cyclic Aliphatic Bromides Cluster (HBCD) Available: https://www.epa.gov/sites/production/files/2018-06/documents/hbcd_problem_formulation_05-31-18.pdf

²⁹ US EPA (2019) EPA – HBCD Draft Risk Evaluation for Cyclic Aliphatic Bromide Cluster, page 54. Available: <https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0237-0002>

³⁰ Id. Pgs. 175-176

³¹ US EPA (2019) EPA – 1,4-Dioxane Draft Risk Evaluation 06-27-2019, page 39. Available: <https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0238-0011>

³² US EPA (2019) 1-4-D Supplement - Data Quality Evaluation Environmental Release and Occupational Exposure 06272019. Available: <https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0238-0010>

identify the stated 36 sources that may have been eliminated due to the ‘hierarchy of preferences’ EPA introduced.

Overall, the ‘hierarchy of preferences’ does not have a valid empirical basis and by excluding relevant studies, EPA is introducing bias into its evaluations. There is also a lack of transparency in how the hierarchy was applied and which sources were ultimately excluded on this basis, which is inconsistent with the basic premise of a systematic review.

1c. EPA’s revised criteria for evaluating the quality of epidemiological studies, making it more likely that relevant epidemiological studies will be excluded.

EPA revised its TSCA method criteria for evaluating the quality of epidemiological studies, but the Agency failed to provide any rationale for the myriad changes and the update has not been peer-reviewed or available for public comment.³³ We have previously commented on the issues with EPA’s scoring methodology for evaluating the quality of the studies, such as its conflation of study quality and reporting quality and the fact that it does not mirror any current scientifically valid systematic review methodology.³⁴ While EPA has made some changes, such as removing references to the STROBE guidelines in some metrics, the new revisions have not eliminated the scoring system, and thus the major point of our previous comments remains unaddressed.

There continues to be no empirical basis for EPA’s scoring method to exclude research based on one single reporting or methodological limitation (their “fatal flaw” methodology).³⁵ These flaws are not indicative of study quality, nor are they all related to limitations that actually impact research results. Thus we reiterate that EPA should 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.

With its revisions, EPA makes it more difficult for epidemiology studies to receive a high score by either creating restrictive criteria to achieve a rating of high, or by removing the option of a high rating all together. (Appendix B) For example, a new addition to Metric 4 (Measurement of Exposure) states that to score high an occupational study must contain: “Detailed employment records which allows for construction of a job-matrix for entire work history of exposure (i.e., cumulative or peak exposures, and time since first exposure).”³⁶ This is an extremely high bar to meet with regard to documentation, and adversely affects the inclusion of epidemiological studies relating to a vulnerable subpopulation that EPA must consider under TSCA§ 6(b)(4).³⁷ Additionally, it is not scientifically necessary for conducting many elements of the risk assessment.

³³ US EPA (2019) 1-4-D Supplement - Data Quality Evaluation Human Health Epi 06272019. Available: <https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0238-0007>

³⁴ UCSF PRHE, et al. (2018) Comments from Academics, Scientists and Clinicians on: The Application of Systematic Review in TSCA Risk Evaluations. Available: https://prhe.ucsf.edu/sites/g/files/tkssra341/f/wysiwyg/2018%2008%2016%20Systematic%20Review%20TSCA%20evaluations%20UCSF%20PRHE%20comments%20EPA_0.pdf

³⁵ US EPA (2019) 1-4-D Supplement - Data Quality Evaluation Human Health Epi 06272019. Available: <https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0238-0007>

³⁶ Id. Pg. 6

³⁷ 15 USC §2602 (12)

Another example is Metric 13 (Statistical Power), where EPA altered its criteria by transferring the description for a High score to a Medium score; so now a study can only score Medium or Unacceptable in Metric 13.³⁸ In fact, with EPA's updated criteria, epidemiological studies can no longer score high on seven metrics, but no such change has been made for the animal or *in vitro* studies.³⁹

The net effect of EPA's changes is to lower the highest score that is possible for an epidemiological study to receive, but there is no empirical basis provided for its original scoring system or the updates⁴⁰, which is contrary to best practices in systematic reviews. Further, this is highly likely to lead to exclusion or downgrading of more epidemiological studies from the evidence base for decision-making, thus biasing the risk assessment. This is concerning because epidemiological studies reflect people's real-world exposures and outcomes, and thus are a critical part of the scientific evidence about how chemicals may harm people, especially susceptible populations like workers, pregnant women and children.

2. EPA should use a peer-reviewed, validated systematic review method for chemical evaluations instead of "Application of systematic review in TSCA risk evaluations."

EPA states that it "...is implementing systematic review methods and approaches within the regulatory context of the amended TSCA. Although EPA will make an effort to adopt as many best practices as practicable from the systematic review community, EPA expects modifications to the process to ensure that the identification, screening, evaluation and integration of data and information can support timely regulatory decision making under the aggressive timelines of the statute."⁴¹

³⁸ US EPA (2019) 1-4-D Supplement - Data Quality Evaluation Human Health Epi 06/27/2019, Page 11. Available: <https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0238-0007>

³⁹ US EPA (2019) 1-4-D Supplement - Data Quality Evaluation Animal and In Vitro Tox 06/27/2019. Available: <https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0238-0005>

⁴⁰ Previously, all epidemiological studies could score High for every applicable metric. OPPT has changed this so that in several instances epidemiological studies cannot receive a score of High for certain metric. The metrics are different for studies with and without biomarkers (metrics 16-22 only apply to studies with biomarkers), the numbers for both are below:

- Studies without biomarkers: 6 out of 15 metrics can no longer be scored High (best score is Medium for each)
- Studies with biomarkers: 7 out of 22 metrics can no longer be scored High (best score is Medium for each)

These changes don't prevent an epidemiological study from scoring High overall, but they certainly put these studies at a disadvantage from the outset by limiting the number of individual metrics that can score High. The overall score range for a study to be considered overall High is 1- 1.7, and to be considered Medium is 1.7-2.3, so these changes push the baseline in that direction and in effect diminish the contribution of epidemiological studies relative to animal or *in vitro* studies.

- Max scores (per EPA's method, lower scores are better):
 - Without biomarkers:
 - Original best score = 1.0
 - New best score = 1.29
 - With biomarkers:
 - Original best score = 1.0
 - New best score = 1.27

⁴¹ US EPA (2019) EPA – HBCD Draft Risk Evaluation for Cyclic Aliphatic Bromide Cluster, page 50. Available: <https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0237-0002>

We have previously detailed why the TSCA systematic review method is invalid, scientifically flawed, and should not be used both in previous comments and in a peer-reviewed publication.^{42,43} In brief, the TSCA systematic review method has not been peer-reviewed or validated, and conflicts with other accepted methods used by EPA and internationally. There are multiple well-developed, science-based, peer-reviewed, and validated methods for conducting systematic reviews in environmental health that EPA could readily apply, including the method and handbook developed by the Office of Health Assessment and Translation at the National Toxicology Program and the Navigation Guide Systematic Review Method.^{44,45} The National Academy of Sciences cited both of these systematic review methods as exemplary of the type of methods EPA should use in hazard and risk assessment.⁴⁶ Therefore, EPA could both use the best available science and help to meet the “aggressive timelines of the statute” by immediately implementing for TSCA risk evaluations the OHAT or Navigation Guide methods that are already developed and ready to use. EPA’s risk determinations are not protective of potentially exposed or susceptible subpopulations.

TSCA requires EPA to determine whether “the manufacture, processing, distribution in commerce, use, or disposal of a chemical substance or mixture, or that any combination of such activities, presents an unreasonable risk of injury to health or the environment,” including to potentially exposed or susceptible sub-populations.⁴⁷ We have recently published important considerations for EPA to include on potentially exposed or susceptible subpopulations based on current science (Appendix A); unfortunately the draft risk evaluations do not meet the mandate of the statute to ensure the protection of these vulnerable populations from unreasonable risks.

3. EPA’s risk determinations are not protective of potentially exposed or susceptible subpopulations.

3a. EPA does not account for biological factors that can increase susceptibility to chemical toxicity.

⁴² UCSF PRHE, et al. (2018) Comments from Academics, Scientists and Clinicians on: The Application of Systematic Review in TSCA Risk Evaluations. Available: https://prhe.ucsf.edu/sites/g/files/tkssra341/f/wysiwyg/2018%2008%2016%20Systematic%20Review%20TSCA%20evaluations%20UCSF%20PRHE%20comments%20EPA_0.pdf

⁴³ Singla, V. I., Sutton, P. M., & Woodruff, T. J. (2019). The Environmental Protection Agency Toxic Substances Control Act Systematic Review Method May Curtail Science Used to Inform Policies, With Profound Implications for Public Health. *American Journal of Public Health*, 109(7), 982–984. doi:10.2105/AJPH.2019.305068

⁴⁴ National Toxicology Program (2015) Handbook for Conducting a Literature-Based Health Assessment Using OHAT Approach for Systematic Review and Evidence Integration. In: U.S. Department of Health and Human Services, editor.: Office of Health Assessment and Translation, Division of National Toxicology Program, National Institute of Environmental Health Sciences.

⁴⁵ Woodruff TJ, Sutton P (2014) The Navigation Guide sytematic review methodology: a rigorous and transparent method for translating environmental health science into better health outcomes. *Environmental Health Perspectives*. 122(10):A283.

⁴⁶ 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, DC.

