March 5, 2025

Comments from Scientists, Academics, and Clinicians on the Draft Risk Evaluation for 1,3-Butadiene 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, unless indicated otherwise by an asterisk.

We appreciate the opportunity to provide written comments on EPA's Draft Risk Evaluation for 1,3-Butadiene, (hereafter referred to as the *1,3-Butadiene Draft Risk Evaluation*) conducted under the Toxic Substances Control Act (TSCA), which requires EPA to evaluate chemical risks based on the "best available science."[1] 1,3-butadiene is used primarily as a chemical intermediate and to manufacture synthetic rubber, elastomers, and other polymers.[2] Where 1,3-butadiene is manufactured or used to make products, people can inhale it on-the-job and near facilities. People can also breathe in 1,3-butadiene from vehicle exhaust, tobacco smoke, burning wood, and wildfires.[3] EPA identified several health hazards of 1,3-butadiene, including cancer and harm to fetuses, pregnant people, and blood and immune system diseases.[4]

EPA found that 1,3-butadiene poses unreasonable risks to workers and people in fenceline communities.[5] The science supports EPA's determination of unreasonable risk. However, EPA has also significantly underestimated risk. As outlined below, EPA should update its hazard, exposure and risk evaluation to be consistent with the best available science so that it can ensure protection of the public's health, especially potentially exposed and susceptible sub-populations (PESS), from the risks of 1,3-butadiene.

EPA underestimates cancer risks from 1,3-butadiene because it relies on industry-funded studies with exposure estimates that are far higher than measured values from the National Institute for Occupational Safety and Health (NIOSH). EPA also underestimates non-cancer risks from 1,3-butadiene because it discounts the most sensitive health effect, ovarian atrophy, based on an industry-funded study that hypothesizes a mechanism of action that other authoritative sources reject.[6] In general, EPA is not following recommendations from the National Academies of Sciences, Engineering, and Medicine (NASEM) to consider bias due to financial conflicts of interest in its evaluation of studies.[7]

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[1] 15 USC §2625(h).
[2] U.S. EPA (2024). Draft Risk Evaluation for 1,3-Butadiene, p. 8.
[3] U.S. EPA (2024). Draft Risk Evaluation for 1,3-Butadiene, p. 8.
[4] U.S. EPA (2024). Draft Risk Evaluation for 1,3-Butadiene, p. 8.
[5] U.S. EPA (2024). Draft Risk Evaluation for 1,3-Butadiene, p. 9.
[6] U.S. EPA (2024). Draft Human Health Hazard Assessment for 1,3-Butadiene. p.21.
[7] National Academies of Sciences, Engineering, and Medicine. 2018. Progress Toward Transforming the Integrated Risk Information System (IRIS) Program: A 2018 Evaluation. Washington, DC: The National Academies Press.

EPA has failed to adequately consider the scientific evidence and continued to rely on a systematic review methodology that is not consistent with best practices, violating TSCA's "best available science" requirement.[8] The NASEM 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.[9] The SACC also recommended best practices in systematic review to the Agency in multiple reports.[10] 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 1,3-butadiene.

EPA repeatedly downplayed or disregarded high risks it calculated for 1,3-butadiene without adequate scientific justification. For example, EPA used only central tendency estimates of chronic 1,3-butadiene exposure and risk for workers in most conditions of use in its unreasonable risk determination, thus disregarding unreasonable risks of cancer and non-cancer effects to workers with exposures greater than median exposure levels (e.g. 50% of the exposures and people). In doing so, EPA continues to set a dangerous precedent that ignores risks to half of all workers who have exposures higher than the median.

The 1,3-Butadiene Draft Risk Evaluation also relies on a dose-response assessment that violates TSCA's "best available science" requirement. While EPA found that reduced fetal weight is a hazard of 1,3-butadiene, it failed to provide quantitative estimates of those non-cancer risks. EPA should apply methods developed by the World Health Organization (WHO) to quantify the risk of reduced fetal weight and ovarian atrophy from chronic 1,3-butadiene exposure.

