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Comments from Scientists, Academics, and Clinicians on the Draft Risk Evaluations for 1,1-Dichloroethane and 1,2-Dichloroethane Under TSCA

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

We appreciate the opportunity to provide written comments on EPA's Draft Risk Evaluation for 1,1-dichloroethane, (hereafter referred to as the *1,1-DCA Draft Risk Evaluation*) and the Draft Human Health Hazard Assessments for 1,2-dichloroethane (hereafter referred to as the *1,2-DCA Draft Hazard* Assessment) conducted under the Toxic Substances Control Act ("TSCA"), which requires EPA to evaluate chemical risks based on the "best available science."[1] 1,1-DCA and 1,2-DCA are associated with serious health harms, and billions of pounds of both chemicals are manufactured in the US each year. 1,1-DCA is primarily used as an industrial and commercial solvent to make other chlorinated solvents used in industrial applications. 1,2-DCA, while structurally similar, is primarily used to manufacture vinyl chloride, a precursor to polyvinyl chloride plastic. For 1,1-DCA alone, the total reported production volume in 2020 from just two corporations was between 100 million and 1 billion pounds, and the reported production volume for 1,2-DCA is between 20 and 30 billion pounds per year. According to data reported to the Toxics Release Inventory (TRI), nearly 500,000 pounds of both chemicals were released into the environment in 2022 alone. EPA has identified both cancer and non-cancer health hazards of 1,1 and 1,2-DCA exposure, including kidney and other cancers, as well as adverse renal, nasal, immune system, and reproductive effects.

In both the 1,1-DCA Draft Risk Evaluation and the 1,2-DCA Draft Hazard Assessment, EPA has **failed to incorporate the best available science and relied on a number of scientifically unsupported methodologies that, if adopted, will result in acceptance of serious risks to human health and set a dangerous precedent for future TSCA risk evaluations**.

For example, EPA continued to rely on a systematic review methodology that is not consistent with best practices, violating TSCA's "best available science" requirement.[2] Both documents relied on systematic review methods that lacked transparency and inappropriately excluded toxicity studies without scientific justification. The National Academies of Sciences, Engineering, and Medicine ("NASEM") has recommended the use of existing systematic review methods and improved approaches for TSCA risk evaluations in 2021, and EPA has still not implemented most of these recommendations.[3] EPA's Science Advisory Committee on Chemicals ("SACC") has also recommended best practices in systematic review to the Agency in

[1] 15 U.S.C. § 2625(h).
[2] 15 U.S.C. § 2625(h).
[3] National Academies of Sciences, Engineering, and Medicine (2021). The Use of Systematic Review in EPA's Toxic Substances Control Act Risk Evaluations.

multiple reports.[4] EPA should prepare a new TSCA systematic review methodology that is aligned with the best available scientific methods and issue updated draft systematic review protocols for all risk evaluations currently in development, including 1,1-DCA and 1,2-DCA.

EPA also continued to rely on the flawed "Margin of Exposure" (MOE) approach to non-cancer risk quantification that violates TSCA's "best available science" requirement. While EPA found that immune and reproductive toxicity are likely hazards of 1,2-DCA (and 1,1-DCA because EPA appropriately selected 1,2-DCA as an analog for characterizing human health risks from 1,1-DCA), it failed to provide quantitative estimates of those non-cancer risks. We applied methods developed by the World Health Organization ("WHO") to quantify the non-cancer risk of immunosuppression from chronic oral 1,2-DCA exposure, and found that EPA's current approach results in acceptance of exposures producing an upper bound risk of 1-in-333, a risk level *3,000 times higher* than the target risk level that EPA typically applies for protection of carcinogenic risks (1-in-1,000,000). We applied these same methods to quantify the non-cancer risk of decreased sperm concentration from chronic inhalation 1,2-DCA exposure, and found that EPA's current approach results in acceptance of exposures producing an upper bound risk of 1-in-4,000, a risk level *250 times higher* than the typical target risk level.

In addition, EPA described an inconsistent application of the MOE approach to risk characterization and risk determination in the 1,1-DCA Draft Risk Evaluation. For example, EPA first described a calculated MOE less than the benchmark MOE "as a human health risk of concern,"[5] but later described it as a "starting point for supporting a determination of unreasonable risk."[6] In doing so, EPA could set a dangerous precedent that calculated risks can be dismissed or downplayed without scientific support, which could lead to flawed risk determinations in future assessments for 1,1,-DCA, 1,2-DCA, and other chemicals.

Another critical concern with the 1,1-DCA Draft Risk Evaluation and the 1,2-DCA Draft Hazard Assessment is EPA's failure to evaluate real world exposures and risks. For example, EPA failed to adequately identify and calculate risks posed to potentially exposed or susceptible subpopulations ("PESS"), as required under TSCA,[7] including residents of fenceline communities. A failure to evaluate risk to these groups violates TSCA and results in risk characterization that is not representative of the human population. EPA also failed to evaluate cumulative risk from exposure to 1,1-DCA and 1,2-DCA, in addition to other toxicologically similar chemicals with co-exposures in the human population that may contribute to cumulative risk. Without the results of this cumulative assessment, EPA cannot make conclusions on hazard or risk for 1,1-DCA or 1,2-DCA individually in a manner that adequately safeguards human health.

Accordingly, EPA must make extensive revisions to both the 1,1-DCA Draft Risk Evaluation and the 1,2-DCA Draft Hazard Assessment to more accurately characterize real-world exposures and risks, including to potentially exposed or susceptible subpopulations. This includes adopting best available scientific methods, like gold-standard systematic review methods that better account

[4] U.S. EPA (2022). Science Advisory Committee on Chemicals Meeting Minutes and Final Report No. 2022-2, p. 71. https://www.regulations.gov/document/EPA-HQ-OPPT-2021-0414-0044.
[5] U.S. EPA (2024). Draft Human Risk Evaluation for 1,1-Dichloroethane (DCA), p. 317.
[6] U.S. EPA (2024). Draft Human Risk Evaluation for 1,1-Dichloroethane (DCA), p. 355.
[7] 15 U.S.C. § 2602(12).

for and incorporate the scientific evidence, and methods that more accurately quantify non-cancer risks. Furthermore, given EPA's delayed release of the 1,2-DCA systematic review protocol, EPA should conduct an additional public comment period and panel peer review of the 1,2-DCA hazard assessment documents following the protocol release.

Our detailed comments on the 1,1-DCA Draft Risk Evaluation and the 1,2-DCA Draft Hazard Assessment address the following issues:

1. **EPA failed to apply the best available science to identify and evaluate relevant and useful health effects studies for 1,1-dichloroethane and 1,2-dichloroethane.**
    a. **EPA has not released a systematic review protocol for 1,2-dichloroethane.**
    b. **EPA did not conduct an up-to-date literature search.**
    c. **EPA used deficient inclusion and exclusion criteria for health effects evidence that inappropriately excluded important toxicity endpoints.**
    d. **EPA reverted to its previous flawed approach for health effects study quality evaluation.**
    e. **EPA should prepare a new TSCA systematic review handbook that is aligned with the best available scientific methods and issue updated draft systematic review protocols for all risk evaluations currently in development.**

2. **EPA's hazard assessment for 1,2-dichloroethane is inconsistent with the best available science.**
    a. **EPA has conducted appropriate analysis that supports its selection of 1,2-dichloroethane as an analog for the toxicity of 1,1-dichloroethane.**
    b. **EPA should use the NTP oral rat study of 1,2-dichloroethane, which provides a 50% greater cancer potency, for characterizing cancer risks of 1,1-dichloroethane and 1,2-dichloroethane in its cancer hazard and dose-response assessment.**
    c. **EPA should apply age-dependent adjustment factors (ADAFs) when calculating cancer risks to the general population, as required under EPA guidelines, for chemicals that are mutagenic.**

3. **EPA should apply best available methods to generate quantitative estimates of non-cancer risks for varying levels of exposure to 1,1- and 1,2-dichloroethane.**

4. **EPA failed to apply a consistent approach to making unreasonable risk determinations.**

5. **EPA failed to adequately identify potentially exposed or susceptible subpopulations (PESS), as required by TSCA.**

6. **EPA failed to adequately evaluate unreasonable risk to fenceline communities.**
    a. **EPA must comprehensively and accurately reflect fenceline communities' real-world exposures and risks.**
    b. **EPA must account for cumulative exposures and risks.**

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

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1. EPA failed to apply the best available science to identify and evaluate relevant and useful health effects studies for 1,1-dichloroethane and 1,2-dichloroethane.

a. EPA has not released a systematic review protocol for 1,2-dichloroethane.

EPA says that its procedures for identifying and reviewing the non-cancer effects evidence for 1,2-dichloroethane (1,2-DCA) are described in a chemical-specific systematic review protocol:

> For **data quality evaluation**, EPA systematically reviewed literature studies for 1,2-dichloroethane first by reviewing screened titles and abstracts and then full texts for relevancy using population, exposure, comparator, and outcome (PECO) screening criteria. Studies that met the PECO criteria were evaluated for data quality using pre-established metrics as specified in the 1,2-Dichloroethane Systematic Review Protocol.[8]
>
> The 2021 Draft Systematic Review Protocol (U.S. EPA, 2021) describes the general process of evidence evaluation and integration, with relevant updates to the process presented in the 1,2-Dichloroethane Systematic Review Protocol.[9]

A systematic review protocol is critical for the process of conducting a TSCA risk evaluation, so it is appropriate for the 1,2-DCA Draft Hazard Assessment to reference a systematic review protocol. However, EPA has not released a protocol for 1,2-DCA to the public for the current comment period, even though it has released many other supplemental files in the docket. This means that EPA has employed methods in preparing the 1,2-DCA Draft Hazard Assessment that have not been disclosed to the public or to the SACC. It is unclear why EPA has withheld the protocol, or why the hazard assessment document cites a protocol that is not available.

This practice is also inconsistent with the best available science. The Institute of Medicine's list of best practices for systematic review include making a protocol available for public comment before conducting the review, and making the final protocol publicly available:

> Provide a public comment period for the protocol and publicly report on disposition of comments.
>
> Make the final protocol publicly available, and add any amendments to the protocol in a timely fashion.[10]

The National Academy of Sciences, Engineering, and Medicine (NASEM) has also recommended to EPA's IRIS program that a systematic review protocol should be comprehensive in describing the methods to be applied in an assessment, and should be made publicly available before the assessment is conducted:

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[8] U.S. EPA (2024). Draft Human Health Hazard Assessment for 1,2-Dichloroethane. p 13.
[9] U.S. EPA (2024). Draft Human Health Hazard Assessment for 1,2-Dichloroethane. p 23.
[10] Institute of Medicine (2011). Finding what works in health care: Standards for systematic reviews, p. 75.

> In a systematic review, the protocol is a complete account of planned methods, which should be registered prior to conduct of the review. The term "registration," in this context, is generally understood to mean the public release of the protocol in a time-stamped, read-only format.[11]

The information on methods that is provided in the 1,2-DCA Draft Hazard Assessment is a limited and unclear summary that cannot be considered a substitute for a protocol. Without a protocol available, EPA has failed to adhere to the "best available science", as required by TSCA,[12] and has failed to provide transparency and opportunity for public input on the methods applied in preparing the 1,2-DCA Draft Hazard Assessment. EPA should conduct an additional public comment period and peer review of the 1,2-DCA Draft Hazard Assessment after it has released the systematic review protocol.

For future TSCA risk evaluations, EPA must publish a comprehensive chemical-specific systematic review protocol for public comment *before* completing the draft risk evaluation, as recommended by the Institute of Medicine and the NASEM as a best practice for systematic review.[13,14]

EPA's IRIS program has established exemplar practices in proactively publishing systematic review protocols. For each assessment, IRIS makes a draft protocol publicly available in advance of its release for public comment. Following the public comment process, the IRIS program then publishes an updated protocol, as needed. For example, for the IRIS assessments of five per- and polyfluoroalkyl substances ("PFAS"), a draft protocol was made available for public comment for 45 days. The IRIS program then followed up with a revised protocol to address public comments, with documentation of the changes, that was published before the release of the PFAS draft assessments.[15] EPA should be following this approach for all TSCA risk evaluations.

b. EPA did not conduct an up-to-date literature search.

The 1,1-DCA Draft Risk Evaluation relies on a literature search that was conducted in 2019 and has not been updated since:

> The search for peer-reviewed and gray literature relevant references was completed in September and May 2019, respectively.[16]

The 1,2-DCA Draft Hazard Assessment does not provide information on the date of the literature search, and no protocol for this document is available. However, the 1,2-DCA Draft Hazard Assessment references the 1,1-DCA protocol in multiple places, suggesting that the most recent

[11] NASEM (2021). Review of US EPA's ORD staff handbook for developing IRIS assessments: 2021 version, p. 5.
[12] 15 U.S.C. §2625 (h).
[13] Institute of Medicine (2011). Finding what works in health care: Standards for systematic reviews.
[14] National Research Council (2014). Review of EPA's Integrated Risk Information System (IRIS) process.
[15] U.S. EPA (2021). Systematic Review Protocol for the PFAS IRIS Assessments. https://cfpub.epa.gov/ncea/iris_drafts/recordisplay.cfm?deid=345065 (accessed 1 February 2024).
[16] U.S. EPA (2024). Draft Risk Evaluation for 1,1-Dichloroethane Supplemental File: Systematic Review Protocol. p. 9.

literature search for 1,2-DCA was also conducted in 2019. Further, the study quality assessment document in the 1,2-DCA docket[17] does not include any studies published after 2019, suggesting that no more recent literature search has been conducted.

Therefore, any toxicological findings on 1,2-DCA published in the past 5 years were simply not considered by EPA, which is not consistent with the best available science; recent guidance on conducting systematic reviews in environmental health recommends that literature searches should be updated no more than 12 months before publication of a review.[18] EPA's current approach runs a high risk of failing to include all reasonably available relevant health effects studies.

c. EPA used deficient inclusion and exclusion criteria for health effects evidence that inappropriately excluded important toxicity endpoints.

Population, exposure, comparator, and outcome (PECO) statements play a critical role in conducting a systematic review as they provide criteria for screening the literature search results to identify which studies are relevant (included in the risk evaluation) and not relevant (excluded from further consideration). The 1,1-DCA Draft Risk Evaluation does not provide the PECO statement that was used to identify relevant epidemiology and toxicology studies, but instead cites EPA's broader 2021 TSCA Draft Systematic Review Protocol. The 1,2-DCA Draft Hazard Assessment also does not provide the PECO statement that was used to identify relevant epidemiology and toxicology studies; presumably the 2021 PECO was also used for 1,2-DCA.

Two different PECO statements were provided for both 1,1-DCA and 1-,2-DCA in the 2021 TSCA Draft Systematic Review Protocol, one for title-abstract screening and one for full-text review, and both of which EPA has never revised to address public comments and SACC recommendations. Since EPA has not conducted an updated search for health effects evidence since 2019, we assume that the 2021 PECOs were applied in preparing the draft hazard assessments for both chemicals.

The PECO statement applied for full-text review of 1,1-DCA and 1,2-DCA search results is deficient and excludes a broad range of important toxicity outcomes from consideration in the draft risk evaluations. For example, the outcome component of the full-text review PECO statement for health effects evidence provides the following criteria for inclusion and exclusion of studies (text added to the full-text PECO as compared with title-abstract PECO is underlined):

> **Human:** All health outcomes (cancer and non-cancer) <u>at the organ level or higher</u>.
> **Animal and Plants:** All <u>apical</u> biological effects (<u>effects measured at the organ level or higher</u>) and bioaccumulation from laboratory studies with concurrently measured media and/or tissue concentrations. <u>Apical endpoints include but are not limited to reproduction, survival, and growth</u>.

[17] U.S. EPA (2024). Draft Risk Evaluation for 1,1-Dichloroethane Systematic Review Supplemental File: Data Quality Evaluation Information for Human Health Hazard Animal Toxicology.
[18] P. Whaley, et al. Recommendations for the conduct of systematic reviews in toxicology and environmental health research (COSTER). Environment International 143 (2020), 105926. https://doi.org/10.1016/j.envint.2020.105926.

Screener note:

- Measurable biological effects relevant for humans, animals and plants may include but are not limited to: mortality, behavioral, population, physiological, growth, reproduction, systemic, point of contact (irritation and sensitization) effects.
- Effects measured at the cellular level of biological organization and below are to be tagged as supplemental, mechanistic.[19]

By limiting the relevant human and animal studies to those with only "apical" effects or those with effects at the "organ level or higher" in the full-text PECO, EPA appears to be excluding studies of important biochemical markers and other outcomes at the cellular level that are strong indicators of hazards, and which have commonly been used as critical effects in previous EPA hazard assessments, including TSCA risk evaluations (see examples below).

EPA's PECO statement also provides very limited guidance for screeners on what effects are to be considered "apical" or "organ-level." The PECO says: "Apical endpoints include but are not limited to reproduction, survival, and growth" and "Measurable biological effects relevant for humans, animals and plants may include but are not limited to: mortality, behavioral, population, physiological, growth, reproduction, systemic, point of contact (irritation and sensitization) effects."[20] The 2021 TSCA Draft Systematic Review Protocol provides no further guidance on which outcomes are to be considered apical or organ-level, and which outcomes are to be considered cellular-level.