⁴⁷ 15 USC §2605(b)

For both HBCD and 1,4-dioxane, EPA states that “The results of the available human health data for all routes of exposure evaluated (i.e., oral, dermal and inhalation) indicate that there is no evidence of increased susceptibility for any single group relative to the general population.”^{48,49}

HBCD

EPA’s assertion that there is no evidence for increased susceptibility to HBCD does not make any sense given that EPA identified developmental and reproductive toxicity, and effects on thyroid as key HBCD toxicity endpoints.⁵⁰ Abundant literature has identified critical windows of susceptibility to such toxicities during early life stages (fetuses, children) and pregnancy. Indeed, EPA itself acknowledges this in the draft risk evaluation, noting:

“Thyroid hormones play a critical role in coordinating complex developmental processes, and perturbations of thyroid hormone levels in a pregnant woman or neonate can have persistent adverse health effects for the child... early development remains a sensitive life stage for hormone deficits, largely due to minimal reserve capacity when compared to adults. Effects on female reproduction parameters are an additional consideration for identifying pregnant and lactating females as a susceptible subpopulation.”⁵¹

Even without accounting for these susceptibilities, EPA already found risks of concern for ‘highly exposed populations’ for developmental toxicity after acute exposures related to fish ingestion; indeed, if the factor between the point of departure and the exposure (the MOE which EPA is inappropriately using for their risk assessment) was made to be 1000 based on increased susceptibility of exposure during early life stages, there would be more risks of concern identified.⁵² This is also true for acute inhalation exposures and chronic exposures related to fish ingestion for consumers⁵³

EPA further notes that because HBCD is bioaccumulative, both people that consume a high-fat diet and people with higher body fat content may have greater susceptibility. Finally, EPA recognizes that people with pre-existing health conditions or genetic pre-dispositions in any of the affected health domains “would also be expected to be especially susceptible to HBCD toxicity, perhaps at significantly lower doses than healthy populations.”⁵⁴ This includes people with liver disease or thyroid disease. According to data from the Centers for Disease Control and Prevention, liver disease is the eighth leading cause of death in the U.S., so the affected population is likely quite large.⁵⁵

However, out of all these populations EPA identifies with greater susceptibility, only one (female workers of reproductive age) is addressed in the quantitative calculation of risk. EPA states “Risk

⁴⁸ US EPA (2019) EPA – HBCD Draft Risk Evaluation for Cyclic Aliphatic Bromide Cluster, page 26. Available: <https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0237-0002>

⁴⁹ US EPA (2019) EPA – 1,4-Dioxane Draft Risk Evaluation 06-27-2019, page 21. Available: <https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0238-0011>

⁵⁰ US EPA (2019) EPA – HBCD Draft Risk Evaluation for Cyclic Aliphatic Bromide Cluster, page 325, Table 3-10. Available: <https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0237-0002>

⁵¹ Id. Pg. 384

⁵² Id. Pg 367

⁵³ Id. Pg. 370, 373

⁵⁴ Id. Pg. 384

⁵⁵ Kim, W., 2002. Burden of liver disease in the United States: Summary of a workshop. *Hepatology*, 36(1), pp.227–242. Available at: <http://www.ncbi.nlm.nih.gov/pubmed/12085369>.

estimates for female workers of reproductive age were 10% lower than workers overall...”⁵⁶ It is unclear how EPA derived this 10% difference, as it does not present data supporting that pregnant women would only be 10% more susceptible to HBCD than other workers.

None of the other populations (early life stages, women of reproductive age who are not workers, people with a high fat diet, people with higher body fat content, people with liver or thyroid disease) are addressed. In the absence of quantitative data on HBCD toxicity in these populations, EPA should use established health-protective default factors in the calculation of risk to account for increased susceptibility, as recommended by the National Academies of Sciences (NAS).⁵⁷

1,4-dioxane

EPA did not account for variability in human response in its calculation of cancer risks for 1,4-dioxane. The NAS has recommended that EPA include a factor to account for human variability in response to carcinogens, and found that a factor of 25- to 50- may account for the variability between the median individual and those with more extreme responses, and recommended 25 as a reasonable default value.⁵⁸

EPA’s assertion that there is no evidence for any population with increased susceptibility to 1,4-dioxane does not make sense given that 1,4-dioxane is a carcinogen and there is significant evidence that the prenatal life stage is more susceptible to carcinogens. California EPA reviewed the evidence on differential susceptibility to carcinogens based on age and life stage and derived age adjustment values for carcinogens which include the prenatal period, proposing “a default Age-Sensitivity Factor of 10 for the third trimester until age 2 years, and a factor of 3 for ages 2 through 15 years to account for potential increased sensitivity to carcinogens during childhood.”⁵⁹ At a minimum, EPA should incorporate factors to account for human variability in response to carcinogens, as well as Cal EPA’s age adjustment values to address these known susceptibilities.

Overall, EPA’s risk calculations for HBCD and 1,4-dioxane do not account for populations with increased susceptibility, and thus EPA has not demonstrated that its risk determinations are protective of susceptible subpopulations.

3b. Due to excluding known exposures, not aggregating exposures, and other problems with the exposure assessment, EPA is underestimating exposures.

The draft risk evaluations do not accurately identify or ensure the protection of populations with greater exposures because EPA excludes numerous known exposure sources, and for the exposures EPA includes, aggregation is not calculated correctly for most populations.

⁵⁶ US EPA (2019) EPA – HBCD Draft Risk Evaluation for Cyclic Aliphatic Bromide Cluster, page 384. Available: <https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0237-0002>

⁵⁷ National Research Council. (2009). *Science and Decisions: Advancing Risk Assessment*. Retrieved from <https://www.nap.edu/catalog/12209/science-and-decisions-advancing-risk-assessment>

⁵⁸ Id. Pg. 168

⁵⁹ California EPA 2009. Cal EPA 2009. California Environmental Protection Agency, Office of Environmental Health Hazard Assessment. Technical Support Document for Cancer Potency Factors: Methodologies for derivation, listing of available values, and adjustments to allow for early life stage exposures. Page 50. <http://oehha.ca.gov/media/downloads/crnrtsdcanerpotency.pdf>

HBCD

A strength in the draft risk evaluation is that consumers also have background exposures experienced by the general population aggregated into the exposure assessment. This is necessary and appropriate to accurately calculate exposure. But these background exposures which EPA acknowledges are experienced by everyone should also be integrated for workers; some workers may also be consumer product users and so there should be an additional calculation for this population. Furthermore, there are many other deficiencies that result in significantly underestimating exposures for all populations.

First, known sources of exposure to HBCD for all populations are excluded from the conditions of use included in the draft risk evaluation, such as “reuse, disposal, and recycling of HBCD-containing products from legacy uses...” and “high impact polystyrene (HIPS) for electrical and electronic appliances, consumer and commercial textiles, adhesives, coatings, children’s products including toys and car seats; furniture (such as bean bag chairs).”⁶⁰

In the framework rules, EPA indicates that with regard to conditions of use it generally supports a prospective interpretation (ex. activities that only reflect ongoing manufacturing, processing or distribution).⁶¹ The Agency also subsequently states that:

“...in a particular risk evaluation, EPA may consider background exposures from legacy use, associated disposal and legacy disposal as part of an assessment of aggregate exposure or as a tool to evaluate the risk of exposures resulting from non-legacy uses.”⁶²

As a chemical with persistent, bioaccumulative and toxic (PBT) characteristics and a wealth of scientific literature around recycling, reuse, and disposal, in drafting the HBCD risk evaluation, EPA should have utilized this framework exception and taken background exposures from legacy uses of HBCD into consideration.⁶³

Second, EPA does not aggregate inhalation and dermal exposures for workers, instead calculating the risks separately.⁶⁴ EPA states that “Combining exposure routes would entail too much uncertainty given the lack of a usable PBPK model.”⁶⁵ However, these exposure routes are combined in the calculation of risk for the general population, so it is unclear why this cannot be done for workers.⁶⁶

Third, for the general population and consumers, EPA accounts for dermal exposures to dust, soil and materials, and inhalation of suspended particles,⁶⁷ but does not account for HBCD exposure that occurs from the air-to-dermal pathway in indoor environments.⁶⁸ Estimates based on established exposure

⁶⁰ US EPA (2019) EPA – HBCD Draft Risk Evaluation for Cyclic Aliphatic Bromide Cluster, page 39. Available: <https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0237-0002>

⁶¹ 40 CFR Part 702. Pg. 33729

⁶² Id. pg 33730

⁶³ Covaci A. et al., 2006. Hexabromocyclododecanes (HBCDs) in the Environment and Humans: A Review. *Environmental Science & Technology*, 40 (12), 3679-3688. DOI: 10.1021/es0602492

⁶⁴ Id. Pg. 353-362

⁶⁵ Id. Pg. 381

⁶⁶ Id. Pg. 267

⁶⁷ Id. Pg. 247

⁶⁸ Weschler, C.J. & Nazaroff, W.W., 2012. SVOC exposure indoors: fresh look at dermal pathways. *Indoor air*, 22(5), pp.356–77.

models predict that the air-to-dermal pathway would contribute to a young child's total residential exposures to HBCD.⁶⁹

Finally, EPA specifically identifies workers, occupational non-users, consumer users and bystanders as populations with greater exposures to HBCD;⁷⁰ but fails to identify fetuses, infants and young toddlers. EPA's analysis of human biomonitoring data shows that placental and fetal tissues have the highest measured doses of HBCD, falling outside EPA's estimated high-end doses range from exposure pathways.⁷¹ As shown in the figure below, EPA's exposure assessment based on central tendency and high-end data clearly shows that infants and young toddlers have the greatest exposures compared to other age groups in the general population.⁷²

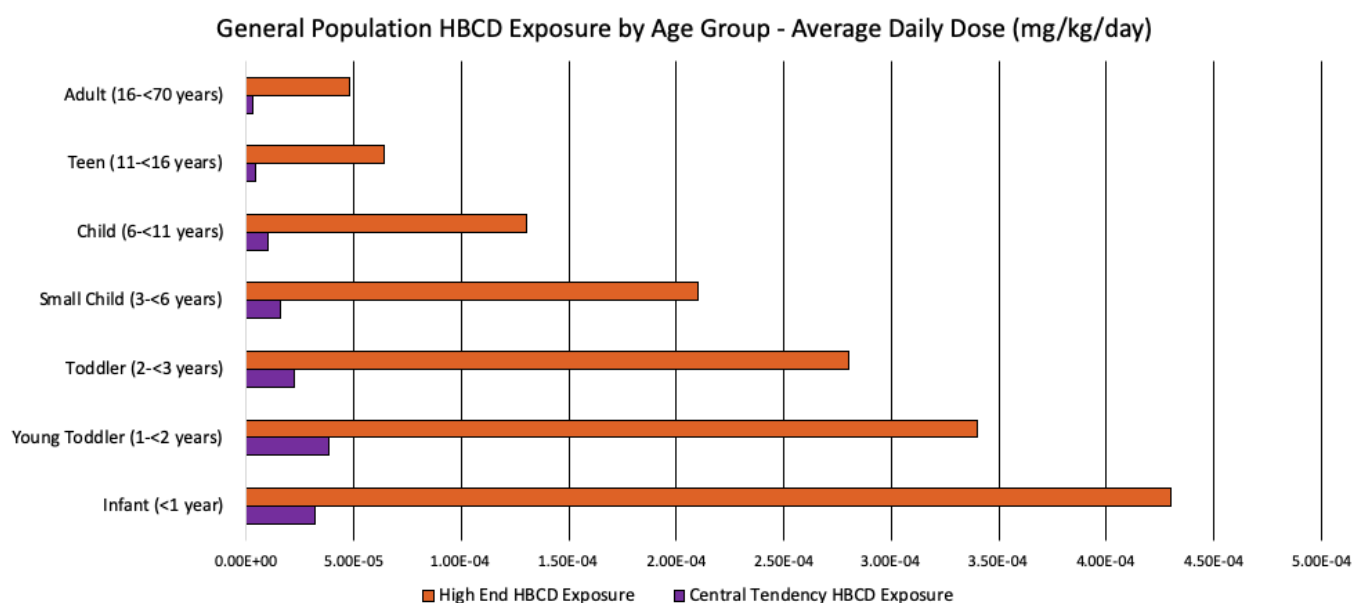


Figure: Average daily dose (mg/kg/day) of HBCD by age group, from EPA HBCD draft risk evaluation data in Tables 2-99 and 2-101.

1,4-dioxane

The deficiencies identified for HBCD are also present in the 1,4-dioxane draft risk evaluation: excluding known sources of exposure such as contaminated drinking water and consumer products and failing to aggregate dermal and inhalation exposures in the calculation of risk. Even worse, in the 1,4-dioxane draft risk evaluation EPA excludes populations other than workers all together.

3c. EPA leaves unreasonable risks for workers unaddressed, as its assumptions about personal protective equipment (PPE) are not scientifically supported.

⁶⁹ Mitro, S.D. et al., 2016. Consumer Product Chemicals in Indoor Dust: A Quantitative Meta-analysis of U.S. Studies. Environmental Science & Technology, p.acs.est.6b02023. See Figure 3.

⁷⁰ US EPA (2019) EPA – HBCD Draft Risk Evaluation for Cyclic Aliphatic Bromide Cluster, page 382. Available: <https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0237-0002>

⁷¹ Id. Pg. 229

⁷² Id. Pg. 267, Table 2-99; Pg. 268, Table 2-101.

Despite failing to aggregate inhalation and dermal pathway risks for workers, EPA still finds risks of concern for each pathway individually for HBCD:

- Acute inhalation exposures: developmental toxicity, high end and central tendency exposures⁷³
- Chronic inhalation exposures: thyroid, liver, female reproductive, developmental toxicity⁷⁴
- Acute dermal exposures: developmental toxicity⁷⁵
- Chronic dermal exposures: thyroid, liver, reproductive, developmental toxicity⁷⁶

EPA assumes use of PPE to mitigate these risks of concern and reach a determination of no unreasonable risk for HBCD, despite the fact that no OSHA standards exist for HBCD.

Use of PPE in the absence of a standard is an unrealistic assumption to say the least, because even when an OSHA standard exists, it is not followed. OSHA found that for its methylene chloride standard, failure to provide PPE was one of most common violations.⁷⁷

EPA itself notes that “The MOEs for these respirator scenarios assume workers are properly trained and fitted on respirator use, and that they wear respirators for the entire duration of the work activity. The MOEs for respirator scenarios following chronic exposure also assume that workers and occupational non-users wear respirators for the entire duration of the work activity throughout their career. Such regular use of respirators in chronic scenarios may not always be feasible...Similar assumptions apply to the use of gloves and their expected elimination of any dermal exposure.”⁷⁸

Because there is no evidence that these assumptions can reasonably be applied to HBCD workers, EPA’s determination of no unreasonable risk is faulty.

4. EPA should use a unified linear approach for dose response analysis and risk calculations for all carcinogens and non-carcinogens as recommended by the NAS and EPA should not use the MOE approach.

The National Academies recommends a unified approach to analyzing health effects from chemical exposures that applies the methods used for mutagenic carcinogens to non-mutagenic carcinogens and non-cancer health effects. Additionally, NAS has recommended that the default approach to the dose-response for all MOAs be linear.⁷⁹ The current EPA practice for assigning “nonlinear” MOAs does not account for mechanistic factors that can create linearity at a low dose, such as when an exposure

⁷³ US EPA (2019) EPA – HBCD Draft Risk Evaluation for Cyclic Aliphatic Bromide Cluster, page 354. Available: <https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0237-0002>

⁷⁴ Id. Pg. 356

⁷⁵ Id Pg. 360

⁷⁶ Id Pg. 361

⁷⁷ U.S. Department of Labor, Occupational Safety and Health Administration. (2010) “Regulatory Review of 29 CFR 1910.1052: Methylene Chloride.” Available: <https://www.osha.gov/dea/lookback/MC-lookback-Feb-2010-final-for-publication-May-2010.pdf>

⁷⁸ US EPA (2019) EPA – HBCD Draft Risk Evaluation for Cyclic Aliphatic Bromide Cluster, page 381. Available: <https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0237-0002>

⁷⁹ National Research Council. Science and Decisions: Advancing Risk Assessment. Ch. 5, page 180. Washington, D.C.: National Academies Press; 2009.

contributes to an existing disease process.⁸⁰ These points were outlined in our previous comments and are reiterated below. Specifically:

- Chemical exposures that add to existing (background) processes, endogenous and exogenous exposures lack a threshold if a baseline level of dysfunction occurs without the toxicant and the toxicant adds to or augments the background process.⁸¹
- Human variability with respect to the individual thresholds for a nongenotoxic cancer mechanism can result in linear dose-response relationships in the population.⁸²
- In animal tests, a specific chemical may cause cancer through a nonlinear dose-response process. But for the human population, the dose-response relationship for the same chemical is likely a low-dose linear one, given the high prevalence of pre-existing disease and background processes that can interact with a chemical exposure, and given the multitude of chemical exposures and high variability in human susceptibility.⁸³

Historically EPA has assumed a linear dose-response with no threshold of effect only for carcinogens that are mutagens or that have high human body burdens. But the science indicates that this linear presumption with no threshold is appropriate regardless of a carcinogen's MOA (mutagenic or non-mutagenic). Therefore, EPA should apply this approach to the dose response analysis for all health endpoints for HBCD and 1,4-dioxane.

In their risk evaluations for both 1,4 dioxane and HBCD, EPA indicates that they use a Margin of Exposure (MOE) approach to “identify potential non-cancer human health risks and allow for a range of risk estimates.”^{84,85} In its 2017 Risk Evaluation Rule, EPA specifically identifies MOE as “just one of several approaches to risk characterization, and agrees that it does not make sense to single out this one particular approach. There will be risk scenarios where one approach may be better than another and, as commenters correctly pointed out, the science of risk characterization is still evolving, particularly for non-cancer hazards.”⁸⁶ EPA indicated that it was not going to codify any specific approach in order to allow its risk evaluation to utilize a number of different approaches, however the Agency's execution for these risk evaluations is to de facto adopt MOE as the only approach.

We have previously commented about the scientific shortcomings of MOE as an analysis method in the risk evaluation process.⁸⁷ MOE does not provide a risk estimate, but is a single number similar to a Reference Dose; this restrictive approach does not provide information about the magnitude of the risks above, at, or below a certain level. Further, it implies that there is a “safe” level of exposure below which no harm will occur. The NAS recognizes that this is not a valid assumption for all chemicals and has recommended moving away from such approaches as they do not establish risk estimates across the

⁸⁰ Id. pg. 129

⁸¹ Id. pg. 130

⁸² Id.

⁸³ Id.

⁸⁴ US EPA (2019) EPA – 1,4-Dioxane Draft Risk Evaluation 06-27-2019, page 20. Available:

<https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0238-0011>

⁸⁵ US EPA (2019) EPA – HBCD Draft Risk Evaluation for Cyclic Aliphatic Bromide Cluster, page 350. Available:

<https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0237-0002>

⁸⁶ 40 CFR Part 702. Pg. 33735.

⁸⁷ UCSF PRHE, et al. (2017) Comments from Academics, Scientists and Clinicians on the Risk Evaluation Scoping Efforts Under TSCA for Ten Chemical Substances. Available:

<https://prhe.ucsf.edu/sites/g/files/tkssra341/f/wysiwyg/01%20Risk%20Evaluation%20Scoping%20Efforts%20Under%20TSCA%20for%20Ten%20Chemical%20Substances.pdf>

full range of exposures.⁸⁸ For 1,4-dioxane, EPA did not use MOE for cancer risks; a similar non-MOE approach should be applied to risk calculations for all other health endpoints.⁸⁹

5. EPA must include HBCD byproducts generated during the conditions of use in the evaluation of risk for HBCD.

EPA does not include byproducts generated from HBCD during manufacturing, processing, use or disposal in the draft risk evaluation.⁹⁰ Specifically, insulation materials containing HBCD generate brominated dioxins during processing and combustion/ incineration that EPA fails to consider.⁹¹

Dioxins are a group of toxic compounds that are persistent environmental pollutants that can be unintentionally formed and released during the production and life cycle of products containing halogenated flame retardants such as HBCD; their release can have adverse effects on the environment and people.^{92,93,94} Exposure to chlorinated dioxins is associated with adverse health effects such as skin and liver problems, impairment of immune, endocrine or reproductive function, effects on the developing nervous system, and certain types of cancer.⁹⁵ Additionally, scientists have found brominated dioxins in the environment, food supply, indoor dust, human milk and tissue.^{96,97}

⁸⁸National Research Council. Science and Decisions: Advancing Risk Assessment. Washington, D.C.: National Academies Press; 2009.

⁸⁹ US EPA (2019) EPA – 1,4-Dioxane Draft Risk Evaluation 06-27-2019, pages 128-129. Available: <https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0238-0011>

⁹⁰ US EPA (2019) EPA – HBCD Draft Risk Evaluation for Cyclic Aliphatic Bromide Cluster, page 72. Available: <https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0237-0002> “All releases assessed are of solid HBCD or solid mixtures containing HBCD.”

⁹¹ Desmet, K., Schelfaut, M., & Sandra, P. (2005). Determination of bromophenols as dioxin precursors in combustion gases of fire retarded extruded polystyrene by sorptive sampling-capillary gas chromatography–mass spectrometry. *Journal of Chromatography A*, 1071(1–2), 125–129. <https://doi.org/10.1016/j.chroma.2004.12.019>

⁹² Babrauskas, Vytenis & Lucas, Donald & Eisenberg, David & Singla, Veena & Dedeo, Michel & Blum, Arlene. (2012). Flame retardants in building insulation: A case for re-evaluating building codes. *Building Research and Information*. 40. 10.1080/09613218.2012.744533.