The NASEM has defined an apical end point as "An observable outcome in a whole organism, such as a clinical sign or pathologic state, that is indicative of a disease state that can result from exposure to a toxicant,"[21] and identified "tumors, birth defects, and neurologic impairments"[22] as examples. No biochemical measures or early biological changes were mentioned among the NASEM examples of apical endpoints.

The definition of an apical effect provided by the EPA IRIS program appears to be narrower than the definition of an adverse effect: "a biochemical change, functional impairment, or pathologic lesion that affects the performance of the whole organism, or reduces an organism's ability to respond to an additional environmental challenge."[23] The IRIS definition of adverse effect includes, for example, "a biochemical change;" such effects appear to be excluded from the 1,1-DCA Draft Risk Evaluation and the 1,2-DCA Draft Hazard Assessment, as they would likely be considered cellular-level effects rather than organ-level or apical effects

[19] U.S. EPA (2021). Draft Systematic Review Protocol Supporting TSCA Risk Evaluations for Chemical Substances, Table_Apx H-11 and Table_Apx H-13.

[20] U.S. EPA (2021). Draft Systematic Review Protocol Supporting TSCA Risk Evaluations for Chemical Substances, Table_Apx H-13.

[21] National Research Council (2007). Toxicity Testing in the 21st Century: A Vision and a Strategy, p. 38.

[22] National Research Council (2007). Toxicity Testing in the 21st Century: A Vision and a Strategy, p. 177.

[23] U.S. EPA. IRIS Glossary. https://www.epa.gov/iris/iris-glossary.

Biochemical and/or cellular-level outcomes have been identified as critical effects in numerous past EPA hazard assessments, including some of the completed TSCA risk evaluations. Examples of these outcomes and past assessments include:

- reduced male fetal testosterone or adult male testosterone levels (2018 and 2019 IRIS staff published systematic reviews of health effects of phthalates, 2023 draft approach to cumulative risk assessment of phthalates under TSCA)[24,25,26]
- reduced thyroid hormone levels (2020 TSCA risk evaluation of HBCD; 2021 toxicity assessment of PFBS) [27,28]
- decreased erythrocyte counts and hemoglobin (2020 TSCA risk evaluation of perchloroethylene)[29]
- measures of immune function, such as increases in immunoglobulin E, lymphocytes, natural killer cells, and interlukin-4 levels (2020 TSCA risk evaluation of perchloroethylene)[30]
- decreased sperm quality or concentration (2020 TSCA risk evaluations of trichloroethylene and perchloroethylene; 2018 and 2019 IRIS staff published systematic reviews of health effects of phthalates)[31,32,33,34]
- acetylcholinesterase inhibition (numerous assessments of pesticides, including cumulative risk assessments of organophosphate and carbamate pesticides)[35,36]

EPA must either document that it has considered outcomes like altered thyroid hormone levels and other biochemical changes or cellular-level effects to be included in the animal and human evidence streams in the 1,1-DCA Draft Risk Evaluation and the 1,2-DCA Draft Hazard

[24] Radke EG, Braun JM, Meeker JD, Cooper GS. Phthalate exposure and male reproductive outcomes: A systematic review of the human epidemiological evidence. Environ Int. 2018 Dec;121(Pt 1):764-793.
[25] Yost EE, Euling SY, Weaver JA, Beverly BEJ, Keshava N, Mudipalli A, Arzuaga X, Blessinger T, Dishaw L, Hotchkiss A, Makris SL. Hazards of diisobutyl phthalate (DIBP) exposure: A systematic review of animal toxicology studies. Environ Int. 2019 Apr;125:579-594.
[26] U.S. EPA (2023). Draft Proposed Approach for Cumulative Risk Assessment of High-Priority Phthalates and a Manufacturer-Requested Phthalate under the Toxic Substances Control Act, p. 102.
[27] U.S. EPA (2020). Risk evaluation for cyclic aliphatic bromide cluster (HBCD).
[28] U.S. EPA (2021). Human health toxicity values for perfluorobutane sulfonic acid and related compound potassium perfluorobutane sulfonate. https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=350888.
[29] U.S. EPA (2020). Risk Evaluation for Percholorethylene (Ethene, 1,1,2,2-Tetrachloro-).
[30] U.S. EPA (2020). Risk Evaluation for Percholorethylene (Ethene, 1,1,2,2-Tetrachloro-).
[31] U.S. EPA (2020). Risk Evaluation for Trichloroethylene.
[32] U.S. EPA (2020). Risk Evaluation for Percholorethylene (Ethene, 1,1,2,2-Tetrachloro-).
[33] Radke EG, Braun JM, Meeker JD, Cooper GS. Phthalate exposure and male reproductive outcomes: A systematic review of the human epidemiological evidence. Environ Int. 2018 Dec;121(Pt 1):764-793.
[34] Yost EE, Euling SY, Weaver JA, Beverly BEJ, Keshava N, Mudipalli A, Arzuaga X, Blessinger T, Dishaw L, Hotchkiss A, Makris SL. Hazards of diisobutyl phthalate (DIBP) exposure: A systematic review of animal toxicology studies. Environ Int. 2019 Apr;125:579-594.
[35] U.S. EPA (2006). Organophosphorus cumulative risk assessment. https://www.regulations.gov/document/EPA-HQ-OPP-2006-0618-0002.
[36] U.S. EPA (2008). Revised N-methyl carbamate cumulative risk assessment. https://www.regulations.gov/document/EPA-HQ-OPP-2008-0347-0029.

Assessment, or provide a justification for why these outcomes should not be considered as potential hazards of the DCAs.

Tagging biochemical and cellular-level outcomes as "supplemental, mechanistic," as directed in the PECO statement above, constrains the role of biochemical outcomes and other cellular changes to possibly providing biological support for apical outcomes, rather than considering precursors to apical outcomes as critical effects. Further, under EPA's proposed method, if no studies have been conducted of apical outcomes related to a biochemical outcome that has been studied, it is unclear whether the biochemical outcome will be considered at all. EPA says that supplemental studies "**may** be reviewed, evaluated for data quality, and incorporated into risk evaluations **as needed** for each chemical assessment"[37] (emphasis added), but it is unclear how a determination would be made to incorporate these studies into the risk evaluation, particularly in the absence of a related apical outcome study. Even if included to support a hazard conclusion based on apical outcomes, it appears that EPA rules out considering such studies for deriving a point of departure.

Exclusive reliance on studies of apical endpoints is also inconsistent with the best available science.[38] An important theme of the NASEM 2007 *Toxicity Testing in the 21st Century* report was that toxicity testing should move away from reliance on testing of apical outcomes. Accordingly, EPA's research programs and other U.S. health agencies have invested heavily in this new direction. Government and academic toxicology labs now rarely conduct studies of apical endpoints because the science has shifted towards examining more sensitive endpoints representing upstream biological changes ("key events") that lead to apical outcomes. In addition, a restriction to consider only apical or organ-level studies may bias the evidence base of the TSCA risk evaluations toward inclusion of industry-funded guidelines studies that are generally focused on apical endpoints.

In addition, EPA revised its PECO after conducting title-abstract screening. Changing the PECO mid-stream, after the initial title-abstract screening but before the full-text screening, can result in inappropriate and unreasonable study inclusions and exclusions. In this scenario, it is possible that studies are excluded at title-abstract screening that would then be eligible for inclusion at full-text screening after the PECO has changed – undermining the entire process by removing eligible studies before they reach the full-text stage.

This practice is also inconsistent with standard systematic review practices and NASEM recommendations to the TSCA program. In its 2021 review of the TSCA systematic review method, the NASEM was critical of changes in inclusion/exclusion criteria:

> In the TSCA evaluation process, eligibility criteria are not predefined in the protocols and shift during the systematic review process.[39]

The NASEM recommended:

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[37] U.S. EPA (2021). Draft systematic review protocol supporting TSCA risk evaluations for chemical substances, p. 345.
[38] 15 U.S.C. § 2625(h).
[39] NASEM (2021). The Use of Systematic Review in EPA's Toxic Substances Control Act Risk Evaluations, p. 34.

> Eligibility criteria need to be based on PECO statements that are formulated in a standard way and need to be predefined in the protocol. The eligibility of outcomes needs to be carefully considered a priori to prevent a systematic exclusion of outcomes that could bias the results, such as excluding studies that have findings counter to those anticipated for the included outcomes.[40]

If changes to a PECO are deemed necessary or useful by the systematic review authors, the literature screening process should be re-started with the revised PECO, with complete documentation in a revised protocol of the change in PECO and the rationale for change, rather than applying the revised PECO in the middle of the process.

d. EPA reverted to its previous flawed approach for health effects study quality evaluation.

EPA's approach to study quality evaluation has changed again. Despite improvements to this important aspect of the systematic process that were applied in the risk evaluations for formaldehyde, diisodecyl phthalate (DIDP), and diisononyl phthalate (DINP), EPA has now reverted to using its earlier approach to study quality evaluation in the 1,1-DCA Draft Risk Evaluation and the 1,2-DCA Draft Hazard Assessment. For both epidemiology and toxicology studies, EPA is again using a deeply flawed study quality approach presented in its 2021 draft systematic review method that has been strongly criticized by the NASEM, the SACC, and public commenters.

The Formaldehyde Draft Risk Evaluation, released earlier this year, was the first to incorporate an important improvement in the TSCA systematic review methodology by substantially revising the number and content of the domains and metrics used to assess the quality of health effects studies, aligning the TSCA approach with the stronger approach that has been used in EPA's IRIS program. In the Formaldehyde Draft Risk Evaluation, EPA said:

> A recurring comment from NASEM, the SACC, and multiple external stakeholders was that TSCA should attempt to align its Systematic Review Protocol with the IRIS Systematic Review Handbook, which had been under development longer and received more rounds of external review.[41]
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> The process of harmonizing the TSCA Systematic Review Protocol with the IRIS Systematic Review Handbook was a collaborative effort between OPPT and ORD... multiple old TSCA metrics were mapped into a smaller number of IRIS metrics (many-to-one).[42]

As a result of these changes, the assessment of epidemiological studies in the Formaldehyde Draft Risk Evaluation involved the application of 7 metrics (organized into 5 domains), a

[40] NASEM (2021). The Use of Systematic Review in EPA's Toxic Substances Control Act Risk Evaluations, p. 34.
[41] U.S. EPA (2024). Draft Risk Evaluation for Formaldehyde. Supplemental File: Systematic Review Protocol, p. 67.
[42] U.S. EPA (2024). Draft Risk Evaluation for Formaldehyde. Supplemental File: Systematic Review Protocol, p. 68.

reduction from 22 metrics previously applied in TSCA systematic reviews. Importantly, the inappropriate metric regarding statistical power that was previously in the TSCA method was not included in the formaldehyde assessment. For evaluation of toxicology studies, the Formaldehyde Draft Risk Evaluation used 9 metrics (organized into 6 domains), a reduction from the 24 metrics previously applied in TSCA systematic reviews.

The study quality evaluation domains and metrics applied in the Formaldehyde Draft Risk Evaluation were also used for the recent draft risk evaluation for DIDP and the draft hazard assessment for DINP. The updated study quality evaluation method applied for formaldehyde, DIDP and DINP is more scientifically defensible and easier to apply than the previous TSCA method, and therefore represented an important advance in the TSCA approach to systematic review. EPA's systematic review protocol for DIDP seemed to say that this was a permanent change when it stated that the new approach, as represented in a form used by EPA assessors when conducting study quality evaluation, would be applied in future TSCA risk evaluations:

> This form is applicable to the data quality evaluation of animal toxicity studies beyond DIDP and thus will also be used in the systematic review of studies reporting exposure to other TSCA High Priority Substances.[43]

The draft risk evaluations for 1,1-DCA and 1,2-DCA are the very next draft risk evaluations released by EPA after DIDP – issued just two months later - and EPA has already contradicted its commitment made in the DIDP protocol.

A major advantage to implementing a comprehensive and systematic review approach is that the methods are consistent from one assessment to the next. This makes the risk evaluation process easier and more predictable for EPA's risk assessors, stakeholders, and peer reviewers. EPA's change in approach to study quality evaluation in the 1,1-DCA Draft Risk Evaluation and the 1,2-DCA Draft Hazard Assessment, with different methods applied in documents released only 2 months apart, is without scientific justification and is a strong indication that EPA does not have a clear understanding of what constitutes the best available science in conducting systematic review. EPA should re-do the study quality assessments for 1,1-DCA and 1,2-DCA using the improved approach that was applied in the recent draft risk evaluations of formaldehyde, DIDP and DINP.

e. EPA should prepare a new TSCA systematic review handbook that is aligned with the best available scientific methods and issue updated draft systematic review protocols for all risk evaluations currently in development.

To adhere to best practices in systematic review, including those recommended by the NASEM and SACC, EPA should issue a new TSCA systematic review methodology document that states methods to be applied consistently to all TSCA risk evaluations. EPA should also prepare a chemical-specific systematic review protocol for each TSCA risk evaluation it conducts, and these protocols should be complete, stand-alone documents that do not refer to the 2021 Draft TSCA Method for critical elements. The chemical-specific protocols for ongoing and future risk evaluations should also be released for public comment well before the draft risk evaluations are

[43] U.S. EPA (2024). Draft Risk Evaluation for Diisodecyl Phthalate (DIDP) – Systematic Review Protocol, p. 69.

completed to allow for public input, scrutiny, and opportunities for improvement. We urge EPA to consistently adopt the practices of the IRIS program for systematic review protocol development and publication across all EPA programs and offices.

2. EPA's hazard assessment for 1,2-dichloroethane is not consistent with the best available science.

a. EPA appropriately selected 1,2-dichloroethane as an analog for the toxicity of 1,1-dichloroethane.

EPA's search of the literature for evidence of health effects of 1,1-dichloroethane was severely inadequate (as described above) and yielded relatively few studies, for which EPA found significant limitations:

> The available toxicity database for 1,1-dichloroethane consists of a small number of animal studies evaluating a limited number of measured parameters… EPA identified data gaps for 1,1-dichloroethane for non-cancer PODs by the acute, short-term/subchronic, and chronic oral, dermal, and inhalation routes; and cancer PODs by the oral, inhalation, and dermal routes.[44]

EPA chose to supplement the health effects literature for 1,1-DCA by identifying a closely-related analog chemical, using established methods, that could be used as a surrogate for toxicity of 1,1-DCA:

> As acceptable human health hazard data were not available to assess risks for 1,1-dichloroethane, EPA chose to use a "read-across" approach using data available for a closely related chemical or analog to evaluate the human health hazard of 1,1-dichloroethane. An analysis of other chlorinated solvents as potential analogs for read-across data was performed following the general principles for read-across as outlined in Lizarraga et al. (2019), taking into consideration structural similarities, physical-chemical properties, metabolism, and toxicological similarities. The analyses resulted in the identification of 1,2-dichloroethane (an isomer of 1,1-dichlorethane) as the most appropriate analog to fill the identified data gaps for 1,1-dichloroethane and a consultation with the EPA Office of Research and Development (ORD) agreed. EPA has high confidence that the 1,2-dichloroethane data will accurately reflect the hazards of 1,1-dichloroethane.[45]

Since EPA has not conducted a robust systematic review to evaluate health effects studies for 1,1-DCA, we strongly support EPA's decision to use analog data to represent the toxicity of 1,1-DCA. EPA has documented a thoughtful process in which 8 chemicals were evaluated for structural similarity to 1,1-DCA, and three priority candidates were then evaluated for similarity for physical and chemical properties. These comparisons identified 1,2-DCA as the preferred

[44] U.S. EPA (2024). Draft Risk Evaluation for 1,1-Dichloroethane p. 231.
[45] U.S. EPA (2024). Draft Risk Evaluation for 1,1-Dichloroethane p. 233.

analog chemical for 1,1-DCA, and further evaluation considered metabolic and toxicologic similarities of the two chemicals. EPA concluded:

> 1,2-Dichloroethane was identified as the best available candidate chemical to fill the identified data gaps for 1,1-dichloroethane. This conclusion is based on the fact that both 1,1-dichloroethane and 1,2-dichloroethane are structurally similar as reactive di-chlorinated ethanes, both are isomers of each other with identical molecular weights and formulas, both have similar physical-chemical properties, both are volatile liquids, both have similar ADME patterns and metabolic pathways, both are reactive alkyl halides, and both possess, overall, similar non-cancer and cancer outcomes (mutagenicity, common tumor types, many common hazard endpoints).[46]

EPA's selection of 1,2-DCA as an analog for the toxicity of 1,1-DCA is well-supported by EPA's analysis, and use of 1,2-DCA toxicity studies to evaluate the hazards of 1,1-DCA represents the best available science.