⁹³ Hanari, N., Kannan, K., Okazawa, T., Kodavanti, P.R.S., Aldous, K.M. and Yamashita, N. (2006) Occurrence of polybrominated biphenyls, polybrominated dibenzo-p-dioxins, and polybrominated dibenzofurans as impurities in commercial polybrominated diphenyl ether mixtures. *Environmental Science and Technology*, 40(14), 4400–4405.

⁹⁴ Shaw, S.D., Blum, A., Weber, R., Kannan, K., Rich, D., Lucas, D., Koshland, C.P., Dobraca, D., Hanson, S. and Birnbaum, L.S. (2010) Halogenated flame retardants: do the fire safety benefits justify the risks? *Reviews on Environmental Health*, 25(4), 261–305.

⁹⁵ World Health Organization (WHO) (1998) Polybrominated Dibenzo-p-Dioxins and Dibenzofurans (EHC 205), WHO, Geneva.

⁹⁶ Suzuki, G., Someya, M., Takahashi, S., Tanabe, S., Sakai, S. and Takigami, H. (2010) Dioxin-like activity in Japanese indoor dusts evaluated by means of in vitro bioassay and instrumental analysis: brominated dibenzofurans are an important contributor. *Environmental Science and Technology*, 44(21), 8330–8336.

⁹⁷ Van den Berg, M., Birnbaum, L.S., Denison, M., De Vito, M., Farland, W., Feeley, M., Fiedler, H. et al. (2006) The 2005 World Health Organization reevaluation of human and Mammalian toxic equivalency factors for dioxins and dioxin-like compounds. *Toxicological Sciences*, 93(2), 223–241.

These byproducts are of particular concern to workers during the manufacturing process as they can be found in final commercial products and in workplace air.⁹⁸ Disposal workers and firefighters are also at risk of exposure as combustion byproducts can be found in the air when halogenated flame retardants burn, either in accidental fires or during intentional incineration for disposal.⁹⁹ By failing to consider this potential health hazard, EPA is underestimating the risk that HBCD and its associated byproducts pose, not just to worker populations, but to nearby vulnerable communities.

⁹⁸ Ebert, J. and Bahadir, M. (2003) Formation of PBDD/F from flame-retarded plastic materials under thermal stress. *Environment International*, 29(6), 711–716.

⁹⁹ Weber, R. and Kuch, B. (2003) Relevance of BFRs and thermal conditions on the formation pathways of brominated and brominated chlorinated dibenzodioxins and dibenzofurans. *Environment International*, 29(6), 699–710.

Appendices:

Appendix A: Koman, P.D., Singla, V. I., Lam, J., & Woodruff, T. J. (2019). Population susceptibility: A vital consideration in chemical risk evaluation under the Lautenberg Toxic Substances Control Act. *PLoS Biology*.

Appendix B: Analysis of revised TSCA Systematic Review data quality criteria for epidemiological studies.

Appendix A: Koman, P.D., Singla, V. I., Lam, J., & Woodruff, T. J. (2019). Population susceptibility: A vital consideration in chemical risk evaluation under the Lautenberg Toxic Substances Control Act. *PLoS Biology*.

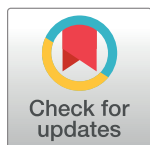
PERSPECTIVE

Population susceptibility: A vital consideration in chemical risk evaluation under the Lautenberg Toxic Substances Control Act

Patricia D. Koman^{1*}, Veena Singla², Juleen Lam³, Tracey J. Woodruff²

1 Environmental Health Sciences, University of Michigan School of Public Health, Ann Arbor, Michigan, United States of America, **2** Obstetrics, Gynecology and Reproductive Sciences, Program on Reproductive Health and the Environment, University of California San Francisco School of Medicine, San Francisco, California, United States of America, **3** Department of Health Sciences, California State University East Bay, Hayward, California, United States of America

* tkoman@umich.edu



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Abbreviations: CASRN, Chemical Abstracts Services registry number; EPA, United States

Abstract

The 2016 Frank Lautenberg Chemical Safety for the 21st Century Act (Lautenberg TSCA) amended the 1976 Toxic Substances Control Act (TSCA) to mandate protection of susceptible and highly exposed populations. Program implementation entails a myriad of choices that can lead to different degrees of public health protections. Well-documented exposures to multiple industrial chemicals occur from air, soil, water, food, and products in our workplaces, schools, and homes. Many hazardous chemicals are associated with or known to cause health risks; for other industrial chemicals, no data exist to confirm their safety because of flaws in 1976 TSCA. Under the 2016 Lautenberg amendments, the United States Environmental Protection Agency (EPA) must evaluate chemicals against risk-based safety standards under enforceable deadlines, with an explicit mandate to identify and assess risks to susceptible and highly exposed populations. Effective public health protection requires EPA to implement the Lautenberg TSCA requirements by incorporating intrinsic and extrinsic factors that affect susceptibility, adequately assessing exposure among vulnerable groups, and accurately identifying highly exposed groups. We recommend key scientific and risk assessment principles to inform health-protective chemical policy such as consideration of aggregate exposures from all pathways and, when data are lacking, the use of health-protective defaults.

Introduction

Hazardous industrially manufactured chemicals are ubiquitous in society despite the 1976 Toxic Substances Control Act (TSCA) (Public Law No. 114–182) [1–3]. Hazardous chemicals are found in products such as bedding, furniture, building materials, clothing, cleaning products, food containers, and toys [4,5]. Multiple industrial chemicals are also present in every person in the US, many at levels that can increase the risk of adverse health outcomes [4].

Environmental Protection Agency; HBCD, hexabromocyclododecane; HIPS, high-impact polystyrene; IRIS, Integrated Risk Information System; Lautenberg TSCA, 2016 Frank Lautenberg Chemical Safety for the 21st Century Act; NMP, N-Methyl-pyrrolidone; NTP, National Toxicology Program; TSCA, 1976 Toxic Substances Control Act.

Provenance: Commissioned; externally peer reviewed.

Approximately 9.5 trillion pounds of over 40,000 industrial chemicals are currently in production [3, 6]. Exposures to chemicals such as asbestos, methylene chloride, organic solvents, toxic metals, and halogenated flame retardants can increase the risk of death, cancer, birth defects, and loss of cognitive capacity in children (e.g., see Table 1) [4,7–10]. The costs of environmental chemical exposures are in the billions of US dollars, with one limited study of children estimating \$76.6 billion annually (2.7%–4.8% of US healthcare costs) for lead poisoning, asthma, cancer, and developmental disabilities [11,12]. The estimated cost of cleaning up chemical waste at the 294,000 hazardous waste sites across the country is \$250 billion, excluding the societal costs of potential health impacts and emerging contaminants [13,14].

Over the past half century, scientists and the public gained a more comprehensive understanding of exposures and health effects from industrial chemicals. Research evaluating exposure to environmental chemicals evolved from directly studying workers to examining consumers and vulnerable populations to assessing potential impacts on future generations (e.g., epigenetics). The understanding of the nature of harm from industrial chemical exposures expanded from one adverse endpoint to many, as well as from one chemical to cumulative exposures and vulnerable periods of exposure across the life course [15]. Health-based regulatory limits have been lowered, not raised, as the science advances [16]. Most importantly, exposures to industrial chemicals and their health consequences remain preventable [17]. Consequently, leading scientists and medical societies have identified environmental pollutants as contributing to adverse health consequences and called for public policies to prevent harmful exposures, emphasizing the need to protect susceptible and highly exposed populations [18–21]. The National Research Council’s report *Science and Decisions: Advancing Risk Assessment* recommended improvements to chemical risk assessment to protect public health (referred to hereafter as “*Science and Decisions*”) [15].

In the US, Congress passes laws such as the 1976 Toxic Substance Control Act (TSCA) that mandate the US Environmental Protection Agency (EPA) implement the law through policies, rule makings, and regulations to limit toxic chemical exposures. The authorizing law sets bounds on EPA’s authority, and EPA also has some discretion in implementing the law.

The limitations of 1976 TSCA contributed to a notoriously ineffective implementation that did not protect public health [1–2,22–25]. For example, under 1976 TSCA, EPA did not have adequate authority to require chemical testing prior to chemicals entering commerce [1,2,20–22]. Health and safety testing is available for just 200 chemicals (about 2% of the total manufactured chemicals) [25,26]. Furthermore, EPA could not effectively regulate chemicals with documented adverse health effects, like asbestos and methylene chloride, partly because of the burden of demonstrating “unreasonable risk” along with consideration of the cost to regulate. As a result, hazardous chemicals remained in production and use [27–32]. Faced with mounting evidence of harms and pressure from public health groups, states and other jurisdictions issued their own requirements to fill gaps left by federal inaction. Chemical manufacturers found the variable local requirements to be onerous in a global market, which set the stage for the 2016 Frank Lautenberg Chemical Safety for the 21st Century Act (Lautenberg TSCA) (Public Law No. 114–182) [33].

An important change is that Lautenberg TSCA directs EPA to identify and protect “potentially exposed or susceptible sub-populations,” defined as “a group of individuals within the general population identified by the [US EPA] 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” (15 USC §2602 [12]) [34]. The law further requires that EPA decisions under Lautenberg TSCA must protect such populations (15 USC §2604 [a] [3][A]; 15 USC §2605 [b][1][B][i], [b][4][A], and [h][1][B]) [35–38]. Finally, the amended law

Table 1. US EPA's first 10 chemicals for risk evaluation under Lautenberg TSCA, exposures and selected health hazards.