However, given the severe limitations in its evaluation of the scientific literature for 1,1-DCA health effects studies (as described above), EPA should have also used its authority under TSCA Section 4 to order manufacturers of 1,1-DCA to conduct toxicity studies relevant to assessing the chemical's human health hazards, in addition to the two studies that were ordered for assessing environmental hazard and worker dermal exposure.

b. EPA should use the NTP oral rat study of 1,2-dichloroethane, which provides a 50% greater cancer potency, for characterizing cancer risks of 1,1-dichloroethane and 1,2-dichloroethane in its cancer hazard and dose-response assessment.

In the 1,1-DCA Draft Risk Evaluation and the 1,2-DCA Draft Hazard Assessment, EPA is using a slope factor of 6.2×10^{-2}, obtained from the EPA 1987 IRIS assessment of 1,2-DCA, for estimation of cancer risks. This slope factor is estimated using a 1978 National Toxicology Program (NTP) mouse study of 1,2-DCA. The analysis of study quality by EPA's Office of Pollution Prevention and Toxics correctly concluded that the study methods are of high quality and has decisively rebutted all concerns that were raised by EPA internal reviewers.[47] No valid reasons have been raised for dropping the NTP mouse study.

However, the final slope factor from the EPA 1987 IRIS assessment was 9.1×10^{-2}, based on a 1978 NTP rat study, indicating a cancer risk 50% greater than the mouse slope factor. EPA's 1,2-DCA Draft Hazard Assessment says the 1978 NTP rat study was "deemed unacceptable by EPA systematic review,"[48] without further explanation. A supplemental file says:

> Rats from all study groups (including both sexes and controls) exhibited high incidences of pneumonia (up to 95%), indicating infections in these animals. This was not discussed

[46] U.S. EPA (2024). Draft Risk Evaluation for 1,1-Dichloroethane p. 239.
[47] U.S. EPA (2024). Synopsis of the OPP/ORD Ad-Hoc Committee Review of the Available Carcinogenicity Studies for 1,1-Dichloroethane and 1,2-Dichloroethane. Memorandum from Janet Burris to Jeff Morris, May 30, 2024.
[48] U.S. EPA (2024). Draft Human Health Hazard Assessment for 1,2-Dichloroethane, p. 81.

> or mentioned by the study authors. It is unclear how these infections impacted study results.[49]

EPA has previously considered how animal infections may affect the results of cancer bioassays.[50] In the previous review, EPA concluded that only data on certain cancers, including leukemias and lymphomas, may have been affected by infections, but that data on other observed tumors were suitable for dose-response analysis despite the infections. The rat tumors used for derivation of the 1,2-DCA slope factor were hepatocarcinomas, not leukemias and lymphomas. Thus, EPA should use the rat data given that infections have not been identified as an issue for hepatocarcinoma tumors. EPA should also revise its "uninformative" rating for the NTP rat study and use the IRIS rat slope factor of 9.1×10^{-2} for characterizing risks of 1,1-DCA and 1,2-DCA.

c. EPA should apply age-dependent adjustment factors (ADAFs) when calculating cancer risks to the general population, as required under EPA guidelines, for chemicals that are mutagenic.

In the 1,1-DCA Draft Risk Evaluation and the 1,2-DCA Draft Hazard Assessment, EPA fails to mention its 2005 *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens*. Under this guidance, EPA recommends that age-dependent adjustment factors (ADAFs) are to be applied in calculating risks of cancer for children exposed to carcinogens acting through a mutagenic mode of action.[51]

EPA has established that there is substantial evidence of the mutagenicity of 1,2-DCA:

> Evidence from *in vivo* studies using multiple animal species and routes of exposure and *in vitro* studies using multiple test systems indicates that 1,2-dichloroethane and/or its metabolites can induce mutations, chromosomal aberrations, DNA damage, and DNA adducts in certain test systems.[52]
>
> *In vivo* rodent studies show…clastogenic effects, DNA damage, and DNA adducts in the mammary gland, lung, liver, and circulatory system tissues … DNA damage (Comet assay) in mouse kidney, bladder, and brain…and DNA binding or DNA adducts in mouse and rat stomach, forestomach, and kidney.[53]
>
> Evidence from *in vivo* studies using multiple animal species and routes of exposure and *in vitro* studies using multiple test systems indicates that 1,2-dichloroethane and/or its metabolites can induce mutations, chromosomal aberrations, DNA damage, and DNA binding/adduct formation in certain test systems. The available data also show that biotransformation of 1,2-dichloroethane to reactive metabolites via a major CYP450-

[49] U.S. EPA (2024). Draft Risk Evaluation for 1,1-Dichloroethane Systematic Review Supplemental File: Data Quality Evaluation Information for Human Health Hazard Animal Toxicology, p. 784.
[50] U.S. EPA (undated). Update on Ramazzini Institute Data in IRIS Assessments. https://www.epa.gov/iris/update-ramazzini-institute-data-iris-assessments [accessed 7 August 2024].
[51] U.S. EPA (2005). Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens.
[52] U.S. EPA (2024). Draft Human Health Hazard Assessment for 1,2-Dichloroethane, p. 34.
[53] U.S. EPA (2024). Draft Human Health Hazard Assessment for 1,2-Dichloroethane, p. 34.

> mediated oxidative pathway and a minor glutathione conjugation pathway contributes to the observed effects.[54]

Given the extensive evidence of 1,2-DCA mutagenicity, it is unacceptable that EPA's draft does not even mention its own *Supplemental Guidance* and the ADAFs. By disregarding its own *Supplemental Guidance*, EPA has violated its recent final rule *Procedures for Chemical Risk Evaluation Under the Toxic Substances Control Act (TSCA)*, which states:

> EPA will use applicable EPA guidance when conducting risk evaluations, as appropriate and where it represents the best available science.[55]

EPA should apply ADAFs in characterizing cancer risks for all scenarios in which children are exposed to 1,1-DCA or 1,2-DCA. Failure to apply ADAFs will result in underestimation of risks and would be inconsistent with the best available science.

3. EPA should apply best available methods to generate quantitative estimates of non-cancer risks for varying levels of exposure to 1,1- and 1,2-dichloroethane.

In its TSCA risk evaluations, EPA typically calculates a margin of exposure ("MOE") for each condition of use (COU). The MOE is calculated as:

> Margin of Exposure = Non-cancer point of departure / Human exposure.

The MOE approach is a scientifically deficient method for characterizing risk and is inconsistent with amended TSCA's requirements to use the "best available science"[56] and to ensure protection of "potentially exposed and susceptible subpopulations" ("PESS").[57]

Use of the MOE, which relies on a point of departure ("POD") with no extrapolation to lower doses, is a simplistic approach that only compares the POD to the exposure level and judges whether this ratio is "interpreted as a human health risk of concern" or if "risk is not considered to be of concern and mitigation is not needed." [58] The MOE does not estimate the proportion of the exposed population projected to experience a specified health endpoint or the number of individuals affected, and it perpetuates the scientifically flawed notion that a "safe" or "no risk" level of chemical exposure can be identified for a diverse exposed population.[59,60]

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[54] U.S. EPA (2024). Draft Human Health Hazard Assessment for 1,2-Dichloroethane, p. 38.
[55] 40 CFR § 702.37.
[56] 15 U.S.C. §2625 (h).
[57] 15 U.S.C. §2602 (12).
[58] U.S. EPA (2024). Draft Risk Evaluation for 1,1-Dichloroethane, p. 317.
[59] Woodruff, T. J., Rayasam, S. D. G., Axelrad, D. A., Koman, P. D., Chartres, N., et al.. (2023). A science-based agenda for health-protective chemical assessments and decisions: overview and consensus statement. Environ Health, 21(Suppl 1), 132. https://doi.org/10.1186/s12940-022-00930-3.
[60] McGartland, A., Revesz, R., Axelrad, D. A., Dockins, C., Sutton, P., Woodruff, T. J. (2017). Estimating the health benefits of environmental regulations. Science, 357(6350), 457-458. https://doi.org/10.1126/science.aam8204.

The National Academies[61] and the World Health Organization[62] ("WHO") have outlined more robust methods for risk estimation that more accurately account for variability and vulnerability across the human population and have been demonstrated in published case studies.[63,64 ,65,66] We applied the WHO methodology to the 1,2-dichloroethane chronic oral endpoint of immunosuppression and the 1,2-dichloroethane chronic inhalation endpoint of decreased sperm concentrations, using the POD values reported by EPA, to estimate risk-specific doses for several levels of incidence (e.g. 1%, 0.1%, etc.). Because EPA has selected 1,2-dichloroethane as an analog for characterizing human health risks to 1,1-dichloroethane, all results of this analysis are applicable to both chemicals.

Based on application of the WHO methodology to 1,2-dichloroethane chronic oral exposures (see Technical Appendix for details), we found that:

- 0.002 mg/kg-d is the lower bound (95% confidence) chronic human oral dose at which immunosuppression expected in 1% of the population.
- 0.0012 mg/kg-d is the lower bound (95% confidence) chronic human oral dose at which immunosuppression expected in 0.5% of the population.
- 0.0006 mg/kg-d is the lower bound (95% confidence) chronic human oral dose at which immunosuppression expected in 0.1% of the population.
- 0.0003 mg/kg-d is the lower bound (95% confidence) chronic human oral dose at which immunosuppression expected in 0.01% (1-in-10,000) of the population.
- 0.0001 mg/kg-d is the lower bound (95% confidence) chronic human oral dose at which immunosuppression expected in 0.001% (1-in-100,000) of the population.
- EPA's POD for chronic oral exposure to 1,2-dichloroethane is 0.89 mg/kg-day, and the benchmark MOE is 1000.[67] This means that EPA concludes "the risk is not considered to be of concern"[68] for any chronic oral exposure less than 0.89 mg/kg-day / 1000 = 0.0009 mg/kg-day. Our analysis finds that the upper bound risk at an oral exposure of 0.0009 mg/kg-day is 0.3% (1-in-333).

Based on application of the WHO methodology to 1,2-dichloroethane chronic inhalation exposures (see Technical Appendix for details), we found that:

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[61] National Research Council (2009). Science and Decisions: Advancing Risk Assessment, Chapter 5.
[62] WHO. (2017). Guidance document on evaluating and expressing uncertainty in hazard characterization. Harmonization project document 11, 2nd edition. https://www.who.int/publications/i/item/9789241513548.
[63] Chiu WA, Axelrad DA, Dalaijamts C, Dockins C, Shao K, Shapiro AJ, Paoli G. Beyond the RfD: broad application of a probabilistic approach to improve chemical dose-response assessment for non-cancer effects. Environmental Health Perspectives, 2018 June;126(6):067009. doi:10.1289/EHP3368.
[64] Nielsen, G. H., Heiger-Bernays, W. J., Levy, J. I., White, R. F., Axelrad, D. A., Lam, J., Chartres, N., Abrahamsson, D. P., Rayasam, S. D. G., Shaffer, R. M., Zeise, L., Woodruff, T. J., Ginsberg, G. L. (2023). Application of probabilistic methods to address variability and uncertainty in estimating risks for non-cancer health effects. Environ Health, 21(Suppl 1), 129. https://doi.org/10.1186/s12940-022-00918-z.
[65] Blessinger, T., Davis, A., Chiu, W. A., Stanek, J., Woodall, G. M., Gift, J., Thayer, K. A., Bussard, D. (2020). Application of a unified probabilistic framework to the dose-response assessment of acrolein. Environ Int, 143,105953. https://doi.org/10.1016/j.envint.2020.105953.
[66] Ginsberg, G. L. (2012). Cadmium risk assessment in relation to background risk of chronic kidney disease. J Toxicol Environ Health A, 75(7),374-390.
[67] U.S. EPA (2024). Draft Human Health Hazard Assessment for 1,2-Dichloroethane, Table ES-1.
[68] U.S. EPA (2024). Draft Risk Evaluation for 1,1-Dichloroethane, p. 317.

- 0.4 ppm is the lower bound (95% confidence) chronic human inhalation dose at which decreased sperm concentration is expected in 1% of the worker population.
- 0.3 ppm is the lower bound (95% confidence) chronic human inhalation dose at which decreased sperm concentration is expected in 0.5% of the worker population.
- 0.1 ppm is the lower bound (95% confidence) chronic human inhalation dose at which decreased sperm concentration is expected in 0.1% of the worker population.
- 0.05 ppm is the lower bound (95% confidence) chronic human inhalation dose at which decreased sperm concentration is expected in 0.01% (1-in-10,000) of the worker population.
- 0.02 ppm is the lower bound (95% confidence) chronic human inhalation dose at which decreased sperm concentration is expected in 0.001% (1-in-100,000) of the worker population.
- EPA's POD for chronic inhalation exposure to 1,2-dichloroethane is 22.0 ppm for a work schedule of 40 hours per week, and the benchmark MOE is 300.[69] This means that EPA concludes "the risk is not considered to be of concern"[70] for any chronic worker inhalation exposure less than 22 ppm / 300 = 0.07 ppm. Our analysis finds that the upper bound risk at an inhalation exposure of 0.07 ppm is 0.025% (1-in-4,000).

EPA should apply the WHO framework to these endpoints to better inform its risk characterization and risk determination for both 1,1- and 1,2-dichloroethane. EPA should also apply the WHO framework to additional noncancer endpoints, including increased kidney weight from the NTP 1991 gavage study in rats,[71] and measures of liver function from the 1978 rat inhalation study by IRFMN.[72]

4. EPA failed to apply a consistent approach to making unreasonable risk determinations.

EPA has typically determined whether a condition of use for a particular chemical contributes to unreasonable risk through comparison to benchmark values. For non-cancer effects, the comparison is to a benchmark MOE that is based on selection of applicable uncertainty factors. If the MOE for a particular exposure scenario, calculated as the POD divided by the estimated human exposure, is less than the identified benchmark MOE, EPA has typically concluded that the exposure constitutes an unreasonable risk. For example, the conditions of use identified by EPA as the supporting basis for the final TSCA unreasonable risk determination for TCE based

[69] U.S. EPA (2024). Draft Human Health Hazard Assessment for 1,2-Dichloroethane, Table ES-1.
[70] U.S. EPA (2024). Draft Risk Evaluation for 1,1-Dichloroethane, p. 317.
[71] NTP. (1991). Toxicity studies of 1,2-dichloroethane (ethylene bichloride) (CAS No. 107-06-2) in F344/N rats, Sprague Dawley rats, Osborne-Mendel rats, and B6C3F1 mice (drinking water and gavage studies). (NTP TOX 4; NIH Publication No. 91-3123). Research Triangle Park, NC. https://ntp.niehs.nih.gov/publications/reports/tox/000s/tox004.
[72] IRFMN. (1978). Clinical chemistry results in adult rats exposed to ethylene dichloride by inhalation for 2326 12 months [TSCA Submission]. (OTS0515737. 86-870001661). Shell Oil Company. 2327 https://ntrl.ntis.gov/NTRL/dashboard/searchResults/titleDetail/OTS0515737.xhtml.

on non-cancer effects to workers and consumers correspond exactly to the exposure scenarios in which the calculated MOEs are lower than the benchmark MOEs.[73]

In the 1,1-DCA Draft Risk Evaluation, EPA says:

> A calculated MOE that is less than the benchmark MOE is a starting point for supporting a determination of unreasonable risk of injury to health, based on non-cancer effects. Similarly, a calculated cancer risk estimate that is greater than the cancer benchmark is a starting point for supporting a determination of unreasonable risk of injury to health from cancer.[74]

This interpretation of the MOE provided for 1,1 DCA is significantly different from what was stated in previous TSCA risk evaluations. EPA's 2023 draft supplement to the risk evaluation for 1,4-dioxane stated that "[t]he MOE estimate is interpreted as **indicating a human health risk** if the MOE estimate is less than the benchmark MOE;"[75] similarly, the 2020 final risk evaluation for methylene chloride says "The MOE estimate was **interpreted as a human health risk** if the MOE estimate was less than the benchmark MOE"[76] (emphasis added).

This interpretation is also inconsistent with approaches described in other parts of the 1,1-DCA Draft Risk Evaluation, where EPA clearly describes the MOE as a bright line indicator of risk:

> The MOE estimate is interpreted as a human health risk of concern if the MOE estimate is less than the benchmark MOE (*i.e.,* the total UF). On the other hand, if the MOE estimate is equal to or exceeds the benchmark MOE, the risk is not considered to be of concern and mitigation is not needed.[77]

In addition, while EPA has not disregarded calculated risk from the high-end estimates in the 1,1-DCA Draft Risk Evaluation, as it did in the DIDP and Formaldehyde Draft Risk Evaluations, EPA does suggest potentially only relying on central tendency estimates in the final risk determination due to the "extreme range in MOEs" between high-end and central tendency estimates for occupational non-users (ONUs):

> EPA is preliminarily determining cancer and non-cancer risks from ONU inhalation exposure to 1,1-dichloroethane in two COUs, processing - repackaging and disposal, contribute to the unreasonable risk based on central tendency. However, considering the many conservative considerations in the risk characterization resulting in the extreme range in MOEs between the high-end (e.g., 45) and the central tendency (e.g., 10,000), EPA may determine in the final risk determination that it is more appropriate to determine whether inhalation exposure for workers contributes to unreasonable risk based on the

[73] U.S. EPA (2022). Risk Evaluation for Trichloroethylene. Final Revised Unreasonable Risk Determination for Trichloroethylene, Tables 5-1 and 5-2. https://www.epa.gov/system/files/documents/2023-01/TCE_Final%20Revised%20RD_12-21-22-FINAL-v2.pdf.
[74] U.S. EPA (2024). Draft Human Risk Evaluation for 1,1-Dichloroethane (DCA), p. 355.
[75] U.S. EPA (2023). Draft Supplement to the Risk Evaluation for 1,4-Dioxane, p. 136.
[76] U.S. EPA (2020). Risk Evaluation for Methylene Chloride (Dichloromethane, DCM), p. 365.
[77] U.S. EPA (2024). Draft Human Risk Evaluation for 1,1-Dichloroethane (DCA), p. 317.

central tendency rather than based on the high-end.[78]

It is imperative that EPA adopt a more transparent and consistent approach to risk quantification and unreasonable risk determination. As discussed previously, EPA should rely on probabilistic methods to quantify both cancer and non-cancer risk that are consistent with the best available science. This includes utilizing the WHO methodology, which does not perpetuate the scientifically flawed notion that a "safe" or "no risk" level of chemical exposure can be identified for a diverse exposed population and more accurately accounts for variability and vulnerability across the human population.[79] If EPA does not implement the WHO approach, it must, at minimum, ensure consistency in its use of the MOE approach across risk evaluations to ensure that risk estimates are not disregarded or downplayed at the final stages of risk determination, only after finding that risks are high—as it did in the Formaldehyde and DIDP Draft Risk Evaluations.

5. EPA failed to adequately identify potentially exposed or susceptible subpopulations (PESS), as required by TSCA.

EPA has failed to meet its requirement under TSCA to identify, consider, and account for risk to "potentially exposed or susceptible subpopulations" ("PESS")[80] in the 1,1-DCA Draft Risk Evaluation, which served as a template for the PESS evaluation in the 1,2-DCA Draft Hazard Assessment. In both documents, EPA failed to identify multiple PESS, and among the PESS identified, EPA did not apply a transparent methodology for quantifying risk of harm that is consistent with the best available science. This flawed approach is consistent with previous risk evaluations, where EPA has regularly underestimated the risk to PESS due to a lack of adequate identification and consideration of PESS. In doing so, EPA is violating TSCA's requirements. EPA, therefore, must adopt a consistent framework for identifying and quantifying the risk of harm to PESS from 1,1-DCA exposures.

Identification and consideration of PESS is a critical aspect of conducting chemical risk evaluations under TSCA, since TSCA requires EPA to:

> determine whether a chemical substance presents an unreasonable risk of injury to health or the environment, without consideration of costs or other nonrisk factors, including an unreasonable risk to a potentially exposed or susceptible subpopulation.[81]

In the final 2024 TSCA Risk Evaluation Framework Rule, EPA defined PESS as:

> Potentially exposed or susceptible subpopulation means a group of individuals within the general population identified by EPA who, due to either greater susceptibility or greater exposure, may be at greater risk than the general population of adverse health effects

[78] U.S. EPA (2024). Draft Human Risk Evaluation for 1,1-Dichloroethane (DCA), p. 357.
[79] WHO. (2017). Guidance document on evaluating and expressing uncertainty in hazard characterization. Harmonization project document 11, 2nd edition. https://www.who.int/publications/i/item/9789241513548.
[80] 15 U.S.C. §2605(b)(4)(A).
[81] 15 U.S.C. §2605(b)(4)(A).

> from exposure to a chemical substance or mixture, such as infants, children, pregnant women, workers, the elderly, or overburdened communities.[82]

EPA must develop and apply a consistent approach to identify all PESS in the 1,1-DCA Draft Risk Evaluation, 1,2-DCA Draft Hazard Assessment, and all future risk evaluations. To date, EPA has failed to employ a consistent or structured approach to identifying PESS in its TSCA risk evaluations, including scope documents for ongoing risk evaluations; EPA's approach for identifying PESS varied considerably in the first 10 risk evaluations. These inconsistencies include: differences in whether health conditions related to a chemical's hazards were considered in identifying PESS; and whether fenceline communities were included as PESS.[83] To remedy the inconsistent and incomplete identification of PESS, Rayasam *et al.* recommended that:

> EPA should prepare a comprehensive methodology to identify PESS and quantify their risks consistently within and across the TSCA risk evaluations.[84]

EPA has not yet proposed such a methodology. While the listing of potential PESS based on increased exposure and susceptibility in Table 5-56 in the 1,1-DCA Draft Risk Evaluation is a useful initial step towards developing a consistent, structured approach to identifying PESS in TSCA risk evaluations,[85] EPA excluded critical and detailed evaluations of certain PESS. For example, Table 5-56 appropriately details explicit consideration of each of the following factors that may define PESS: lifestage, pre-existing disease, lifestyle activities, sociodemographic factors, geographic and site-specific, and genetics/epigenetics; however, EPA excluded the consideration of nutrition factors, unique activities, and other chemical and non-chemical stressors that may also increase susceptibility to harm (see Table 1 below). [86] EPA also failed to fully consider all PESS within each category identified. For example, EPA only considered race/ethnicity as a sociodemographic factor that could be used to identify PESS. Multiple high-powered systematic reviews have shown that other sociodemographic indicators, including socioeconomic status, are strongly correlated to increased susceptibility to harm from chemical exposures.[87]

EPA also concluded for the identified PESS that, due to a lack of chemical specific data for each PESS, no further evaluation was necessary. EPA cannot make this conclusion without considering the full breadth of both intrinsic and extrinsic factors that influence susceptibility to harm from chemical exposures when identifying PESS. TSCA does not require chemical-specific

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[82] U.S. EPA (2024). Procedures for Chemical Risk Evaluation Under the Toxic Substances Control Act, § 702.33.
[83] Rayasam, S. D. G., Koman, P. D., Axelrad, D. A., Woodruff, T. J., Chartres, N. (2022). Toxic Substances Control Act (TSCA) Implementation: How the Amended Law Has Failed to Protect Vulnerable Populations from Toxic Chemicals in the United States. Environmental science & technology, 56(17), 11969–11982. https://doi.org/10.1021/acs.est.2c02079.
[84] Rayasam, S. D. G., Koman, P. D., Axelrad, D. A., Woodruff, T. J., Chartres, N. (2022). Toxic Substances Control Act (TSCA) Implementation: How the Amended Law Has Failed to Protect Vulnerable Populations from Toxic Chemicals in the United States. Environmental science & technology, 56(17), 11969–11982. https://doi.org/10.1021/acs.est.2c02079.
[85] U.S. EPA (2024). Draft Human Risk Evaluation for 1,1-Dichloroethane (DCA), p. 319, Table 5-56.
[86] U.S. EPA (2024). Draft Human Risk Evaluation for 1,1-Dichloroethane (DCA), p. 319, Table 5-56.
[87] Vesterinen, H. M., Morello-Frosch, R., Sen, S., Zeise, L., & Woodruff, T. J. (2017). Cumulative effects of prenatal-exposure to exogenous chemicals and psychosocial stress on fetal growth: Systematic-review of the human and animal evidence. *PLOS ONE*, *12*(7), e0176331. https://doi.org/10.1371/journal.pone.0176331.

quantitative data to identify or evaluate risks to PESS. Instead, TSCA requires EPA to rely on the "best available science" when evaluating risks to PESS. The best available science demonstrates that both intrinsic factors, which include biological traits like age, genetic makeup, and pre-existing health conditions, and extrinsic factors, which include psychosocial stress from experiencing income inequality, violence, racism, healthcare inequity, or food insecurity, can individually or collectively increase susceptibility to harm from chemical exposures.[88] EPA should therefore focus first on identifying susceptible subpopulations based on either chemical-specific evidence or the broader literature on intrinsic and extrinsic susceptibility factors, and then, as a separate step, consider how to adequately account for the elevated risks for each group, in some cases by using scientifically-supported uncertainty factors. The initial identification of PESS, however, should not be contingent on chemical-specific data. Once the appropriate groups are identified as PESS, EPA should then consider the availability of chemical-specific data. When such data are absent, the application of appropriate adjustment factors (beyond the customary 10x factor for human variability) should be applied to ensure that risks to PESS are not underestimated.[89]

EPA's evaluation and application of uncertainty factors aimed at protecting PESS are inconsistent with the best available science and inadequate for protecting PESS. EPA quantitatively adjusted for differences in human susceptibility only with the application of the standard human variability uncertainty factor of 10X. However, the WHO and other authoritative bodies have demonstrated that the traditional 10X uncertainty factor is insufficient for fully accounting for risk in sensitive groups and recommend the use larger uncertainty factors (at minimum, 42X).[90] Instead of increasing the use of uncertainty factors to account for the wide range of vulnerability and variability in the human population, EPA uses inadequate default uncertainty factors, which

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[88] Woodruff, T. J., Rayasam, S. D. G., Axelrad, D. A., Koman, P. D., Chartres, N., Bennett, D. H., Birnbaum, L. S., Brown, P., Carignan, C. C., Cooper, C., Cranor, C. F., Diamond, M. L., Franjevic, S., Gartner, E. C., Hattis, D., Hauser, R., Heiger-Bernays, W., Joglekar, R., Lam, J., … Zeise, L. (2023). A science-based agenda for health-protective chemical assessments and decisions: Overview and consensus statement. Environmental Health,21(1), 132. https://doi.org/10.1186/s12940-022-00930-3; Rachel Morello-Frosch et al., Understanding the Cumulative Impacts of Inequalities in Environmental Health: Implications for Policy, 30 Health Affs. 879 (2011), https://www.healthaffairs.org/doi/pdf/10.1377/hlthaff.2011.0153; Cliona M. McHale et al., Assessing Health Risks from Multiple Environmental Stressors: Moving from G×E to I×E, 775 Mutational Rsch. 11 (2018), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5863617/; Devon C. Payne-Sturges et al., Methods for Evaluating the Combined Effects of Chemical and Nonchemical Exposures for Cumulative Environmental Health Risk Assessment, 15 Int'l. J. Env't Rsch. & Pub. Health 2797 (2018), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6313653/; Gilbert C. Gee et al., Environmental Health Disparities: A Framework Integrating Psychosocial and Environmental Concepts, 112 Env't Health Persps. 1645 (2004), https://doi.org/10.1289/ehp.7074; Gina M. Solomon et al., Cumulative Environmental Impacts: Science and Policy to Protect Communities 37 Ann. Rev. Pub. Health 83, 87–88 (2016), https://www.annualreviews.org/doi/pdf/10.1146/annurev-publhealth-032315-021807; Patricia D. Koman et al., Population Susceptibility: A Vital Consideration in Chemical Risk Evaluation Under the Lautenberg Toxic Substances Control Act, 17 PLoS Biology 1, 4 (2019), https://journals.plos.org/plosbiology/article?id=10.1371/.

[89] Varshavsky et al. Current Practice and Recommendations for Advancing How Human Variability and Susceptibility Are Considered in Chemical Risk Assessment, 21(Suppl 1) Env't Health Article No. 133, at 3 (2023), https://doi.org/10.1186/s12940-022-00940-1

[90] Varshavsky, J. R., Rayasam, S. D. G., Sass, J. B., Axelrad, D. A., Cranor, C. F., Hattis, D., Hauser, R., Koman, P. D., Marquez, E. C., Morello-Frosch, R., Oksas, C., Patton, S., Robinson, J. F., Sathyanarayana, S., Shepard, P. M., & Woodruff, T. J. (2023). Current practice and recommendations for advancing how human variability and susceptibility are considered in chemical risk assessment. Environmental Health, 21(Suppl 1), 133. https://doi.org/10.1186/s12940-022-00940-1.

will result in an underestimation of risk, particularly for PESS. Table 1 describes the PESS considerations listed in the 1,1-DCA Draft Risk Evaluation, the gaps in PESS identification or consideration, and recommended science-based uncertainty factors that should be employed to fully account for risk posed to each group. We have provided further details on each proposed PESS category below.

Table 1. PESS considerations and recommended uncertainty factors (UFs).

PESS category	PESS identified by EPA	EPA Proposed UFs	PRHE Recommended UFs
Lifestage	Infants, children, women of reproductive age, pregnant people, and older adults	No additional UFs beyond the 10X identified for general human variability: POD for developmental endpoints is thought to be protective of effects at different lifestages	42X and additional 10X for susceptible life stages
Pre-existing disease or disorder	Health outcomes/target organs, toxicokinetics, neurological disorders	No additional UFs beyond the 10X identified for general human variability	42X and an additional 10X for pre-existing disease
Lifestyle activities	Smoking and subsistence and tribal fishers	No additional UFs beyond the 10X identified for general human variability	42X and an additional 10X for non-chemical stressors
Socio-demographic factors	Race/ethnicity	No additional UFs beyond the 10X identified for general human variability	42X and an additional 10X for non-chemical stressors
Geographic factors	Child care centers, public schools, and residential communities	No additional UFs beyond the 10X identified for general human variability	42X and an additional 10X for non-chemical stressors
Genetics/epigenetics	Individuals with certain genetic variants	No additional UFs beyond the 10X identified for target organs; No quantitative assessment for individuals with genetic variants	42X
Nutrition	None identified	N/A	42X and an additional 10X for non-chemical stressors

Unique activities	None identified	N/A	42X and an additional 10X for non-chemical stressors
Other chemical and non-chemical stressors	None identified	N/A	42X and an additional 10X for multiple chemical and non-chemical stressors

Lifestage. EPA should apply stronger uncertainty factors for accounting for the risk across life-stages. Enhanced susceptibility of infants, children, women of reproductive age and people of age 65 years or older is well-established, and EPA should be relying on adequate science-based uncertainty factors to account for this enhanced susceptibility, regardless of whether there are chemical-specific data to quantify those differences. Instead, EPA applied a 10x human uncertainty factor which, as discussed previously, is not sufficient to address human variability in response to chemical exposures.[91] The WHO's International Programme on Chemical Safety ("IPCS") found that an adjustment factor of approximately 42X is needed to account for the range in human variability among healthy adults in response to chemical exposures when estimating a risk-specific dose intended for a risk of 1% (1-in-100), with larger factors necessary for protection of the population at lower risk levels.[92]

Pre-existing disease. EPA should broaden its consideration of pre-existing disease as PESS to also include all individuals with pre-existing diseases or conditions in any organ that is a target of the chemical under consideration. EPA should also apply appropriate adjustments to the estimation of risks of each outcome for these groups.

EPA states:

> Observed impaired motor activity and CNS depression, from evidence in rats following 1,1-dichloroethane exposure, have potential implications for greater susceptibility in people with Parkinson's Disease, other neurological disorders.[93]

Despite acknowledging the potential for increased susceptibility among individuals with neurological disorders, EPA does not qualitatively nor quantitatively account for pre-existing neurological conditions in its hazard or risk assessments. While EPA states that target organ effects, such as liver effects, are addressed through the 10X UF for human variability, no adjustments are made for other pre-existing conditions. Additionally, as discussed above, an adjustment of 10X is not sufficient for accounting for the full range of human variability in response to chemical exposures among healthy adults;[94] an adjustment factor of 42X would be needed to account for human variability in response to chemical exposures among healthy adults,

[91] Julia R. Varshavsky et al., Current Practice and Recommendations for Advancing How Human Variability and Susceptibility Are Considered in Chemical Risk Assessment, 21(Suppl 1) Env't Health Article No. 133, at 3 (2023), https://doi.org/10.1186/s12940-022-00940-1.
[92] WHO (2017). Guidance document on evaluating and expressing uncertainty in hazard characterization. Harmonization project document 11, 2nd edition, Table 4.5. https://www.who.int/publications/i/item/9789241513548.
[93] U.S. EPA (2024). Draft Human Risk Evaluation for 1,1-Dichloroethane (DCA), p. 319, Table 5-56.
[94] Julia R. Varshavsky et al., Current Practice and Recommendations for Advancing How Human Variability and Susceptibility Are Considered in Chemical Risk Assessment, 21(Suppl 1) Env't Health Article No. 133, at 3 (2023), https://doi.org/10.1186/s12940-022-00940-1.

and an additional 10X would be needed to account for enhanced susceptibility among individuals with pre-existing disease.

Lifestyle activities. EPA identifies lifestyle activities to include smoking and subsistence and Tribal fishing. However, EPA fails to consider a number of other lifestyle activities when identifying PESS, and does not adequately adjust for the identified PESS in the 1,1 DCA Draft Risk Evaluation. A failure to holistically examine lifestyle factors when identifying PESS will underestimate risk to susceptible subgroups. For example, EPA failed to consider people who engage in recreational exercise in fenceline communities (including non-residents of these communities), such as running, hiking, or playing outdoor sports, as PESS. These groups may have increased inhalation exposure to 1,1 DCA or 1,2-DCA, and face greater health risks as a result. EPA only mentioned smoking as a lifestyle factor that could influence susceptibility, but failed to identify smokers as PESS because it found no chemical-specific information. Smoking tobacco has numerous health harms that could enhance susceptibility to the hazards of 1,1-DCA and 1,2-DCA, such as adverse effects on the lungs and other organ systems. Smokers should also be considered as PESS even if there is no chemical specific evidence. In addition, we recommend using the term "individual activities" instead of "lifestyle activities."