Selected Information From US EPA Scoping and Problem Formulation Documents (based on available information, February 2019)		
Chemical (Other Names or Abbreviations)/CASRN	Uses and Potential Routes of Exposure	Some Identified Health Hazards
1,4-Dioxane ^a /123-91-1	Uses include industrial and commercial processes such as chemical manufacturing and textile processing; present in consumer products (e.g., as a contaminant in shampoo); drinking-water contaminant	Designated "likely to be carcinogenic to humans" (EPA); liver, kidney toxicity
1-Bromopropane (n-propylbromide, 1-BP) ^b /106-94-5	Uses include solvent in industrial and commercial processes such as dry cleaning; consumer products including stain removers; air emissions from industrial facilities	Reproductive/developmental toxicity; neurotoxicity; designated as "reasonably anticipated to be a human carcinogen" (US Department of Health and Human Services, NTP)
Asbestos ^c /1332-21-4	Uses include chemical manufacturing, chlor-alkali industry, brakes; present in wide range of building/infrastructure materials including cement pipes, roofing, flooring, and insulation	Designated as "known to be a human carcinogen" (NTP)
Carbon tetrachloride ^d /56-23-5	Uses include industrial and commercial processes such as chemical manufacturing; water and indoor air contaminant	Designated "likely to be carcinogenic to humans" (EPA); liver, kidney toxicity
Cyclic aliphatic bromide cluster (HBDC) ^e /25637-99-4	Uses include flame retardant in plastics, electronic cases, wire and cables, building insulation, textiles for furniture and floors; indoor air and dust contaminant	Reproductive/developmental toxicity; developmental neurotoxicity; thyroid toxicity
Methylene chloride (Dichloromethane, DCM) ^f /75-09-2	Uses include as solvent in industrial and commercial processes for cleaning and degreasing; consumer products including paint strippers and adhesives; air emissions from industrial and commercial facilities; drinking-water contaminant	Designated "likely to be carcinogenic to humans" (EPA); acute toxicity; neurotoxicity
N-Methyl-pyrrolidone (NMP) ^g / 872-50-4	Uses include as solvent in industrial and commercial processes for cleaning and degreasing; consumer products including paint strippers, adhesives, and printer inks; air emissions from industrial and commercial facilities; drinking-water contaminant	Reproductive/ developmental toxicity; systemic toxicity
Pigment Violet 29 (Anthra [2,1,9-def:6,5,10-d'e'f]diisoquinoline-1,3,8,10 [2H,9H]-tetrone) ^h / 81-33-4	Uses include in industrial and commercial plastics, rubber, paints, coatings; printing inks; consumer water and acrylic paints	Limited industry-sponsored guideline studies available with sponsors concluding lack of toxicity
Trichloroethylene (TCE) ⁱ / 79-01-6	Uses include as solvent in industrial and commercial processes for cleaning and degreasing; consumer products including adhesives, carpet cleaners, and spot removers; air emissions from industrial and commercial facilities; indoor air and drinking-water contaminant	Designated "carcinogenic to humans" (EPA); reproductive/ developmental toxicity; neurotoxicity; immunotoxicity
Tetrachloroethylene (perchloroethylene, PERC) ^j / 127-18-4	Uses include as solvent in industrial and commercial processes for dry cleaning and degreasing; consumer products including adhesives, cleaners, and spot removers; air emissions from industrial and commercial facilities; indoor air and drinking-water contaminant	Designated "likely to be carcinogenic to humans" (EPA); reproductive/developmental toxicity; neurotoxicity

^aUS EPA (2018) Problem Formulation of the Risk Evaluation for 1,4-Dioxane; US EPA (2017) Scope of the Risk Evaluation for 1,4-Dioxane.

^bUS EPA (2018) Problem Formulation of the Risk Evaluation for 1-Bromopropane; US EPA (2017) Scope of the Risk Evaluation for 1-Bromopropane.

^cUS EPA (2018) Problem Formulation of the Risk Evaluation for Asbestos; US EPA (2017) Scope of the Risk Evaluation for Asbestos.

^dUS EPA (2018) Problem Formulation of the Risk Evaluation for Carbon Tetrachloride (Methane, Tetrachloro-); US EPA (2017) Scope of the Risk Evaluation for Carbon Tetrachloride (Methane, Tetrachloro-).

^eUS EPA (2018) Problem Formulation of the Risk Evaluation for Cyclic Aliphatic Bromides Cluster (HBDC); US EPA (2017) Scope of the Risk Evaluation for Cyclic Aliphatic Bromides Cluster.

^fUS EPA (2018) Problem Formulation of the Risk Evaluation for Methylene Chloride (Dichloromethane, DCM); US EPA (2017) Scope of the Risk Evaluation for Methylene Chloride (Dichloromethane, DCM).

^gUS EPA (2018) Problem Formulation of the Risk Evaluation for N-Methylpyrrolidone (2-Pyrrolidinone, 1-Methyl-); US EPA (2017) Scope of the Risk Evaluation for N-Methylpyrrolidone (2-Pyrrolidinone, 1-Methyl-).

^hUS EPA (2018) Problem Formulation of the Risk Evaluation for C.I. Pigment Violet 29 (Anthra[2,1,9-def:6,5,10-d'e'f]diisoquinoline- 1,3,8,10(2H,9H)-tetrone); US EPA (2017) Scope of the Risk Evaluation for C.I. Pigment Violet 29 (Anthra[2,1,9-def:6,5,10-d'e'f]diisoquinoline- 1,3,8,10(2H,9H)-tetrone).

ⁱUS EPA (2018) Problem Formulation of the Risk Evaluation for Trichloroethylene; US EPA (2017) Scope of the Risk Evaluation for Trichloroethylene.

^jUS EPA (2018) Problem Formulation of the Risk Evaluation for Perchloroethylene (Ethene, 1,1,2,2-Tetrachloro); US EPA (2017) Scope of the Risk Evaluation for Perchloroethylene (Ethene, 1,1,2,2-Tetrachloro).

Abbreviations: CASRN, Chemical Abstracts Services registry number; EPA, US Environmental Protection Agency; Lautenberg TSCA, 2016 Frank Lautenberg Chemical Safety for the 21st Century Act; NTP, National Toxicology Program

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articulates scientific standards: "to the extent that the [U.S. EPA] Administrator makes a decision based on science, the Administrator shall use scientific information, technical procedures,

measures, methods, protocols, methodologies, or models, employed in a manner consistent with the best available science” (15 USC §2625 [h]) [39]. In this context, we discuss scientific risk assessment principles necessary to meet legal requirements to safeguard the health of susceptible and highly exposed populations under Lautenberg TSCA. These principles are articulated in *Science and Decisions* and other documents and based on current scientific understanding of chemical exposures and biological and health effects [15,40–42] (Table 2). These provisions are consistent with the significant agreement among the public health community that US chemical policy should reflect contemporary science and provide public health protection, especially for susceptible and highly exposed groups [43–45].

Although Lautenberg TSCA introduced some potential improvements, implementation of the law leaves critical decisions to EPA [45]. Lautenberg TSCA requires that EPA determine to what extent chemicals pose an “unreasonable risk” to health based solely on scientific data and irrespective of compliance costs. It also requires that EPA ensures chemical uses do not pose an “unreasonable risk” to susceptible and highly exposed populations, such as pregnant women, children, workers, and the elderly. However, the amended law does not require chemical manufacturers to provide a minimum set of data on health risks and exposure for susceptible and highly exposed groups. Furthermore, Lautenberg TSCA did not fully define unreasonable risk, and EPA must develop an operational definition as well as its specific risk evaluation and decision-making processes. Thus, EPA must determine the details of how to collect and assess scientific evidence for determining risks and what information to require from manufacturers or its own research to meet statutory requirements. In implementing Lautenberg TSCA, EPA will set precedents for the type of scientific data necessary to collect and the assessment of susceptible populations and exposures across its current and future risk evaluation decisions. This process is occurring primarily through two steps: (1) general provisions in the final “framework rules” (Risk Prioritization: July 20, 2017 [FR 33753][FRL–9964–24], Risk Evaluation: July 20, 2017 [FR 33726][FRL–9964–38]) [53,54] and (2) each specific chemical risk evaluation.

Public health protection will be heavily dependent on these federal decisions because Lautenberg TSCA includes new state preemption provisions—meaning that states are precluded from taking further action once EPA determines that a chemical does not pose an unreasonable risk or when EPA takes final action in the risk management phase (Public Law No. 114–182) [33]. New state action is paused during EPA’s risk evaluation of high-priority chemicals.

In Table 2, we recommend scientific principles EPA should incorporate to assure adequate assessments of susceptible and highly exposed populations to support health-protective chemical policy as required by law. In the next sections, we analyze EPA decisions to date (as of June 2019) with a focus on susceptibility and exposure considerations that are now required under Lautenberg TSCA. We acknowledge there are many other factors contributing to risk, including cumulative impacts, timing of exposures during sensitive periods of human development, and uncertainty in the data (see Table 2).

Population susceptibility

As shown in Fig 1, population variability in susceptibility and coexposures combine to determine biological response to chemical exposure [55]. To accurately identify subpopulations at greater risk, EPA’s analysis must incorporate the current scientific understanding of factors that contribute to greater susceptibility and to greater or more impactful exposures. These include intrinsic factors (e.g., life stage, genetics, underlying disease status, nutrition), extrinsic factors (e.g., social and life circumstances such as poverty and life stress), and exposures to other chemicals (Fig 1) [15,56].

Table 2. Recommendations for US EPA to support scientifically based health-protective chemical policy considering susceptible and highly exposed populations.

Recommendations for primary prevention	
Support the strongest protections for human health, especially regarding susceptible and highly exposed populations, in EPA's interpretation of the legal requirements of Lautenberg TSCA. Environmental exposures to harmful industrial chemicals are a preventable source of adverse health consequences [18,46].	
Vulnerable populations	Identify and assess aggregate exposures to susceptible and highly exposed populations including but not limited to children, pregnant women, elderly, workers (including people planning families), and fenceline communities as required by law (Fig 1) [15,47,48]. Improve the basis of accounting for variability and susceptibility across the population by identifying potential susceptible populations based on established, scientifically supported extrinsic and intrinsic factors that increase vulnerability [41,49].
Aggregate exposure	Account for aggregate exposures—people's exposures to the same chemical from all uses and through multiple exposure pathways (such as air, water, food, dermal contact), including all pathways that can be reasonably anticipated [15,41,50].
Health-protective defaults	Given limited data for a particular chemical or exposure, when necessary data cannot be developed in a timely way, use evidence-based health-protective defaults that reflect the range of variability and susceptibility in the population to ensure risks are not underestimated (e.g., child-specific defaults, pregnancy defaults) [15,42].
Windows of susceptibility	Identify and evaluate timing of "windows of susceptibility" to toxic chemicals during development or other sensitive life stages [51]. Ensure adequate data and/or defaults to assess and address the timing of these impacts.
Cumulative exposure and risk	Account for populations' simultaneous exposure to a multitude of different chemicals and social stressors in the real world, many of which contribute to similar adverse health effects resulting in increased risk (cumulative risks, see Fig 1) [15, 52].
Uncertainty	Appropriately characterize uncertainty by developing and further integrating monitoring, measurement, and modeling efforts and communicating levels of confidence to support decision-making [15]. Ensure sufficient data to characterize factors that influence uncertainty in the risk evaluations.