Socio-demographic factors. Studies have demonstrated that socio-demographic factors can influence a person's susceptibility to harm from toxic chemicals. These factors include income, housing status, access to healthy food, health care, access to green space and other neighborhood factors that can impact a person's exposure to toxic chemicals[95] as well as their susceptibility to harm from those exposures. For example, people experiencing poverty or racial discrimination may experience psychosocial stress that can enhance susceptibility to the adverse effects of toxic chemicals.[96] These groups must be identified as PESS, even if there is not direct chemical-specific evidence.

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[95] Payne-Sturges, D. C., Taiwo, T. K., Ellickson, K., Mullen, H., Tchangalova, N., Anderko, L., Chen, A., & Swanson, M. (2023). Disparities in Toxic Chemical Exposures and Associated Neurodevelopmental Outcomes: A Scoping Review and Systematic Evidence Map of the Epidemiological Literature. *Environmental Health Perspectives*, *131*(9), 096001. https://doi.org/10.1289/EHP11750; Morello-Frosch, R., & Shenassa, E. D. (2006). The environmental "riskscape" and social inequality: Implications for explaining maternal and child health disparities. *Environmental Health Perspectives*, *114*(8), 1150–1153. https://doi.org/10.1289/ehp.8930; Pullen Fedinick, K., Yiliqi, I., Lam, Y., Lennett, D., Singla, V., Rotkin-Ellman, M., & Sass, J. (2021). A Cumulative Framework for Identifying Overburdened Populations under the Toxic Substances Control Act: Formaldehyde Case Study. *International Journal of Environmental Research and Public Health*, *18*(11), Article 11. https://doi.org/10.3390/ijerph18116002

[96] Vesterinen, H. M., Morello-Frosch, R., Sen, S., Zeise, L., & Woodruff, T. J. (2017). Cumulative effects of prenatal-exposure to exogenous chemicals and psychosocial stress on fetal growth: Systematic-review of the human and animal evidence. *PLOS ONE*, *12*(7), e0176331. https://doi.org/10.1371/journal.pone.0176331; Varshavsky, J. R., Rayasam, S. D. G., Sass, J. B., Axelrad, D. A., Cranor, C. F., Hattis, D., Hauser, R., Koman, P. D., Marquez, E. C., Morello-Frosch, R., Oksas, C., Patton, S., Robinson, J. F., Sathyanarayana, S., Shepard, P. M., & Woodruff, T. J. (2023). Current practice and recommendations for advancing how human variability and susceptibility are considered in chemical risk assessment. Environmental Health, 21, 1–20. https://doi.org/10.1186/s12940-022-00940-1; McHale, C. M., Osborne, G., Morello-Frosch, R., Salmon, A. G., Sandy, M. S., Solomon, G., Zhang, L., Smith, M. T., & Zeise, L. (2018). Assessing health risks from multiple environmental stressors: Moving from G×E to I×E. Mutation research. Reviews in mutation research, 775, 11–20. https://doi.org/10.1016/j.mrrev.2017.11.003; Payne-Sturges, D. C., Scammell, M. K., Levy, J. I., Cory-Slechta, D. A., Symanski, E., Carr Shmool, J. L., Laumbach, R., Linder, S., & Clougherty, J. E. (2018). Methods for Evaluating the Combined Effects of Chemical and Nonchemical

EPA failed to recognize that sociodemographic factors apart from race/ethnicity can lead to increased chemical exposures and susceptibility.[97] For example, housing age and quality can influence the intrusion of toxic chemicals from the outdoor environment to the indoor environment.[98] Individuals from low-income backgrounds generally experience poorer indoor air quality.[99] Despite this evidence, "EPA did not identify sociodemographic factors that influence susceptibility" apart from race/ethnicity.[100] At a minimum, EPA should comprehensively assess the demographic profile of populations living in locations likely to experience elevated exposures (e.g. sites with 1,1-DCA and/or 1,2-DCA environmental releases) using readily available databases and tools, and use this assessment to inform the identification of PESS and the evaluation of risk to these groups. EPA conducted such an analysis for the proposed TSCA risk management rule for trichloroethylene (TCE),[101] and this approach can be applied to future TSCA risk evaluations. In addition, the best available science indicates that EPA should include science-based uncertainty factors (in addition to the 42X WHO UF to account for human variability) to account for enhanced susceptibility due to socio-demographic factors,[102] especially in scenarios where chemical-specific data is not available.

Geographic factors. Geographic factors were evaluated in the 1,1 DCA Draft Risk Evaluation, but "EPA did not identify geographic factors that influence susceptibility"[103] In general, people living in fenceline communities are more likely to be people of color and are more likely to experience increased exposures to multiple chemical and non-chemical stressors that make them more susceptible to harm, including a broad range of non-chemical stressors like pre-existing disease, racism, and poverty.[104] EPA is therefore required under TSCA to account for these

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Exposures for Cumulative Environmental Health Risk Assessment. International Journal of Environmental Research and Public Health, 15(12). https://doi.org/10.3390/ijerph15122797.

[97] Gan, W. Q., Sanderson, W. T., Browning, S. R., & Mannino, D. M. (2017). Different types of housing and respiratory health outcomes. Preventive Medicine Reports, 7, 124. https://doi.org/10.1016/j.pmedr.2017.05.018.

[98] Brody, J. G., Morello-Frosch, R., Zota, A., Brown, P., Pérez, C., & Rudel, R. A. (2009). Linking Exposure Assessment Science With Policy Objectives for Environmental Justice and Breast Cancer Advocacy: The Northern California Household Exposure Study. American Journal of Public Health, 99(S3), S600–S609. https://doi.org/10.2105/AJPH.2008.149088.

[99] Ferguson, L., Taylor, J., Davies, M., Shrubsole, C., Symonds, P., & Dimitroulopoulou, S. (2020). Exposure to indoor air pollution across socio-economic groups in high-income countries: A scoping review of the literature and a modelling methodology. Environment International, 143, 105748. https://doi.org/10.1016/j.envint.2020.105748 Brody, J. G., Morello-Frosch, R., Zota, A., Brown, P., Pérez, C., & Rudel, R. A. (2009). Linking Exposure Assessment Science With Policy Objectives for Environmental Justice and Breast Cancer Advocacy: The Northern California Household Exposure Study. *American Journal of Public Health*, *99*(S3), S600–S609. https://doi.org/10.2105/AJPH.2008.149088.

[100] U.S. EPA (2024). Draft Human Risk Evaluation for 1,1-Dichloroethane (DCA), p. 320, Table 5-56.

[101] U.S. EPA (2023). Economic Analysis of the Proposed Regulation of Trichloroethylene Under TSCA Section 6(a), Section 10.6.

[102] Varshavsky, J. R., Rayasam, S. D. G., Sass, J. B., Axelrad, D. A., Cranor, C. F., Hattis, D., Hauser, R., Koman, P. D., Marquez, E. C., Morello-Frosch, R., Oksas, C., Patton, S., Robinson, J. F., Sathyanarayana, S., Shepard, P. M., & Woodruff, T. J. (2023). Current practice and recommendations for advancing how human variability and susceptibility are considered in chemical risk assessment. Environmental Health, 21(Suppl 1), 133. https://doi.org/10.1186/s12940-022-00940-1.

[103] U.S. EPA (2024). Draft Human Risk Evaluation for 1,1-Dichloroethane (DCA), p. 320, Table 5-56.

[104] Ronald White et al., Env't Just. Health All. For Chem. Pol'y Reform et al., Life at the Fence line: Understanding Cumulative Health Hazards in Environmental Justice Communities (2018), https://ej4all.org/assets/media/documents/Life%20at%20the%20Fenceline%20-%20English%20-%20Public.pdf.

enhanced susceptibilities when evaluating risks to fenceline communities. Accordingly, EPA must apply an adjustment factor of 42X to account for baseline human variability in response to chemical exposures, and an additional 10X to account for enhanced susceptibility among individuals living in proximity to facilities emitting 1,1-DCA and/or 1,2-DCA.

Genetics/Epigenetics. EPA identified people with a certain aldehyde dehydrogenase-2 mutation as PESS, which is more prevalent among individuals of Asian descent. However, EPA also stated that "Cancer studies in animals with the aldehyde dehydrogenase-2 clearance enzyme mutation are not available to quantitatively assess this PESS group."[105] PESS groups that are identified, such as people with genetic susceptibility, should always be quantitatively adjusted for, even when chemical-specific data is not available.

EPA also stated that "indirect evidence that genetic variants may increase susceptibility of the target organ was addressed through a 10× UF for human variability."[106] EPA assumes that a 10-fold factor is sufficient to account for human variability in response to chemical exposures, including the impacts of genetics and all the other susceptibility factors listed in Table 1 above, even though the National Academies of Sciences, Engineering, and Medicine (NASEM) and the WHO have both recommended that a larger factor is necessary to ensure public health protection. Accordingly, EPA must apply an adjustment factor of at least 42X to account for baseline human variability in response to chemical exposures, including genetic susceptibility.

Nutrition. In Table 5-56, EPA states that "EPA did not identify nutritional factors that influence susceptibility",[107] however, people with food insecurity or lack of access to nutritious food can experience enhanced susceptibility to the adverse effects of toxic chemicals, including 1,1-DCA and 1,2-DCA, and should be identified as PESS in all risk assessments, even if there is not direct chemical-specific evidence. Accordingly, EPA must apply an adjustment factor of 42X to account for baseline human variability in response to chemical exposures, and an additional 10X to account for enhanced susceptibility from inadequate nutrition.

Other chemical and non-chemical stressors. Fifteen years ago, the NASEM recommended that EPA consider exposures to multiple chemical and non-chemical stressors in its chemical risk assessments.[108] Yet, EPA continues to ignore the impact of combined chemical and non-chemical stressors in all ongoing chemical risk assessments. In the both the 1,1-DCA Draft Risk Evaluation and the 1,2-DCA Draft Hazard Assessment, EPA failed to consider as PESS groups that may be co-exposed to chemicals with shared adverse health outcomes or key characteristics, including 1,1-DCA and 1,2-DCA. As a result of the narrow consideration of PESS, EPA has ignored important factors that contribute to enhanced risk from 1,1-DCA and 1,2-DCA exposures. The relationship between co-exposures to 1,1 DCA, 1,2-DCA, and other chemicals with shared adverse health outcomes is further exacerbated by the various susceptibility factors, including socio-demographic factors, that collectively increase susceptibility to harm. In the

[105] U.S. EPA (2024). Draft Human Risk Evaluation for 1,1-Dichloroethane (DCA), p. 320, Table 5-56.
[106] U.S. EPA (2024). Draft Human Risk Evaluation for 1,1-Dichloroethane (DCA), p. 320, Table 5-56.
[107] U.S. EPA (2024). Draft Human Risk Evaluation for 1,1-Dichloroethane (DCA), p. 320, Table 5-56.
[108] National Research Council. (2009). Science and Decisions: Advancing Risk Assessment. National Academies Press (US). http://www.ncbi.nlm.nih.gov/books/NBK214630/

absence of chemical-specific quantitative data, EPA should use science-based uncertainty factors to account for the increased susceptibility to harm that results from 1) co-exposures to 1,1-DCA, 1,2-DCA, and other chemicals with shared adverse health outcomes and 2) exposure to non-chemical stressors, including socio-demographic factors that can enhance the health harms resulting from 1,1 DCA exposures. We recommend that EPA apply an adjustment factor of 42X to account for baseline human variability in response to chemical exposures, and an additional 10X to account for enhanced susceptibility among individuals experiencing additional chemical and non-chemical stressors.

Overall, EPA must expand its identification of PESS to, at minimum, consider the factors described above. EPA must also develop a comprehensive, consistent, and structured methodology for identifying PESS in all TSCA risk evaluations to strengthen protections for susceptible subgroups.

6. EPA failed to adequately evaluate unreasonable risk to fenceline communities.

We support EPA's decision to consider impacts to fenceline communities in the 1,1-DCA Draft Risk Evaluation, which is needed to comply with TSCA. We also support EPA's decision to consider multiple years of chemical releases reported to the TRI, NEI, and DMR, which addressed uncertainty associated with the year-to-year variability that exists in the release data and illustrates the potential impact of considering multiple years of TRI, NEI, and DMR data on risk calculations. We also support EPA's decision to examine aggregate exposures from multiple TRI facilities, and to consider data reported to the National Response Center and the DOT Hazmat Incident Report Data. However, the 1,1-DCA Draft Risk Evaluation fails to comprehensively account for the ways that fenceline communities are exposed to and harmed by 1,1-DCA and 1,2-DCA, and thus understates the harm that fenceline residents face from these exposures.

In 1,1-DCA Draft Risk Evaluation, EPA evaluated risk to fenceline communities from 1,1-DCA exposures largely based on methodologies outlined in its Draft TSCA Screening Level Approach for Assessing Ambient Air and Water Exposures to Fenceline Communities Version 1.0 (the "Fenceline Assessment Approach").[109] While EPA has made some significant improvements to this methodology since its initial publication, as highlighted above, EPA's current methodology still does not accurately capture fenceline communities' exposures and risks. EPA's Scientific Advisory Committee on Chemicals ("SACC") identified several flaws in EPA's Fenceline Assessment Approach, including a failure to consider aggregate and cumulative exposures, non-chemical stressors, and reasonably available chemical release data when evaluating fenceline community risk, all of which EPA has failed to address in the 1,1-DCA Draft Risk Evaluation.[110]

[109] U.S. EPA. (2022) *Draft TSCA Screening Level Approach for Assessing Ambient Air and Water Exposures to Fenceline Communities Version 1.0*. Document No. EPA-744-D-22-001. Available: https://www.regulations.gov/document/EPA-HQ-OPPT-2021-0415-0012.

[110] U.S. EPA. (2022). Final Report on Draft TSCA Screening Level Approach for Assessing Ambient Air and Water Exposures to Fenceline Communities Version 1.0.Available: https://www.epa.gov/system/files/documents/2022-01/draft-fenceline-report_sacc.pdf.

Under TSCA, EPA's must consider and address the real-world risks to fenceline communities from 1,1-DCA exposures. TSCA further requires EPA to evaluate and regulate chemicals "in a manner consistent with the best available science"[111] and determine whether a chemical presents unreasonable risk to any "potentially exposed or susceptible subpopulation," which is defined as a group that "may be at greater risk than the general population" due to greater chemical exposures, greater susceptibility, or both.[112] The best available scientific protocols and methodologies for conducting risk assessments require consideration of all exposure pathways, taking into account aggregate and cumulative exposures, as well as increased susceptibility to harm. [113] Residents of fenceline communities must be considered a "susceptible subpopulation" because they face greater chemical exposures due to their proximity to polluting facilities and contaminated sites, and they often experience greater harm from those exposures due to their cumulative exposures to multiple chemicals as well as other non-chemical stressors such as poverty and racial discrimination.

EPA failed to consider all relevant aggregate exposures, cumulative risks, non-chemical stressors, and reasonably available chemical release data when evaluating risk to fenceline communities in the 1,1-DCA Draft Risk Evaluation. Together, these critical omissions result in an underestimation of risk to fenceline community residents. Even without conducting a comprehensive analysis, EPA still found that certain conditions of use pose high cancer risk (greater than 1-in-1,000,000) from 1,1-DCA ambient air exposures for fenceline community residents living within 1000m from at least 10 TRI facilities and at least 78 NEI facilities releasing 1,1-DCA. However, EPA dismissed these risks based on a land-use analysis that was highly uncertain and variable, according to its own uncertainty analysis. EPA also failed to evaluate whether there were residential communities surrounding the 78 NEI facilities associated with high cancer risks.

a. EPA must comprehensively and accurately reflect fenceline communities' real-world exposures and risks.

In the 1,1-DCA Draft Risk Evaluation, EPA fails to comprehensively consider real-world 1,1-DCA exposures in fenceline communities. For example, EPA did not consider complete chemical release data to support its fenceline exposure assessment. While we support EPA's decision to consider multiple years of chemical releases reported to the TRI, NEI, and DMR, as well as data reported to the National Response Center and the DOT Hazmat Incident Report Data, EPA did not consider other sources of chemical release data, including all reasonably available data sources indicating chemical accidents, spills, and other peak emission events. The impacts of chemical accidents, spills, or releases that can result in acute risks to fenceline communities are "known" and "reasonably foreseen" consequences of chemical manufacturing, transportation, use, and disposal, and therefore, they must be considered under TSCA.[114] EPA also failed to account for the peak exposures that fenceline communities experience during facility start-up,

[111] 15 U.S.C. § 2625(h).
[112] 15 U.S.C. § 2605(b)(4)(A); 15 U.S.C. § 2602(12).
[113] Rayasam, S. D. G., Koman, P. D., Axelrad, D. A., Woodruff, T. J., & Chartres, N. (2022). Toxic Substances Control Act (TSCA) Implementation: How the Amended Law Has Failed to Protect Vulnerable Populations from Toxic Chemicals in the United States. *Environmental science & technology*, *56*(17), 11969–11982. https://doi.org/10.1021/acs.est.2c02079.
[114] 15 U.S.C. § 2602(4).

shutdown, and malfunction conditions; as this administration has acknowledged, "*[start-up, shutdown, and malfunction]* events have the potential to lead to higher *emissions* and endanger public health."[115]

In addition, EPA's modeling from TRI, NEI, and DMR reported releases effectively erases facilities' peak chemical releases by using a continuous exposure scenario that averages a facility's annual emissions over its estimated period of operations, which EPA has estimated ranges from 250-365 days.[116] Data on peak emissions releases are available from chemical incident reports, stack and facility monitoring records, and other sources that are "reasonably available" to EPA. EPA should rely on these sources to more comprehensively estimate 1,1-DCA exposures occurring as a result of environmental releases.

While we support EPA's decision to examine aggregate exposures resulting from releases from multiple TRI facilities, EPA failed to apply this same methodology to NEI facilities and failed to aggregate fenceline and worker exposures, even though fenceline community residents may also be exposed to the same chemical in their workplaces and their homes. The SACC raised these concerns in its evaluation of the Fenceline Assessment Approach and stated that "[t]he accuracy and/or completeness of the data used to develop the screening analysis was not adequately supported in the document" and "it did not defensibly represent actual exposure of fenceline communities." The SACC further recommended that EPA consider "multiple source exposures, aggregate exposures, and double aggregate and occupational exposures from workers living near and working at the facilities" where chemicals like 1,1-DCA are released.[117]

EPA also failed to consider increased susceptibility when assessing risks to fenceline communities. EPA thus fails to use risk assessment methodologies that are "consistent with the best available science,"[118] and understates the risks posed to fenceline communities. It is well established in the scientific literature that people living in fenceline communities are more likely to experience adverse health effects from chemical exposures than the general population due to a variety of factors that make them more susceptible to harm.[119,120] These factors can include biological traits like age, genetic makeup, and pre-existing health conditions, which are

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[115] Memorandum from Janet McCabe, Deputy Adm'r, EPA, to Reg'l Adm'rs, EPA 2 (Sept. 30, 2021), https://www.epa.gov/system/files/documents/2021-09/oar-21-000-6324.pdf (withdrawing Oct. 9, 2020, memorandum addressing startup, shutdown, and malfunctions in state implementation plans).
[116] U.S. EPA (2024). Draft Human Risk Evaluation for 1,1-Dichloroethane (DCA), p. 59.
[117] U.S. EPA (2022). Final Report on Draft TSCA Screening Level Approach for Assessing Ambient Air and Water Exposures to Fenceline Communities Version 1.0 pp 15.Available: https://www.epa.gov/system/files/documents/2022-01/draft-fenceline-report_sacc.pdf.
[118] 15 U.S.C. § 2625(h).
[119] McHale, C. M., Osborne, G., Morello-Frosch, R., Salmon, A. G., Sandy, M. S., Solomon, G., Zhang, L., Smith, M. T., & Zeise, L. (2018). Assessing health risks from multiple environmental stressors: Moving from G×E to I×E. Mutation research. Reviews in mutation research, 775, 11–20. https://doi.org/10.1016/j.mrrev.2017.11.003.
[120] Rayasam, S. D. G., Koman, P. D., Axelrad, D. A., Woodruff, T. J., & Chartres, N. (2022). Toxic Substances Control Act (TSCA) Implementation: How the Amended Law Has Failed to Protect Vulnerable Populations from Toxic Chemicals in the United States. Environmental science & technology, 56(17), 11969–11982. https://doi.org/10.1021/acs.est.2c02079.

collectively considered *intrinsic* factors.[121] For example, studies examining air pollution exposure found that underlying diabetes increased the risk of cardiovascular disease from exposure to particulate matter.[122] Susceptibility to harm from chemical exposures can also be increased by external stressors, which include psychosocial stress from experiencing income inequality, violence, racism, healthcare inequity, or food insecurity.[123, 124,125,126,127,128,129] In general, people of color in the United States experience disproportionately high levels of these external stressors, collectively known as *extrinsic* susceptibility factors, and as a result, people of color are more susceptible to negative health outcomes from chemical exposures.[130,131]

While any individual internal or external factor can enhance susceptibility, people living in fenceline communities often experience multiple intrinsic and extrinsic factors simultaneously, which increases the potential for even greater susceptibility to adverse effects from chemical

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[121] National Academies of Sciences, Engineering, and Medicine. 2023. Building Confidence in New Evidence Streams for Human Health Risk Assessment: Lessons Learned from Laboratory Mammalian Toxicity Tests. Washington, DC: The National Academies Press. https://doi.org/10.17226/26906.

[122] Zanobetti, A., & Schwartz, J. (2001). Are diabetics more susceptible to the health effects of airborne particles?. American journal of respiratory and critical care medicine, 164(5), 831–833. https://doi.org/10.1164/ajrccm.164.5.2012039; Zanobetti, A., Schwartz, J., & Gold, D. (2000). Are there sensitive subgroups for the effects of airborne particles?. Environmental health perspectives, 108(9), 841–845. https://doi.org/10.1289/ehp.00108841.

[123] Morello-Frosch, R., Zuk, M., Jerrett, M., Shamasunder, B., & Kyle, A. D. (2011). Understanding the cumulative impacts of inequalities in environmental health: implications for policy. Health affairs (Project Hope), 30(5), 879–887. https://doi.org/10.1377/hlthaff.2011.0153.

[124] McHale, C. M., Osborne, G., Morello-Frosch, R., Salmon, A. G., Sandy, M. S., Solomon, G., Zhang, L., Smith, M. T., & Zeise, L. (2018). Assessing health risks from multiple environmental stressors: Moving from G×E to I×E. Mutation research. Reviews in mutation research, 775, 11–20. https://doi.org/10.1016/j.mrrev.2017.11.003.

[125] Payne-Sturges, D. C., Scammell, M. K., Levy, J. I., Cory-Slechta, D. A., Symanski, E., Carr Shmool, J. L., Laumbach, R., Linder, S., & Clougherty, J. E. (2018). Methods for Evaluating the Combined Effects of Chemical and Nonchemical Exposures for Cumulative Environmental Health Risk Assessment. International journal of environmental research and public health, 15(12), 2797. https://doi.org/10.3390/ijerph15122797.

[126] Gee, G. C., & Payne-Sturges, D. C. (2004). Environmental health disparities: a framework integrating psychosocial and environmental concepts. Environmental health perspectives, 112(17), 1645–1653. https://doi.org/10.1289/ehp.7074.

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

[128] Koman, P. D., Singla, V., Lam, J., & Woodruff, T. J. (2019). Population susceptibility: A vital consideration in chemical risk evaluation under the Lautenberg Toxic Substances Control Act. PLoS biology, 17(8), e3000372. https://doi.org/10.1371/journal.pbio.3000372.

[129] National Academies of Sciences, Engineering, and Medicine. 2023. Building Confidence in New Evidence Streams for Human Health Risk Assessment: Lessons Learned from Laboratory Mammalian Toxicity Tests. Washington, DC: The National Academies Press. https://doi.org/10.17226/26906.

[130] Gee, G. C., & Payne-Sturges, D. C. (2004). Environmental health disparities: a framework integrating psychosocial and environmental concepts. Environmental health perspectives, 112(17), 1645–1653. https://doi.org/10.1289/ehp.7074.

[131] Payne-Sturges, D. C., Scammell, M. K., Levy, J. I., Cory-Slechta, D. A., Symanski, E., Carr Shmool, J. L., Laumbach, R., Linder, S., & Clougherty, J. E. (2018). Methods for Evaluating the Combined Effects of Chemical and Nonchemical Exposures for Cumulative Environmental Health Risk Assessment. International journal of environmental research and public health, 15(12), 2797. https://doi.org/10.3390/ijerph15122797.

exposures.[132] A study examining nine fenceline communities across the United States found that people living within three miles of a polluting facility were more likely to be low-income people of color with reduced access to quality healthcare and healthy foods. In addition, the risk of developing cancer or respiratory illness from air pollution exceeded national averages in all but one of these communities.[133]

Accordingly, both intrinsic and extrinsic factors can increase susceptibility and thus must be taken into consideration when evaluating risks to "potentially exposed or susceptible subpopulations,"[134,135,136,137] including fenceline communities. The National Academy of Sciences has warned that failing to account for both intrinsic and extrinsic susceptibility factors could lead to a vast underestimation of risks from chemical exposures in the human population.[138] The SACC raised similar concerns in its evaluation of EPA's proposed Fenceline Assessment Approach, and stressed the importance of considering the impact of non-chemical stressors in chemical risk evaluation.[139] The SACC further recommended that EPA could apply safety factors to account for factors like co-occurrence of multiple chemical and non-chemical stressors.[140] To comply with TSCA and adhere to recommendations provided by EPA's own scientific peer reviewers, EPA must consider not only fenceline communities' increased exposures but also their heightened susceptibility to 1,1-DCA as a result of intrinsic and extrinsic susceptibility factors.

Despite these shortcomings, EPA still found that certain conditions of use pose high cancer risk to fenceline communities that constitutes unreasonable risk, even without appropriately accounting for all exposures and risks. For example, EPA found that 1,1-DCA ambient air exposures resulting from releases reported to the TRI and NEI for at least 88 total facilities were

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[132] Environmental Justice Health Alliance for Chemical Policy Reform et al. (2018). Life at the Fenceline: Understanding Cumulative Health Hazards in Environmental Justice Communities. https://ej4all.org/assets/media/documents/Life%20at%20the%20Fenceline%20-%20English%20-%20Public.pdf.

[133] Environmental Justice Health Alliance for Chemical Policy Reform et al. (2018). Life at the Fenceline: Understanding Cumulative Health Hazards in Environmental Justice Communities. https://ej4all.org/assets/media/documents/Life%20at%20the%20Fenceline%20-%20English%20-%20Public.pdf.

[134] National Research Council. 2009. Science and Decisions: Advancing Risk Assessment. pp 110-111.Washington, DC: The National Academies Press. https://doi.org/10.17226/12209

[135] Morello-Frosch, R., Zuk, M., Jerrett, M, Shamasunder, B., & Kyle, A. D. (2011). Understanding the cumulative impacts of inequalities in environmental health: implications for policy. Health affairs (Project Hope), 30(5), 879–887. https://doi.org/10.1377/hlthaff.2011.0153

[136] McHale, C. M., Osborne, G., Morello-Frosch, R., Salmon, A. G., Sandy, M. S., Solomon, G., Zhang, L., Smith, M. T., & Zeise, L. (2018). Assessing health risks from multiple environmental stressors: Moving from G×E to I×E. Mutation research. Reviews in mutation research, 775, 11–20. https://doi.org/10.1016/j.mrrev.2017.11.003.

[137] Payne-Sturges, D. C., Scammell, M. K., Levy, J. I., Cory-Slechta, D. A., Symanski, E., Carr Shmool, J. L., Laumbach, R., Linder, S., & Clougherty, J. E. (2018). Methods for Evaluating the Combined Effects of Chemical and Nonchemical Exposures for Cumulative Environmental Health Risk Assessment. International journal of environmental research and public health, 15(12), 2797. https://doi.org/10.3390/ijerph15122797.

[138] National Research Council. 2009. Science and Decisions: Advancing Risk Assessment. pp 9-10.Washington, DC: The National Academies Press. https://doi.org/10.17226/12209.

[139] U.S. EPA (2022). Final Report on Draft TSCA Screening Level Approach for Assessing Ambient Air and Water Exposures to Fenceline Communities Version 1.0 pp 49.Available: https://www.epa.gov/system/files/documents/2022-01/draft-fenceline-report_sacc.pdf.

[140] U.S. EPA (2022). Final Report on Draft TSCA Screening Level Approach for Assessing Ambient Air and Water Exposures to Fenceline Communities Version 1.0 pp 65.Available: https://www.epa.gov/system/files/documents/2022-01/draft-fenceline-report_sacc.pdf.

associated with cancer risk (more than 1 x 10^{-6}) to fenceline residents for three conditions of use.[141] However, EPA failed to acknowledge the risk associated with 78 NEI facilities, and dismissed the risks associated with 10 TRI facilities, claiming that due to a "land use assessment," EPA could not identify any residential communities within 1000m of the TRI facilities associated with high cancer risk. EPA stated that "fenceline community exposures are not anticipated for any of the GIS located facilities with risk for all three of the COUs that rely on release data reported to TRI."[142] However, EPA itself acknowledged that this land use assessment was associated with uncertainties, including assumptions that residents will not move in proximity to facilities in the future, and the inherent uncertainty associated with mapping TRI emission sources. EPA acknowledges:

> "[I]n some cases, the TRI coordinates may be located at the edge of the facility complex, such as at an entrance to the facility, a mailbox address, or a road leading up to the facility, which may not capture the actual site of emission."[143]

Given the current uncertainty in pinpointing TRI emissions sources, EPA cannot conclusively determine that residents of fenceline communities are not within 1,000 meters of a polluting facility without incorporating a larger buffer to account for precision errors. Therefore, the EPA should not minimize or disregard estimated risks to fenceline communities based solely on this single land use assessment, which carries significant uncertainty.

To address the potential underestimation of risk due to critical methodological flaws in the fenceline assessment approach, EPA should more comprehensively account for fenceline community risk by making easily implemented revisions to its fenceline analysis. For example, EPA could use existing chemical release data and the same models and information included in the fenceline analysis to better account for all relevant 1,1-DCA exposure routes, pathways, and combinations thereof in fenceline communities.[144] As detailed above, EPA could also utilize science-based adjustment factors to better account for the known but unquantified increase in fenceline communities' susceptibility to 1,1-DCA, including the increased susceptibility from cumulative exposures to multiple chemical and non-chemical stressors. To account for increased susceptibility to harm in younger age groups, California EPA's Office of Environmental Health Hazard Assessment ("OEHHA") now relies on a 30X intra-species adjustment factor that is three times higher than the one currently used by EPA. We recommend that EPA apply an expanded intra-species adjustment factor of 42X, consistent with the 42-fold human variability in toxicokinetic and toxicodynamic responses to chemical exposures observed by the WHO using a probabilistic method.[145] Application of this expanded adjustment factor will more adequately capture human variability in the response to 1,1-DCA exposures, including in highly exposed or susceptible subpopulations, and is consistent with recommendations made by scientific

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[141] U.S. EPA (2024). Draft Risk Evaluation for 1,1-Dichloroethane p. 336-340.
[142] U.S. EPA (2024). Draft Risk Evaluation for 1,1-Dichloroethane p. 350.
[143] U.S. EPA (2024). Draft Risk Evaluation for 1,1-Dichloroethane p. 467.
[144] U.S. EPA (2022) *Draft TSCA Screening Level Approach for Assessing Ambient Air and Water Exposures to Fenceline Communities Version 1.0*. Document No. EPA-744-D-22-001. Available: https://www.regulations.gov/document/EPA-HQ-OPPT-2021-0415-0012
[145] WHO IPCS. (2017). Guidance Document on Evaluating and Expressing Uncertainty in Hazard Characterization. Available: http://www.inchem.org/documents/harmproj/harmproj/harmproj11.pdf.

experts.[146]

b. EPA must account for cumulative exposures and risks.

The 1,1-DCA Draft Risk Evaluation also fails to consider communities' cumulative exposures to other chemicals, in addition to 1,2-DCA, from a variety of sources and pathways. In doing so, EPA is ignoring the real-world exposures and risks faced by many fenceline communities**.** EPA's failure to consider cumulative exposures in the 1,1-DCA Draft Risk Evaluation is particularly problematic since EPA has determined that 1,2-DCA is an appropriate hazard analog for 1,1-DCA. Chemical release data reported to the TRI indicates that certain facilities release both 1,1-DCA and 1,2-DCA in high volumes.[147] EPA must, at minimum, evaluate potential cumulative risk posed by exposures to 1,1-DCA and 1,2-DCA, in addition to other chemicals that contribute towards common adverse health outcomes, which could increase the likelihood of harm to exposed communities.[148,149,150, 151,152] This includes chemicals like 1,1,1-trichloroethane and vinyl chloride, which are structurally and pharmacologically related to 1,1-DCA.[153] For EPA to assess fenceline communities' risks without taking into account their cumulative exposures is not "consistent with the best available science,"[154] in violation of TSCA. The National Research Council has not only recommended the consideration of cumulative exposures in risk evaluations, but has also warned that "risk assessment might become irrelevant in many decision contexts" without it.[155,156] TSCA requires EPA to use scientifically supported approaches and

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[146] Varshavsky, J. R., Rayasam, S. D. G., Sass, J. B., Axelrad, D. A., Cranor, C. F., Hattis, D., Hauser, R., Koman, P. D., Marquez, E. C., Morello-Frosch, R., Oksas, C., Patton, S., Robinson, J. F., Sathyanarayana, S., Shepard, P. M., & Woodruff, T. J. (2023). Current practice and recommendations for advancing how human variability and susceptibility are considered in chemical risk assessment. Environmental health : a global access science source, 21(Suppl 1), 133. https://doi.org/10.1186/s12940-022-00940-1.