Abbreviations: EPA, US Environmental Protection Agency; Lautenberg TSCA, 2016 Frank Lautenberg Chemical Safety for the 21st Century Act

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Unfortunately, in its assessment plans for the first 10 chemicals (as of June 2019), EPA has not yet incorporated these established, scientifically supported intrinsic and extrinsic factors that increase susceptibility or exposure [57]. For eight of the first 10 evaluations (i.e., perchloroethylene; asbestos; trichloroethylene; N-Methyl-pyrrolidone [NMP]; methylene chloride; carbon tetrachloride; 1,4-dioxane; and pigment violet 29), EPA does not currently identify pregnant women, infants, children, families living near current and former industrial sites, or any other potentially highly exposed or susceptible subpopulation under the amended TSCA (as of June 2019) [58–66]. For example, the prenatal life stage can be the most sensitive to developmental and reproductive toxicants [8,21], and people of child-bearing age are a susceptible subpopulation for chemicals with such hazards [67], such as trichloroethylene. EPA's Integrated Risk Information System (IRIS) assessment of trichloroethylene concluded that toxicity to the developing fetus was one of the most sensitive observed adverse effects [68]; however, EPA's TSCA risk evaluation omits this consideration.

For many industrial chemicals, there is ample evidence from the literature and IRIS assessments of increased susceptibility due to age, life stage, preexisting disease, genetic variation, and many other factors that should be incorporated into the TSCA evaluations [29–31,68–71]. In general, populations with these and other established factors should be considered a susceptible population for each chemical, unless there are chemical-specific data showing otherwise.

Science and Decisions recommends that risk assessments should quantitatively incorporate factors like susceptibility that influence the likelihood of disease and, when specific data are lacking, incorporate scientifically based default values in their assessments [15,49]. For

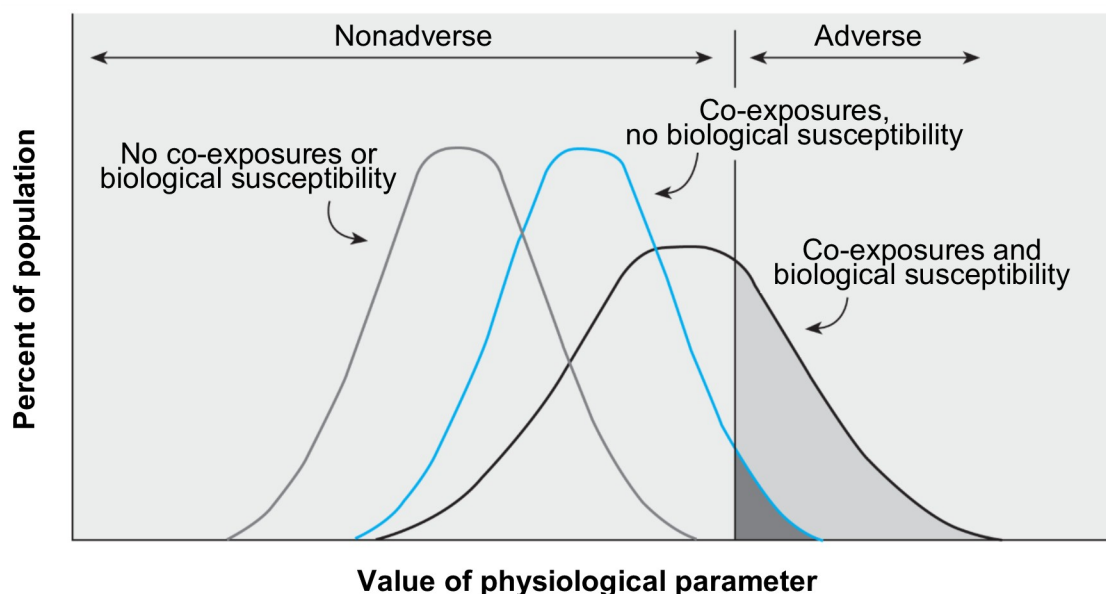


Fig 1. How coexposures to other chemical stressors and variability in biological susceptibility combine to influence population risk. Figure reproduced with permission from Environmental Health Perspectives [55].

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example, the California EPA developed risk values for chemicals (e.g., atrazine, chlorpyrifos, lead, nickel, manganese) that address child-specific routes of exposure and differences in children's susceptibility compared to adults [72]. For cancer, *Science and Decisions* recommended 25 as a reasonable default value to include in the calculation of risk to account for the population variability in response to chemical exposure between the median individual and those with more extreme responses [15]. Because the scientific basis for these defaults is already developed, EPA could easily integrate them into assessments. If EPA fails to incorporate established science to adequately identify and assess susceptible and highly exposed groups, the resulting risk determinations will underestimate risk of a chemical and fail to protect public health, as required by law.

Highly exposed populations

Established scientific principles for exposure assessment, including from EPA guidance documents, recognize the importance of including aggregate exposures to accurately detect highly exposed populations [43,50,56]. Aggregate exposure is defined as the combined exposures to an individual from a single chemical substance from all uses and across multiple pathways (such as air, water, food, dermal contact). However, EPA's statements in the first 10 chemical problem formulations and framework rules indicate that it will not conduct full aggregate assessments; instead, EPA plans to consider exposure pathways in isolation and will separate and narrow which chemical uses will be included (called "conditions of use") (see Table 1 references). These decisions systematically underestimate risk. Specifically, this approach could miss populations with greater exposures by excluding contemporary exposures from past common chemical uses (e.g., asbestos in buildings and flame-retardant chemicals in furniture, textiles, and electronics); reasonably foreseeable ongoing chemical uses contaminating land, air, and water; and uses for which a chemical is present unintentionally as a contaminant or by-product.

For instance, regarding previously common uses of the flame-retardant cyclic aliphatic bromide cluster (hexabromocyclododecane, HBCD), EPA states, “There is no longer manufacture, processing or distribution of HBCD for [high-impact polystyrene] HIPS or textiles; and therefore, those uses are not included in the scope of the risk evaluation of HBCD” [62]. HBCD was used as an additive flame retardant in HIPS casing for electronics such as TVs, DVD players, and computers. The number of home electronics has been correlated with the amount of HBCD on people’s hands (an exposure metric used to estimate dermal absorption and hand-to-mouth ingestion), indicating that flame retardant use in home electronics is a significant current source of exposure for the general population [73]. An exposure calculation excluding this ongoing source would underestimate exposure to HBCD. Furthermore, because of increased hand-to-mouth activities, toddlers and young children, a potential susceptible subpopulation, can have greater exposures to environmental chemicals compared to adults because of their behaviors and physiological differences [48,74–77]. EPA’s draft risk evaluations systematically exclude previously common uses of chemicals (which EPA calls “legacy” uses) (see [62] and EPA Risk Evaluation final rule: July 20, 2017 [FR 33726][FRL–9964–38] [54]) despite ongoing exposures.

Accurate assessment of aggregate exposure is important because it can reveal risks to susceptible populations that would be missed if only a single exposure source was considered. This is illustrated by EPA’s 2005 risk assessment of the pesticide sulfuryl fluoride (67 FR 5740, February 7, 2002, as amended at 69 FR 3257, January 23, 2004; 70 FR 40908, July 15, 2005, Title 40, Chapter I subpart E, Part 180 Subpart C, Sect. 180.575) [78–80]. With an aggregate exposure assessment, EPA concluded that most people in the US are not exposed to unsafe levels of fluoride, yet “aggregate fluoride exposure for infants and children under the age of 7 years old, where drinking water contains high levels of natural fluoride, exceeds the level that can cause severe dental fluorosis” [81]. Had EPA only considered the risk from fluoride residues contributed by sulfuryl fluoride in isolation, its assessment would not have identified the existing risks to infants and children, a susceptible population (76 *Federal Register* 3421 [January 19, 2011]) [82]. Thus, aggregate exposure assessment of all sources and pathways is critical for EPA to accurately identify the populations most at risk. Note that although pesticides are excluded from TSCA, this example demonstrates an appropriate evaluation of aggregate exposure that can be applied to any chemical.

Conclusions

Much is at stake for the public’s health and the role of science in decision-making with Lautenberg TSCA implementation. EPA’s decisions over the next several years will influence the level of toxic chemicals in our homes, communities, and bodies. Exposures to industrial chemicals and their harmful health consequences are preventable. If current levels of exposure to chemicals continue unabated, the consequences will be an even greater toxic legacy for future generations, especially for susceptible and highly exposed populations. For eight of the first 10 risk evaluations (as of June 2019), EPA does not identify pregnant women, infants, children, families living near current and former industrial sites, or any other potentially highly exposed or susceptible subpopulation. For all regulated chemicals, EPA must act quickly to identify susceptible and highly exposed populations, evaluate risks, and safeguard health through primary prevention. The challenge ahead for EPA is to incorporate current scientific principles and address the data deficits in the process of identifying, evaluating, and mitigating unreasonable risks. By adopting these recommendations regarding susceptibility and exposure, EPA will ensure that it is accounting for risks to the whole population and thus set the stage for risk management that yields widespread public health benefits.

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Appendix B: Analysis of revised TSCA Systematic Review data quality criteria for epidemiological studies.

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Metrics	Old Language	New Language	Implications
Metric 1: Participant Selection	<ul style="list-style-type: none"> High: For all study types: All key elements of the study design are reported (i.e., setting, participation rate described at all steps of the study, inclusion and exclusion criteria, and methods of participant selection or case ascertainment) <p>AND</p> <p>The reported information indicates that selection in or out of the study (or analysis sample) and participation was not likely to be biased (i.e., the exposure-outcome distribution of the participants is likely representative of the exposure-outcome distributions in the overall population of eligible persons.)</p> <ul style="list-style-type: none"> Medium: For all study types: Some key elements of the study design were not present but available information indicates a low risk of selection bias (i.e., the exposure-outcome distribution of the participants is likely representative of the exposure-outcome distributions in the overall population of eligible persons.) Low: For all study types: Key elements of the study design and information on the comparison group (i.e., setting, participation rate described at most steps of the study, inclusion and exclusion criteria, and methods of participant selection or case ascertainment) are not reported [STROBE checklist 4, 5 and 6] Unacceptable: For all study types: The reported information indicates that selection in or out of the study (or analysis sample) and participation was likely to be significantly biased (i.e., the exposure-outcome distribution of the participants are likely not representative of the exposure-outcome distributions in the overall population of eligible persons.) 	<ul style="list-style-type: none"> No Substantive Changes 	Studies can still be scored low for reporting reasons.
Metric 2: Attrition	<ul style="list-style-type: none"> To Score High: "outcome data were largely complete" To Score Low: 	<ul style="list-style-type: none"> To Score High: "outcome and exposure data were largely complete" <ul style="list-style-type: none"> One "OR" has been changed to "AND" in the set of requirements for a cohort 	EPA removed references to the STROBE guidelines and no longer allows a study to be excluded on reporting grounds (though it can still be scored Unacceptable for substantive reasons relevant to this metric)

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	<ul style="list-style-type: none"> • Cohort studies: “There was large subject attrition during the study (or exclusion from the analysis sample)” • Case-control and cross-sectional studies: “There was large subject withdrawal from the study (or exclusion from the analysis sample)” • To Score Unacceptable: <ul style="list-style-type: none"> • For cohort studies: The loss of subjects (i.e., incomplete outcome data) was large and unacceptably handled (as described above in the low confidence category) (Source: OHAT). OR Numbers of individuals were not reported at important stages of study (e.g., numbers of eligible participants included in the study or analysis sample, completing follow-up, and analyzed). Reasons were not provided for non-participation at each stage [STROBE Checklist Item 13 (Von Elm et al., 2008)]. • For case-control and cross-sectional studies: The exclusion of subjects from analyses was large and unacceptably handled (as described above in the low confidence category). OR Reasons were not provided for non-participation at each stage [STROBE Checklist Item 13] 	<p>study to score High (seems like this may just be correcting an error in the original criteria – see. P. 234 in original SR doc)</p> <ul style="list-style-type: none"> • To Score Low: <ul style="list-style-type: none"> • Cohort studies: The loss of subjects...was moderate and unacceptably handled. • Case-control and cross-sectional studies: The exclusion of subjects from analyses was moderate and unacceptably handled. • To Score Unacceptable: <ul style="list-style-type: none"> • Exactly the same as the previous description for a score of Low, meaning that a study that would previously score Low would now be scored Unacceptable. • Description for Unacceptable score has dropped all references to the STROBE checklist. 	
Metric 3: Comparison Group	<ul style="list-style-type: none"> • To Score Unacceptable: <ul style="list-style-type: none"> ○ For Cohort Studies: “Subjects in all exposure groups were not similar, recruited within very different time frames, or had the very different participation/response rates (NTP, 2015a).” ○ For Case-Control Studies: “Controls were drawn from a very dissimilar population than cases or recruited within very different time frames (NTP, 2015a).” 	<ul style="list-style-type: none"> • To Score Unacceptable: <ul style="list-style-type: none"> ○ For Cohort Studies: “Subjects in all exposure groups were not similar. Potential differences in exposure groups [or case and control groups, depending on study type] were not controlled for in the statistical analysis. OR Subjects in the exposure groups had very 	<p>EPA kept STROBE references, but added an additional requirement to be scored Unacceptable: "Potential differences in exposure groups [or case and control groups, depending on study type] were not controlled for in the statistical analysis"</p> <p>We still disagree with the ‘unacceptable/ fatal flaw’ approach.</p>

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	<ul style="list-style-type: none"> ○ For Cross-sectional Studies: “Subjects in all exposure groups were not similar, recruited within very different time frames, or had the very different participation/response rates (NTP, 2015a).” 	<p>different participation/response rates (NTP, 2015).”</p> <ul style="list-style-type: none"> ○ Added additional guidance for studies reporting standardized mortality ratios (SMRs) or standardized incidence ratios (SIRs) ○ Modified and added additional requirements for Unacceptable score. References to STROBE checklist 6 remain. ○ For case-control studies: ○ Added an additional requirement to be scored Unacceptable: “Potential differences in the case and control groups were not controlled for in the statistical analysis.” ○ For cross-sectional studies: ○ Added an additional requirement to be scored Unacceptable: “Potential differences in exposure groups were not controlled for in the statistical analysis.” 	
Metric 4: Measurement of Exposure	<ul style="list-style-type: none"> ● To Score High: <ul style="list-style-type: none"> ○ “Exposure was consistently assessed (i.e., under the same method and time-frame) using well-established methods (e.g., personal and/or industrial hygiene data used to determine levels of exposure, a frequently used biomarker of exposure) that directly measure exposure (e.g., measurement of the chemical in the environment (air, drinking water, consumer product, etc.) or measurement of the chemical concentration in a biological matrix such as blood, plasma, urine, etc.) (NTP, 2015a). “ 	<ul style="list-style-type: none"> ● To Score High: <ul style="list-style-type: none"> ○ Added: Study/source must contain detailed employment records which allow for construction of a job-matrix for entire work history of exposure (i.e. cumulative or peak exposures, and time since first exposure) ● To Score Medium: <ul style="list-style-type: none"> ○ Added: “Source contains detailed employment records for only a 	The criteria added to ensure that a study scores high is quite restrictive.

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	<ul style="list-style-type: none"> • To Score Medium: <ul style="list-style-type: none"> ○ “Exposure was directly measured and assessed using a method that is not well-established (e.g., newly developed biomarker of exposure), <i>but</i> is validated against a well-established method and demonstrated a high agreement between the two methods. “ • To Score Low: <ul style="list-style-type: none"> ○ “A less-established method (e.g., newly developed biomarker of exposure) was used and no method validation was conducted against well-established methods, but there was little to no evidence that the method had poor validity and little to no evidence of significant exposure misclassification (e.g., differential recall of self-reported exposure) (Source: OHAT).” • To Score Unacceptable: <ul style="list-style-type: none"> ○ “Exposure variables were not well defined, and sources of data and detailed methods of exposure assessment were not reported [STROBE Checklist 7 and 8 (Von Elm et al., 2008)]. OR Exposure was assessed using methods known or suspected to have poor validity (Source: OHAT). OR There is evidence of substantial exposure misclassification that would significantly alter results.” 	<p>portion of participant's work history (i.e. only early years or later years), such that extrapolation of the missing years is required.</p> <ul style="list-style-type: none"> • To Score Low: <ul style="list-style-type: none"> ○ Added: Exposure was estimated solely using professional judgement. • Unacceptable score description did not change. 	
Metric 5: Exposure Levels	<ul style="list-style-type: none"> • Studies could only be scored High or Unacceptable (scoring document specifically said for Medium and Low, "Do not select for this metric"). • To Score High: <ul style="list-style-type: none"> ○ The levels of exposure are sufficient* or adequate to detect an effect of exposure {Cooper, 2016, 3121908}. * Sufficient or adequate for cohort and cross-sectional studies includes the reporting of at least 2 levels of exposure (referent group + 1 or more exposure groups) (Cooper) that capture exposure spatial and temporal variability within the study population (Source: IRIS). 	<ul style="list-style-type: none"> • Now, studies cannot score High, but can score Medium, Low, or Unacceptable. • To Score Medium: <ul style="list-style-type: none"> ○ Range and distribution of exposure is sufficient or adequate to develop an exposure-response estimate AND the study reports 3 or more levels of exposure or an exposure-response model (previously, to score High, this was worded as "sufficient or adequate to detect an effect of exposure") 	Now, cannot score as high and the criteria for medium scoring are much more involved.

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	<ul style="list-style-type: none"> • To Score Unacceptable: <ul style="list-style-type: none"> ○ “The levels of exposure are not sufficient or adequate to detect an effect of exposure OR No description is provided on the levels or range of exposure.” 	<ul style="list-style-type: none"> ○ EPA has now appears to have upped the ante with “sufficient or adequate” defined as requiring “3 or more levels of exposure (i.e., referent group and 2 or more)...” to score <u>Medium</u>. • To Score Low: <ul style="list-style-type: none"> ○ Range of exposure in the population is limited OR the study reports 2 levels of exposure (e.g. exposed/unexposed) • To Score Unacceptable: <ul style="list-style-type: none"> ○ Range and distribution of exposure are not adequate to determine an exposure-response relationship OR no description is provided on the levels or range of exposure 	
Metric 6: Temporality	<ul style="list-style-type: none"> • To Score Unacceptable: <ul style="list-style-type: none"> ○ Study lacks an established time order, such that exposure is not likely to have occurred prior to outcome (Lakind et al., 2014). OR Exposures clearly fell outside of relevant exposure window for the outcome of interest. OR For each variable of interest (outcome and predictor), sources of data and details of methods of assessment were not reported (e.g. periods of exposure, dates of outcome ascertainment, etc.) [STROBE Checklist 8] 	<ul style="list-style-type: none"> • To Score Unacceptable Added: <ul style="list-style-type: none"> ○ There was inadequate follow-up of the cohort for the expected latency period. ○ Also changed "sources of data and details of methods of assessment were not reported" to "were not sufficiently reported" 	EPA changed “not reported” to “not sufficiently reported” to receive a score of Unacceptable. (Unsure, but based on sufficiency may lead to more epidemiological studies being binned as unacceptable instead of low.)
Metric 7: Outcome Measurement or Characterization	<ul style="list-style-type: none"> • To Score High: <ul style="list-style-type: none"> ○ For cohort studies: The outcome was assessed using well-established methods (e.g., the “gold standard”) AND Subjects had been followed for the same length of time in all study groups. ○ For case-control studies: The outcome was assessed in cases (i.e., case definition) and controls using well-established methods (the 	<ul style="list-style-type: none"> • Removed requirement that subjects had been followed for the same length of time in all study groups. 	