[147] EPA, TRI Explorer, https://enviro.epa.gov/triexplorer/tri_release.chemical.

[148] National Research Council. 2008. Phthalates and Cumulative Risk Assessment: The Tasks Ahead. pp 4-11. Washington, DC: The National Academies Press. https://doi.org/10.17226/12528.

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

[150] Rayasam, S. D. G., Koman, P. D., Axelrad, D. A., Woodruff, T. J., & Chartres, N. (2022). Toxic Substances Control Act (TSCA) Implementation: How the Amended Law Has Failed to Protect Vulnerable Populations from Toxic Chemicals in the United States. *Environmental science & technology*, *56*(17), 11969–11982. https://doi.org/10.1021/acs.est.2c02079.

[151] Vandenberg, L. N., Rayasam, S. D. G., Axelrad, D. A., Bennett, D. H., Brown, P., Carignan, C. C., Chartres, N., Diamond, M. L., Joglekar, R., Shamasunder, B., Shrader-Frechette, K., Subra, W. A., Zarker, K., & Woodruff, T. J. (2023). Addressing systemic problems with exposure assessments to protect the public's health. Environmental health : a global access science source, 21(Suppl 1), 121. https://doi.org/10.1186/s12940-022-00917-0.

[152] Pullen Fedinick, K., Yiliqi, I., Lam, Y., Lennett, D., Singla, V., Rotkin-Ellman, M., & Sass, J. (2021). A Cumulative Framework for Identifying Overburdened Populations under the Toxic Substances Control Act: Formaldehyde Case Study. International journal of environmental research and public health, 18(11), 6002. https://doi.org/10.3390/ijerph18116002.

[153] U.S. Department of Health and Human Services. (2004). Interaction Profile for 1,1-Dichloroethane, 1,1-Trichloroethane, Trichloroethylene. https://www.atsdr.cdc.gov/interactionprofiles/ip-vocs/ip02.pdf.

[154] 15 U.S.C. § 2625(h).

[155] National Research Council. 2009. Science and Decisions: Advancing Risk Assessment. pp 9-10.Washington, DC: The National Academies Press. https://doi.org/10.17226/12209.

[156] National Research Council. 2008. Phthalates and Cumulative Risk Assessment: The Tasks Ahead.pp 4-11. Washington, DC: The National Academies Press. https://doi.org/10.17226/12528.

methodologies to "integrate and assess available information on hazards and exposures"—including those that contribute to cumulative risks in fenceline communities.[157] This information includes a recent study that outlined methods for identifying cumulative exposures to chemicals that contribute to similar adverse health effects in highly exposed and susceptible groups.[158] Consistent with recommendations made by scientific experts,[159] EPA should conduct a cumulative risk assessment for 1,1-DCA, 1,2-DCA, and other chemicals like vinyl chloride and 1,1,1-trichloroethane. In place of such an assessment, EPA should, at minimum, apply additional adjustment factors to account for any cumulative risks that were not measured in the 1,1-DCA Draft Risk Evaluation.

[157] 15 U.S.C. § 2605(b)(4)(F)(i).

[158] Pullen Fedinick, K., Yiliqi, I., Lam, Y., Lennett, D., Singla, V., Rotkin-Ellman, M., & Sass, J. (2021). A Cumulative Framework for Identifying Overburdened Populations under the Toxic Substances Control Act: Formaldehyde Case Study. International journal of environmental research and public health, 18(11), 6002. https://doi.org/10.3390/ijerph18116002.

[159] Varshavsky, J. R., Rayasam, S. D. G., Sass, J. B., Axelrad, D. A., Cranor, C. F., Hattis, D., Hauser, R., Koman, P. D., Marquez, E. C., Morello-Frosch, R., Oksas, C., Patton, S., Robinson, J. F., Sathyanarayana, S., Shepard, P. M., & Woodruff, T. J. (2023). Current practice and recommendations for advancing how human variability and susceptibility are considered in chemical risk assessment. Environmental health : a global access science source, 21(Suppl 1), 133. pp.3. https://doi.org/10.1186/s12940-022-00940-1.

Technical Appendix: Analysis of 1,1-dichloroethane and 1,2-dichloroethane non-cancer risk using IPCS methodology

In the *1,1-dichloroethane Draft Risk Evaluation and the 1,2-dichloroethane Draft Hazard Assessment*, EPA selected immunosuppression for estimation of risks from chronic oral exposures and decreased sperm concentrations for estimation of risks from chronic inhalation exposures. Points of departure for each endpoint were obtained from subchronic studies of 1,2-dichloroethane in mice, and are applied for risk characterization for both chemicals.

For risk characterization of non-cancer health effects, TSCA risk evaluations calculate a "margin of exposure" (MOE) for each exposure scenario, which is the ratio of the point of departure (POD) to the exposure level. For chronic oral exposures, the 1,1-DCA *Draft Risk Evaluation* concludes that an MOE of 1000 or more indicates that "the risk is not considered to be of concern,"[160] and a similar conclusion is made for chronic inhalation exposures and an MOE of 300 or more.

EPA's approach to risk characterization does not actually estimate risks of adverse effects in the population with chronic exposure to 1,1-DCA, but instead simply applies a "bright line" judgment of whether or not the MOE is adequate. A more informative approach for both risk characterization and risk management would be to apply the probabilistic dose-response assessment methods of the International Programme on Chemical Safety (IPCS),[161] part of the World Health Organization (WHO), to estimate the risk of adverse effects at various levels of exposure. The IPCS methodology has previously been described and applied in several peer-reviewed journal articles.[162,163,164,165,166]

We applied the IPCS approach for "quantal-deterministic" endpoints and the "approximate probabilistic" calculation (see IPCS report Fig 3.5, panel C)[167] to estimate risks of immunosuppression from chronic oral exposure to 1,2-dichloroethane and risks of decreased sperm concentrations from chronic inhalation exposures to 1,2-dichloroethane. Because EPA has selected 1,2-dichloroethane as an analog for characterizing human health risks to 1,1-

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[160] U.S. EPA (2024). Draft Risk Evaluation for1,1-Dichloroethane, p. 317.

[161] World Health Organization, International Programme on Chemical Safety (2017). Guidance document on evaluating and expressing uncertainty in hazard characterization, 2nd edition.

[162] Chiu WA, Slob W. A Unified Probabilistic Framework for Dose–Response Assessment of Human Health Effects. Environmental Health Perspectives, 2015 December;123(12): 1241–1254. doi:10.1289/ehp.1409385

[163] Nielsen, G. H., Heiger-Bernays, W. J., Levy, J. I., White, R. F., Axelrad, D. A., Lam, J., Chartres, N., Abrahamsson, D. P., Rayasam, S. D. G., Shaffer, R. M., Zeise, L., Woodruff, T. J., Ginsberg, G. L. (2023). Application of probabilistic methods to address variability and uncertainty in estimating risks for non-cancer health effects. Environ Health, 21(Suppl 1), 129. https://doi.org/10.1186/s12940-022-00918-z

[164] Chiu WA, Axelrad DA, Dalaijamts C, Dockins C, Shao K, Shapiro AJ, Paoli G. Beyond the RfD: broad application of a probabilistic approach to improve chemical dose-response assessment for non-cancer effects. Environmental Health Perspectives, 2018 June;126(6):067009. doi:10.1289/EHP3368

[165] Blessinger T, Davis A, Chiu WA, Stanek J, Woodall GM, Gift J, Thayer KA, Bussard D. Application of a unified probabilistic framework to the dose-response assessment of acrolein. Environment International, 2020 October;143:105953. doi: 10.1016/j.envint.2020.105953

[166] Chiu WA, Paoli GM. Recent Advances in Probabilistic Dose–Response Assessment to Inform Risk-Based Decision Making. Risk Analysis, 2021 April;41(4):596-609. doi: 10.1111/risa.13595

[167] World Health Organization, International Programme on Chemical Safety (2017). Guidance document on evaluating and expressing uncertainty in hazard characterization, 2nd edition.

dichloroethane, all results of this analysis are applicable to both chemicals. The analysis involved the following steps:

1. Derivation of IPCS POD and corresponding uncertainty adjustments
2. Application of study duration adjustments
3. Application of interspecies adjustments
4. Application of intraspecies adjustments
5. Calculation of HD_M^I - the human dose (HD) of 1,2-DCA associated with a particular magnitude of effect M at a particular population incidence I.

For each aspect of the analysis, including the values used to derive the IPCS POD and the adjustment factors applied to derive the HD_M^I, the IPCS methodology uses a 50th percentile value (P50) as a central estimate and the ratio of 95th percentile to 50th percentile (P95/P50) as a measure of uncertainty in the central estimate. The POD and HD_M^I values presented in this analysis for oral exposures represent daily exposures expressed in milligrams per kilogram per day (mg/kg-day), and for inhalation exposures represent exposure concentrations for a work schedule of 40 hours per week in parts per million (ppm).

We demonstrate each of these steps starting with the EPA PODs to derive a set of oral and inhalation HD_M^I values for different levels of population incidence.

STEP 1: Derivation of IPCS POD and corresponding uncertainty adjustments

The IPCS methodology requires the use of an ED_{50} (median effective dose) value as the POD for quantal-deterministic endpoints. Since an ED_{50} is not available from the EPA risk evaluation for either the oral or inhalation study, we began with EPA's chosen POD from each study and applied adjustments provided by the IPCS methodology. At the same time, we incorporated quantitative uncertainties for each of these adjustments. Because EPA's oral POD is a lowest-observed-adverse-effect level (LOAEL) and its inhalation POD is the lower confidence limit on a benchmark concentration (BMCL), the adjustments applied to determine the IPCS POD (i.e., the ED_{50}) are different between the oral and inhalation analyses.

EPA used a LOAEL of 4.89 mg/kg-day as the POD for chronic oral exposure. The first adjustment to derive an ED_{50}, as required by the IPCS methodology, is to apply a factor to convert the LOAEL to a no-observed-adverse-effect level (NOAEL). For this adjustment, Chiu et al. 2018 recommends applying as a central estimate (P50) the traditional LOAEL-to-NOAEL uncertainty factor reported in the existing EPA assessment (which is a factor of 3 for 1,1-DCA and 1,2-DCA), and the P95/P50 ratio representing uncertainty equal to 3.[168]

[168] Chiu WA, Axelrad DA, Dalaijamts C, Dockins C, Shao K, Shapiro AJ, Paoli G. Beyond the RfD: broad application of a probabilistic approach to improve chemical dose-response assessment for non-cancer effects. Environmental Health Perspectives, 2018 June;126(6):067009. Figure 4. doi:10.1289/EHP3368.

The second adjustment is to apply a factor to convert the NOAEL to an ED_{50}. For quantal-deterministic endpoints, the IPCS framework recommends a central estimate (P50) of 2/9 and a P95/P50 ratio representing uncertainty equal to 5.[169]

The median (P50) estimate of the ED_{50} is then derived by dividing the LOAEL by the two adjustment factors (P50). The uncertainty adjustments (P95/P50) for each POD aspect are combined into a composite P95/P50 value. In the IPCS approximate probabilistic calculation template, those values are entered as follows:

Determination of point of departure (POD) and its uncertainty[a] for probabilistic dose-response analysis of chronic 1,2-dichloroethane oral exposure		
Aspect	**P50**	**P95/P50**
LOAEL	4.89 mg-kg-day	1
$AF_{LOAEL\text{-}to\text{-}NOAEL}$[b]	3	3
$AF_{NOAEL\text{-}to\text{-}ED50}$[c]	0.22	5
IPCS POD = ED_{50}	**7.3 mg/kg-day**	**7.02**[d]

[a] Uncertainty is expressed as the ratio of the 95th percentile (P95) to the 50th percentile (P50).
[b] The EPA draft risk evaluations for 1,1-DCA and 1,2-DCA apply a LOAEL-to-NOAEL uncertainty factor of 3, which is then the P50 value for the IPCS adjustment factor, per Chiu et al. (2018), Table 4.
[c] World Health Organization, International Programme on Chemical Safety (2017). Guidance document on evaluating and expressing uncertainty in hazard characterization, 2nd edition, Table 4.1
[d] (Composite P95/P50) = $10^{[(\log 1)^2 + (\log 3)^2 + (\log 5)^2]^{0.5}} = 7.02$

EPA used a benchmark response (BMR) of 5% to derive the BMCL for decreased sperm concentrations from 1,2-DCA inhalation exposure. The chronic inhalation non-cancer $BMCL_{05}$ for a work schedule of 40 hours per week (rather than continuous exposure) is 22.0 ppm, and the BMC_{05} is 27.7 ppm.[170] The IPCS framework uses the BMC as the P50 estimate. The P95/P50 ratio, representing uncertainty in the BMC, is equal to the BMC/BMCL ratio (27.7 ppm / 22.0 ppm = 1.26).

The ED_{50} and its uncertainty are derived by applying the following conversion from Chiu et al. 2018: "if ED50 not reported: BMD at the reported BMR is multiplied by an additional factor of 3.0; additional uncertainty through adding 1.5^2 to $(P95/P50)^2$."[171]

[169] World Health Organization, International Programme on Chemical Safety (2017). Guidance document on evaluating and expressing uncertainty in hazard characterization, 2nd edition, Table 4.1.
[170] U.S. EPA (2024). Draft Risk Evaluation for 1,1-Dichloroethane, p. 273 and Table 5-51.
[171] Chiu WA, Axelrad DA, Dalaijamts C, Dockins C, Shao K, Shapiro AJ, Paoli G. Beyond the RfD: broad application of a probabilistic approach to improve chemical dose-response assessment for non-cancer effects. Environmental Health Perspectives, 2018 June;126(6):067009. Figure 4. doi:10.1289/EHP3368

The median (P50) estimate of the ED_{50} is then calculated by multiplying the BMC_{05} by the two adjustment factors (P50). The uncertainty adjustments (P95/P50) for each POD aspect are combined into a composite P95/P50 value. In the IPCS approximate probabilistic calculation template, those values are entered as follows:

Determination of point of departure (POD) and its uncertainty[a] for probabilistic dose-response analysis of chronic 1,2-dichloroethane inhalation exposure		
Aspect	**P50**	**P95/P50**
BMC_{05}[b]	27.7 ppm	1.26
BMC-to-ED_{50} adjustment[c]	3.0	1.5
IPCS POD = ED_{50}	**83.1 ppm**	**1.59**[d]

[a] Uncertainty is expressed as the ratio of the 95th percentile (P95) to the 50th percentile (P50)
[b] U.S. EPA (2024). Draft Risk Evaluation for Draft Risk Evaluation for 1,1-Dichloroethane, p. 273 and Table 5-51.
[c] Chiu WA, Axelrad DA, Dalaijamts C, Dockins C, Shao K, Shapiro AJ, Paoli G. Beyond the RfD: broad application of a probabilistic approach to improve chemical dose-response assessment for non-cancer effects. Environmental Health Perspectives, 2018 June;126(6):067009, Figure 4.
[d] (Composite P95/P50) = $10^{[(\log 1.26)^2 + (\log 1.5)^2]^{0.5}} = 1.59$

STEP 2: Application of study duration (subchronic-to-chronic) adjustments

EPA applied a study duration adjustment for both the oral 2-week study and the inhalation 4-week study of 1,2-DCA. We applied the IPCS adjustments for subchronic-to-chronic study duration: a central estimate (P50) of 2, and a P95/P50 factor of 4 to represent uncertainty in the central estimate.[172]

In the IPCS approximate probabilistic calculation template, those values are entered as follows:

Duration adjustment ($AF_{Subchronic}$) for probabilistic dose-response analysis of chronic 1,2-dichloroethane oral and inhalation exposure		
Aspect	**P50**	**P95/P50**
$AF_{Subchronic}$	2	4

STEP 3: Application of interspecies (animal-to-human) adjustments

For interspecies (animal-to-human) adjustments, the IPCS methodology first considers a factor for body-size scaling, and then a factor for remaining toxicokinetic (TK) and toxicodynamic (TD) differences. The IPCS framework provides equations for calculating the body size scaling adjustment factor for oral exposure, based on the assumed human body weight and test species body weight. We applied EPA's assumptions for human

[172] World Health Organization, International Programme on Chemical Safety (2017). Guidance document on evaluating and expressing uncertainty in hazard characterization, 2nd edition, Table 4.2.

body weight (80 kg) and mouse body weight (0.025 kg)[173] to derive the appropriate central tendency (P50) factor and its uncertainty (P95/P50).