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	<p>gold standard). AND Subjects had been followed for the same length of time in all study groups.</p> <ul style="list-style-type: none"> ○ For cross-sectional studies: There is direct evidence that the outcome was assessed using well-established methods (the gold standard) (NTP, 2015a). 		
Metric 8: Reporting Bias		<ul style="list-style-type: none"> • No Significant Changes. 	
Metric 9: Covariate Adjustment		<ul style="list-style-type: none"> • Added additional guidance for studies reporting SMRs or SIRs 	
Metric 10: Covariate Characterization	<ul style="list-style-type: none"> • To Score High: <ul style="list-style-type: none"> ○ Primary covariates (excluding co-exposures) and confounders were assessed using valid and reliable methodology (e.g., validated questionnaires, biomarker). • To Score Medium: <ul style="list-style-type: none"> ○ A less-established method was used and no method validation was conducted against well-established methods, but there was little to no evidence that that the method had poor validity and little to no evidence of confounding. • To Score Low: <ul style="list-style-type: none"> ○ The primary covariate (excluding co-exposures) and confounder assessment method is an insensitive instrument or measure or a method of unknown validity. • To Score Unacceptable: <ul style="list-style-type: none"> ○ Primary covariates (excluding co-exposures) and confounders were not assessed. 	<ul style="list-style-type: none"> • Removed mentions of "covariates" - all score descriptions now mention only "confounders" when previously they included both terms 	This change seems alright.
Metric 11: Co-Exposure confounding/Moderation/Mediation	<ul style="list-style-type: none"> • Originally this metric could only be scored High or Unacceptable. • To Score High: <ul style="list-style-type: none"> ○ For all study types: Any co-exposures to pollutants that are not the target exposure that would likely bias the results were not present OR Co-exposures to pollutants were appropriately measured and adjusted for. • To Score Unacceptable: 	<ul style="list-style-type: none"> • EPA has now changed this so that studies can only be scored Medium or Low for this metric. 	<p>Cannot score High, also cannot score unacceptable.</p> <p>A study that would previously be scored High would now be Medium; a study that would have scored Unacceptable would now be Low. The descriptions are identical to the original ones, just shifted to the new score.</p>

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	<ul style="list-style-type: none"> ○ For cohort and cross-sectional studies: There is direct evidence that there was an unbalanced provision of additional co-exposures across the primary study groups, which were not appropriately adjusted for. ○ For case-control studies: There is direct evidence that there was an unbalanced provision of additional co-exposures across cases and controls, which were not appropriately adjusted for, and significant indication a biased exposure-outcome association. 		
Metric 12: Study Design and Metrics	<ul style="list-style-type: none"> • Studies can only score High or Unacceptable • To Score High: <ul style="list-style-type: none"> ○ For all study types: The study design chosen was appropriate for the research question (e.g. assess the association between exposure levels and common chronic diseases over time with cohort studies, assess the association between exposure and rare diseases with case-control studies, and assess the association between exposure levels and acute disease with a cross-sectional study design) AND The study uses an appropriate statistical method to address the research question(s) (e.g., repeated measures analysis for longitudinal studies, logistic regression analysis for case-control studies). • To Score Unacceptable: <ul style="list-style-type: none"> ○ For all study types: The study design chosen was not appropriate for the research question OR Inappropriate statistical analyses were applied to assess the research questions. 	<ul style="list-style-type: none"> • The original description for High is now the description for Medium (studies can now only be scored Medium or Unacceptable) 	EPA is unilaterally making it more difficult for epi studies to score High on the quality metrics.
Metric 13: Statistical Power	<ul style="list-style-type: none"> • To Score High: <ul style="list-style-type: none"> ○ For cohort and cross-sectional studies: The number of participants are adequate to detect an effect in the exposed population and/or subgroups of the total population OR The paper 	<ul style="list-style-type: none"> • Original description for High is now the description for Medium, everything else is the same. Studies can only score Medium or Unacceptable now. 	EPA is unilaterally making it more difficult for epi studies to score High on the quality metrics.

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	<p>reported statistical power high enough ($\geq 80\%$) to detect an effect in the exposure population and/or subgroups of the total population.</p> <ul style="list-style-type: none"> ○ For case-control studies: The number of cases and controls are adequate to detect an effect in the exposed population and/or subgroups of the total population OR The paper reported statistical power was high ($\geq 80\%$) to detect an effect in the exposure population and/or subgroups of the total population. ● To Score Unacceptable: <ul style="list-style-type: none"> ○ For cohort and cross-sectional studies: The number of participants are inadequate to detect an effect in the exposed population and/or subgroups of the total population. ○ For case-control studies: The number of cases and controls are inadequate to detect an effect in the exposed population and/or subgroups of the total population. 		
Metric 14: Reproducibility of Analyses	<ul style="list-style-type: none"> ● You can only score high or low. ● To Score High: <ul style="list-style-type: none"> ○ The description of the analysis is sufficient to understand precisely what has been done and to be reproducible. ● To Score Low: <ul style="list-style-type: none"> ○ The description of the analysis is insufficient to understand what has been done and to be reproducible OR a description of analyses are not present (e.g., statistical tests and estimation procedures were not described, variables used in the analysis were not listed, transformations of continuous variables (such as logarithm) were not explained, rules for categorization of continuous variables were not presented, deleting of outliers were not elucidated and how 	<ul style="list-style-type: none"> ● Original description for High is now description for Medium. Studies can only be scored Medium or Low now. ● To Score Medium: <ul style="list-style-type: none"> ○ The description of the analysis is sufficient to understand precisely what has been done and to be conceptually reproducible with access to the analytic data. 	<p>EPA unilaterally making it more difficult for epi studies to score High on the quality metrics.</p> <p>EPA has changed the scoring for this metric so that it can no longer be scored High, only Medium or Low. The previous description for High is now the description for Medium, with slight revisions; it now reads, "The description of the analysis is sufficient to understand precisely what has been done and to be conceptually reproducible with access to the analytic data."</p>

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	missing values are dealt with was not mentioned).		
Metric 15: Statistical Methods	<ul style="list-style-type: none"> Can only be scored high or low. To Score High: <ul style="list-style-type: none"> For all study types: The statistical model building process is transparent (it is stated how/why variables were included or excluded from the multivariate model) AND model assumptions were met. To Score Low: <ul style="list-style-type: none"> For all study types: The statistical model building process is not transparent OR it is not stated how/why variables were included or excluded from the multivariate model OR model assumptions were not met OR a description of analyses are not present OR no sensitivity analyses are described OR model assumptions were not discussed [STROBE Checklist 12e (Von Elm et al., 2008)]. 	<ul style="list-style-type: none"> Original description for High is now the description for Medium and studies can only score Medium or Low. 	EPA unilaterally making it more difficult for epidemiological studies to score High on the quality metrics.
Metric 16: Use of Biomarker of Exposure		<ul style="list-style-type: none"> No Significant Changes 	EPA inappropriately applies an adverse outcome pathway (AOP) standard to effect biomarkers.
Metric 17: Effect Biomarker		<ul style="list-style-type: none"> No substantive changes; minor clarification to description for High 	EPA inappropriately applies an adverse outcome pathway (AOP) standard to effect biomarkers.
Metric 18: Method Sensitivity	<ul style="list-style-type: none"> Can only be scored as High or Unacceptable. To Score High: <ul style="list-style-type: none"> Limits of detection are low enough to detect chemicals in a sufficient percentage of the samples to address the research question. To Score Unacceptable: 	<ul style="list-style-type: none"> Changed and now can only score Medium or Low. Description for High is now description for Medium; also added requirement that LOD and LOQ are reported to be scored Medium. 	Studies cannot be given scores of high or unacceptable, only medium or low.

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	<ul style="list-style-type: none"> ○ Frequency of detection too low to address the research hypothesis OR LOD/LOQ (value or %) are not stated. 		
Metric 19: Biomarker Stability	<ul style="list-style-type: none"> • Can only be scored High Low or Unacceptable. • To Score High: <ul style="list-style-type: none"> ○ Samples with a known history and documented stability data or those using real-time measurements. • To Score Low: <ul style="list-style-type: none"> ○ Samples have known losses during storage, but the difference between low and high exposures can be qualitatively assessed. • To Score Unacceptable: <ul style="list-style-type: none"> ○ Samples with either unknown storage history and/or no stability data for target analytes and high likelihood of instability for the biomarker under consideration. 	<ul style="list-style-type: none"> • Original descriptions for Low and Unacceptable have been bumped up to describe Medium and Low, so a study can no longer be scored Unacceptable. 	Studies cannot be given scores of Unacceptable. EPA inappropriately applies an adverse outcome pathway (AOP) standard to effect biomarkers.
Metric 20: Sample Contamination		<ul style="list-style-type: none"> • No Significant Changes 	
Metric 21: Method Requirements	<ul style="list-style-type: none"> • Can only be scored High, Low, or Unacceptable. • To Score High: <ul style="list-style-type: none"> ○ Instrumentation that provides unambiguous identification and quantitation of the biomarker at the required sensitivity (e.g., GC–HRMS, GC–MS/MS, LC–MS/MS). • To Score Low: <ul style="list-style-type: none"> ○ Instrumentation that allows for identification of the biomarker with a high degree of confidence and the required sensitivity (e.g., GC–MS, GC–ECD). • To Score Unacceptable: <ul style="list-style-type: none"> ○ Instrumentation that only allows for possible quantification of the biomarker, but the method has known interferants (e.g., GC–FID, spectroscopy). 	<ul style="list-style-type: none"> • Previously could not be scored Medium; now original descriptions for Low and Unacceptable have been bumped up to describe Medium and Low, so a study can no longer be scored Unacceptable 	Studies cannot be given scores of Unacceptable

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<p>Metric 22: Matrix Adjustment</p>	<ul style="list-style-type: none"> • Can only be scored High, Low, and Unacceptable. • To Score High: <ul style="list-style-type: none"> ○ If applicable for the biomarker under consideration, study provides results, either in the main publication or as a supplement, for adjusted and unadjusted matrix concentrations (e.g., creatinine-adjusted or SG-adjusted and non-adjusted urine concentrations) and reasons are given for adjustment approach. • To Score Low: <ul style="list-style-type: none"> ○ If applicable for the biomarker under consideration, study only provides results using one method (matrix-adjusted or not). • To Score Unacceptable: <ul style="list-style-type: none"> ○ If applicable for the biomarker under consideration, no established method for matrix adjustment was conducted. 	<ul style="list-style-type: none"> • Previously could not be scored Medium; now original descriptions for Low and Unacceptable have been bumped up to describe Medium and Low, so a study can no longer be scored Unacceptable 	<p>Studies cannot be given scores of Unacceptable</p>
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