For body size scaling of the chronic inhalation POD, EPA used a default regional gas dose ratio (RGDR) of 1 to determine of the HEC.[174] Following IPCS framework, we similarly applied a value of 1 as the central estimate (P50) for body size adjustment, with a P95/P50 value representing uncertainty in the central estimate of 2.[175]

For the TK/TD differences remaining after body size scaling for both oral and inhalation exposure, the IPCS report recommends a central estimate (P50) of 1 (i.e., no additional interspecies differences) and representing uncertainty in the central estimate with a P95/P50 factor of 3.[176]

The IPCS recommendations are entered In the IPCS approximate probabilistic calculation template as follows:

Interspecies adjustments ($AF_{Interspecies}$) for probabilistic dose-response analysis of chronic 1,2-dichloroethane oral exposure		
Aspect	**P50**	**P95/P50**
$AF_{Interspecies\text{-}BS}$	11.26[a]	1.38[a]
$AF_{Interspecies\text{-}TK/TD}$	1	3
[a] Calculated from IPCS equation 4-2 using EPA assumptions regarding body weight of humans (80 kg) and mice (0.025 kg).		

Interspecies adjustments ($AF_{Interspecies}$) for probabilistic dose-response analysis of chronic 1,2-dichloroethane inhalation exposure		
Aspect	**P50**	**P95/P50**
$AF_{Interspecies\text{-}BS}$	1	2
$AF_{Interspecies\text{-}TK/TD}$	1	3

STEP 4: Application of intraspecies (human variability) adjustments

[173] U.S. EPA (2024). Draft Human Health Hazard Assessment for 1,2-Dichloroethane, Appendix A.
[174] U.S. EPA (2024). Draft Human Health Hazard Assessment for 1,2-Dichloroethane, p. 170.
[175] World Health Organization, International Programme on Chemical Safety (2017). Guidance document on evaluating and expressing uncertainty in hazard characterization, 2nd edition, Table 4.26
[176] World Health Organization, International Programme on Chemical Safety (2017). Guidance document on evaluating and expressing uncertainty in hazard characterization, 2nd edition, Table 4.3.

In the IPCS methodology, the value of the human variability adjustment factor ($AF_{intraspecies}$) varies depending on the incidence of the adverse effect in the exposed population – with a larger adjustment factor necessary to extrapolate from the POD to lower levels of incidence. The IPCS report provides $AF_{intraspecies}$ for several incidence (I) values. The P50 and P95/P50 values for $AF_{intraspecies}$ provided by IPCS for several values of I, along with additional values of I of interest for this analysis, are provided in the following table:

Lognormal approximation of uncertainty distributions for intraspecies variability ($AF_{Intraspecies}$) for varying levels of population incidence (I)		
Incidence (I)	**$AF_{Intraspecies}$**	
	P50	**P95/P50**
5%[a]	4.98	2.82
1%[a]	9.69	4.32
0.5%[a]	9.69	4.32
0.3% (1-in-333)[b]	14.61	5.64
0.1% (1-in-1,000)[a]	20.42	6.99
0.025% (1-in-4,000)[b]	29.89	8.94
0.01% (1-in-10,000)[a]	37.71	10.39
0.001% (1-in-100,000)[b]	64.25	14.65

[a] IPCS Table 4.5
[b] Calculated for this analysis using the same methods that were used to derive IPCS Table 4.5.

STEP 5: Calculation of HD_M^I

The output of the IPCS methodology is generically described as an HD_M^I value – the human dose (HD) associated with a particular magnitude of effect M at a particular population incidence I. For this analysis, the "M" represents the outcomes of immunosuppression (for oral exposure) and decreased sperm concentration (for inhalation exposure). The following tables present the HD_M^I results for I = 0.1% and 0.01% using the POD, $AF_{Subchronic}$, $AF_{Interspecies}$, and $AF_{Intraspecies}$ values shown above. HD_M^I values for other levels of incidence can be determined by substituting the $AF_{Intraspecies}$ values appropriate for each level of incidence into the tables below and then recalculating HD_M^I using the substituted $AF_{Intraspecies}$. Because the IPCS framework has applied interspecies adjustments, all HD_M^I values are human equivalent doses/concentrations.

The IPCS approach is a probabilistic method, so the HD_M^I is a distribution; selected values from that distribution are presented in the tables as follows:

- P05: 5th percentile estimate (lower confidence limit) of HD_M^I (this value is shown in **bold**)
- P50: 50th percentile estimate (median) of HD_M^I

- P95: 95th percentile estimate (upper confidence limit) of HD_M^I.

Calculation of HD_M^I for chronic oral exposure to 1,2-dichloroethane: immunosuppression (Incidence = 0.1%)		
Aspect	**P50**	**P95/P50**
LOAEL	4.89 mg-kg-day	1
$AF_{LOAEL\text{-}to\text{-}NOAEL}$	3	3
$AF_{NOAEL\text{-}to\text{-}ED50}$	0.22	5
IPCS POD = ED_{50}	**7.3 mg/kg-day**	**7.02**
$AF_{Subchronic}$	2	4
$AF_{Interspecies\text{-}BS}$	11.26	1.38
$AF_{Interspecies\text{-}TK/TD}$	1	3
$AF_{Intraspecies\ (I=0.1\%)}$	20.42	6.99
HD_M^I	0.02 mg/kg-day[a]	26.8[b]
	P05	**P95**
$HD_M^{I\ (c)}$	**0.0006 mg/kg-day**	0.4 mg/kg-day

[a] HD_M^I (P50) = IPCS POD / ($AF_{Subchronic}$ x $AF_{Interspecies\text{-}BS}$ x $AF_{Interspecies\text{-}TK/TD}$ x $AF_{Intraspecies}$)
[b] (Composite P95/P50) = $10^{[(\log 7.02)^2 + (\log 4)^2 + (\log 1.38)^2 + (\log 3)^2 + (\log 6.99)^2]^{0.5}} = 26.8$
[c] HD_M^I (P05) = HD_M^I (P50) / (Composite P95/P50)
HD_M^I (P95) = HD_M^I (P50) x (Composite P95/P50)

Calculation of HD_M^I for chronic oral exposure to 1,2-dichloroethane: immunosuppression (Incidence = 0.01%)		
Aspect	**P50**	**P95/P50**
LOAEL	4.89 mg-kg-day	1
$AF_{LOAEL\text{-}to\text{-}NOAEL}$	3	3
$AF_{NOAEL\text{-}to\text{-}ED50}$	0.22	5
IPCS POD = ED_{50}	**7.3 mg/kg-day**	**7.02**
$AF_{Subchronic}$	2	4
$AF_{Interspecies\text{-}BS}$	11.26	1.38
$AF_{Interspecies\text{-}TK/TD}$	1	3
$AF_{Intraspecies\ (I=0.01\%)}$	37.71	10.39
HD_M^I	0.01 mg/kg-day[a]	34.4[b]
	P05	**P95**
$HD_M^{I\,(c)}$	**0.0003 mg/kg-day**	0.3 mg/kg-day

[a] HD_M^I (P50) = IPCS POD / ($AF_{Subchronic}$ x $AF_{Interspecies\text{-}BS}$ x $AF_{Interspecies\text{-}TK/TD}$ x $AF_{Intraspecies}$)
[b] (Composite P95/P50) = $10^{[(\log 7.02)^2 + (\log 4)^2 + (\log 1.38)^2 + (\log 3)^2 + (\log 10.39)^2]^{0.5}} = 34.4$
[c] HD_M^I (P05) = HD_M^I (P50) / (Composite P95/P50)
HD_M^I (P95) = HD_M^I (P50) x (Composite P95/P50)

Calculation of HD_M^I for chronic inhalation exposure to 1,2-dichloroethane: decreased sperm concentration (Incidence = 0.1%)		
Aspect	**P50**	**P95/P50**
BMC_{05}	27.7 ppm	1.26
BMC-to-ED_{50} adjustment	3.0	1.5
IPCS POD = ED_{50}	**83.1 ppm**	**1.59**
$AF_{Subchronic}$	2	4
$AF_{Interspecies-BS}$	1	2
$AF_{Interspecies-TK/TD}$	1	3
$AF_{Intraspecies\ (I=0.1\%)}$	20.42	6.99
HD_M^I	2.0 ppm[a]	15.8[b]
	P05	**P95**
$HD_M^{I\ (c)}$	**0.1 ppm**	32 ppm

[a] HD_M^I (P50) = IPCS POD / ($AF_{Subchronic}$ x $AF_{Interspecies-BS}$ x $AF_{Interspecies-TK/TD}$ x $AF_{Intraspecies}$)
[b] (Composite P95/P50) = $10^{[(\log 1.59)^2 + (\log 4)^2 + (\log 2)^2 + (\log 3)^2 + (\log 6.99)^2]^{0.5}} = 15.8$
[c] HD_M^I (P05) = HD_M^I (P50) / (Composite P95/P50)
HD_M^I (P95) = HD_M^I (P50) x (Composite P95/P50)

Calculation of HD_M^I for chronic inhalation exposure to 1,2-dichloroethane: decreased sperm concentration (Incidence = 0.01%)		
Aspect	**P50**	**P95/P50**
BMC_{05}	27.7 ppm	1.26
BMC-to-ED_{50} adjustment	3.0	1.5
IPCS POD = ED_{50}	**83.1 ppm**	**1.59**
$AF_{Subchronic}$	2	4
$AF_{Interspecies-BS}$	1	2
$AF_{Interspecies-TK/TD}$	1	3
$AF_{Intraspecies\ (I=0.01\%)}$	37.71	10.39
HD_M^I	1.1 ppm[a]	21.1[b]
	P05	**P95**
$HD_M^{I\ (c)}$	**0.05 ppm**	23 ppm

[a] HD_M^I (P50) = IPCS POD / ($AF_{Subchronic}$ x $AF_{Interspecies-BS}$ x $AF_{Interspecies-TK/TD}$ x $AF_{Intraspecies}$)
[b] (Composite P95/P50) = $10^{[(\log 1.59)^2 + (\log 4)^2 + (\log 2)^2 + (\log 3)^2 + (\log 10.39)^2]^{0.5}} = 21.1$
[c] HD_M^I (P05) = HD_M^I (P50) / (Composite P95/P50)
HD_M^I (P95) = HD_M^I (P50) x (Composite P95/P50)

The National Academies and the WHO/IPCS have both recommended using the lower confidence limit (LCL) on a probabilistic dose-response distribution for use in decision-making, in place of a traditional reference dose (RfD) or reference concentration (RfC). The National Academies said in *Science and Decisions* that:

> multiple risk-specific doses could be provided…in the various risk characterizations that EPA produces to aid environmental decision-making.[177]
>
> A Risk-Specific Reference Dose: For quantal effects, the RfD can be defined to be the dose that corresponds to a particular risk specified to be de minimis (for example, 1 in 100,000) at a defined confidence level (for example, 95%) for the toxicity end point of concern.[178]

The WHO/IPCS said:

[177] National Research Council (2009). Science and Decisions: Advancing Risk Assessment, p. 140.
[178] National Research Council (2009). Science and Decisions: Advancing Risk Assessment, p. 140.

the LCL of the HD_M^I can be used as a probabilistic RfD to replace the deterministic RfD. In this case, the probabilistic RfD is the dose that protects the population from a specified magnitude and incidence of effect with a pre-specified per cent coverage (confidence).[179]

Consistent with the guidance from the National Academies and the IPCS, we summarize the above results in the following table of the lower confidence limit (5th percentile or P05) risk-specific doses (HD_M^I) for multiple levels of risk (incidence or I), for both oral and inhalation exposures.

Risk-specific dose estimates for non-cancer effects of chronic exposure oral and inhalation exposures to 1,2-dichloroethane		
Incidence (I)	**HD_M^I lower -confidence limit (P05)**	
	Oral (immunosuppression)	**Inhalation (decreased sperm concentration)**
5%	0.004 mg/kg-day	0.9 ppm
1%	0.002 mg/kg-day	0.4 ppm
0.5%	0.0012 mg/kg-day	0.3 ppm
0.3% (1-in-333)[b]	0.0009 mg/kg-day	--
0.1% (1-in-1,000)[a]	0.0006 mg/kg-day	0.1 ppm
0.025% (1-in-4,000)[b]	--	0.07 ppm
0.01% (1-in-10,000)	0.0003 mg/kg-day	0.05 ppm
0.001% (1-in-100,000)	0.0001 mg/kg-day	0.02 ppm

Interpretation of results

Based on application of the WHO/IPCS methodology to 1,2-dichloroethane chronic oral exposures, we find that:

- 0.002 mg/kg-d is the lower bound (95% confidence) chronic human oral dose at which immunosuppression expected in 1% of the population.
- 0.001 mg/kg-d is the lower bound (95% confidence) chronic human oral dose at which immunosuppression expected in 0.5% of the population.
- 0.0006 mg/kg-d is the lower bound (95% confidence) chronic human oral dose at which immunosuppression expected in 0.1% of the population.
- 0.0003 mg/kg-d is the lower bound (95% confidence) chronic human oral dose at which immunosuppression expected in 0.01% (1-in-10,000) of the population.

[179] World Health Organization, International Programme on Chemical Safety (2017). Guidance document on evaluating and expressing uncertainty in hazard characterization, 2nd edition, p. 12.

- 0.0001 mg/kg-d is the lower bound (95% confidence) chronic human oral dose at which immunosuppression expected in 0.001% (1-in-100,000) of the population.
- EPA's POD for chronic oral exposure to 1,2-dichloroethane is 0.89 mg/kg-day (HED), and the benchmark MOE is 1000.[180] This means that EPA concludes "the risk is not considered to be of concern"[181] for any chronic inhalation exposure less than 0.89 mg/kg-day / 1000 = 0.0009 mg/kg-day. Our analysis finds that the upper bound risk at an oral exposure of 0.0009 mg/kg-day is 0.3% (1-in-333).

Based on application of the WHO/IPCS methodology to 1,2-dichloroethane chronic inhalation exposures, we find that:

- 0.4 ppm is the lower bound (95% confidence) chronic human inhalation dose at which decreased sperm concentration is expected in 1% of the worker population.
- 0.3 ppm is the lower bound (95% confidence) chronic human inhalation dose at which decreased sperm concentration is expected in 0.5% of the worker population.
- 0.1 ppm is the lower bound (95% confidence) chronic human inhalation dose at which decreased sperm concentration is expected in 0.1% of the worker population.
- 0.05 ppm is the lower bound (95% confidence) chronic human inhalation dose at which decreased sperm concentration is expected in 0.01% (1-in-10,000) of the worker population.
- 0.02 ppm is the lower bound (95% confidence) chronic human inhalation dose at which decreased sperm concentration is expected in 0.001% (1-in-100,000) of the worker population.
- EPA's POD for chronic inhalation exposure to 1,2-dichloroethane is 22.0 ppm (HEC) for a work schedule of 40 hours per week, and the benchmark MOE is 300.[182] This means that EPA concludes "the risk is not considered to be of concern"[183] for any chronic worker inhalation exposure less than 22 ppm / 300 = 0.07 ppm. Our analysis finds that the upper bound risk at an inhalation exposure of 0.07 ppm is 0.025% (1-in-4,000).

Because EPA has selected 1,2-dichloroethane as an analog for characterizing human health risks to 1,1-dichloroethane, all results of this analysis are applicable to both chemicals.

The estimates of HD_M^I presented here were based entirely on input values and equations available from the WHO/IPCS methodology document and from EPA's draft risk evaluation documents for 1,1-dichloroethane and 1,2-dichloroethane. An important caveat to these calculations is that the values used to represent human variability may be understated. The IPCS default human variability distribution is based on 37 data sets for human toxicokinetic variability and 34 data sets for human toxicodynamic variability. Most of these data sets were obtained from controlled human exposure studies of pharmaceuticals conducted in small samples of healthy adults, representing considerably less variability than found in the general

[180] U.S. EPA (2024). Draft Human Health Hazard Assessment for 1,2-Dichloroethane, Table ES-1.
[181] U.S. EPA (2024). Draft Risk Evaluation for1,1-Dichloroethane, p. 317.
[182] U.S. EPA (2024). Draft Human Health Hazard Assessment for 1,2-Dichloroethane, Table ES-1.
[183] U.S. EPA (2024). Draft Risk Evaluation for1,1-Dichloroethane, p. 317.

population.[184,185,186] If human variability is underestimated, then the actual dose associated with each incidence level (e.g. I =1%, I = 0.1%) will be lower than the values obtained from this analysis – or in other words, risk at each dose will be underestimated.

[184] WHO. (2017). *Guidance document on evaluating and expressing uncertainty in hazard characterization. Harmonization project document 11, 2nd edition.* https://www.who.int/publications/i/item/9789241513548

[185] Hattis, D., Lynch, M.K. (2007). Empirically observed distributions of pharmacokinetic and pharmacodynamic variability in humans—Implications for the derivation of single-point component uncertainty factors providing equivalent protection as existing reference doses. In Lipscomb, J.C. & Ohanian, E.V. (Eds.), *Toxicokinetics in risk assessment* (pp. 69-93). Taylor & Francis Group. https://doi.org/10.1201/b14275

[186] Axelrad, D. A., Setzer, R. W., Bateson, T. F., DeVito, M., Dzubow, R. C., Fitzpatrick, J. W., Frame, A. M., Hogan, K. A., Houck, K., Stewart, M. (2019). Methods for evaluating variability in human health dose-response characterization. Hum Ecol Risk Assess, 25, 1-24. https://doi.org/10.1080/10807039.2019.1615828