Another critical concern with the 1,3-Butadiene Draft Risk Evaluation is EPA's failure to evaluate real world exposures and risks. For example, EPA fails to consider exposures from "non-TSCA" conditions of use of 1,3-butadiene, including exposures from vehicle exhaust, wood burning and fires. Given that vehicle exhaust and other fuel burning are ubiquitous sources of exposure to 1,3-butadiene, EPA will understate the risk to the general population from the TSCA uses of these chemicals if it does not account for the background exposures from these and other non-TSCA uses. The SACC recently criticized EPA's decision to disregard exposures outside of the jurisdiction of TSCA.[11]

EPA also failed to adequately identify potentially exposed or susceptible subpopulations (PESS) and calculate risks posed to these groups, as required under TSCA.[12] In the 1,3-Butadiene Draft Risk Evaluation, EPA failed to consider all PESS in several categories and did not evaluate individual level activities, nutrition, unique activities, or other chemical and non-chemical

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[8] 15 U.S.C. § 2625(h).
[9] National Academies of Sciences, Engineering, and Medicine (2021). The Use of Systematic Review in EPA's Toxic Substances Control Act Risk Evaluations.
[10] 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.
[11] U.S. EPA (2024). Science Advisory Committee on Chemicals (SACC) Meeting Minutes and Final Report for the "Draft Risk Evaluation for Di-isodecyl Phthalate (DIDP) and Draft Hazard Assessments for Di-isononyl Phthalate (DINP)," p. 16.
[12] 15 U.S.C. §§ 2602(12).

stressors that may also increase susceptibility to harm from 1,3-butadiene exposure. A failure to evaluate risk to these groups violates TSCA and results in risk characterization that is not representative of the human population.

Finally, EPA has not conducted a cumulative risk assessment of 1,3-butadiene with other chemicals that have similar health impacts. Without the results of this assessment, EPA cannot make conclusions on unreasonable risk of 1,3-butadiene in a manner that adequately safeguards human health.

Accordingly, EPA must make revisions to the 1,3-Butadiene Draft Risk Evaluation to more accurately characterize real-world exposures and risks, including to potentially exposed or susceptible subpopulations. This includes revising the risk evaluation to reflect an IUR based on measured exposures, quantitative non-cancer risk estimates for ovarian atrophy, using high-end exposure and risk estimates for all conditions of use and all exposure durations, removing the use of any scientifically unsupported justifications that downplay or disregard risk, and adopting best available scientific methods, like gold-standard systematic review methods that better account for and incorporate the scientific evidence.

Our detailed comments on the 1,3-Butadiene Draft Risk Evaluation address the following issues:

1. **EPA appropriately affirmed the mutagenic mode of action but underestimates cancer risks because of failure to account for prenatal susceptibility of pregnant workers and pregnant people in fenceline communities, failure to account for risks of breast and bladder cancers, and reliance on inaccurate exposure estimates in the calculation of inhalation unit risk (IUR).**

2. **EPA underestimates non-cancer risks because it inappropriately excludes the most sensitive non-cancer endpoint, ovarian atrophy, without appropriate scientific justification.**

3. **EPA must apply best available methods to generate quantitative estimates of noncancer risks for varying levels of exposure to 1,3-butadiene.**

4. **EPA's determination of unreasonable risk in occupational settings inappropriately discounts and disregards exposure levels of 50% of workers, including high-end exposures, without justification and violates TSCA's requirement to assess risks to groups with greater exposures.**

5. **EPA underestimates risks to fenceline communities because it did not consider real-world exposures, increased susceptibility, and cumulative exposures.**
    a. **EPA did not adequately evaluate real world exposures to 1,3-butadiene.**
    b. **EPA did not account for increased susceptibility of fenceline communities.**
    c. **EPA did not consider cumulative risk of exposures to multiple chemicals sharing common adverse outcomes with 1,3-butadiene.**

6. **EPA did not apply the best available science to identify and evaluate relevant and useful health effects studies for 1,3-butadiene.**
    a. **EPA did not conduct a comprehensive and up-to-date literature search.**
    b. **EPA used deficient inclusion and exclusion criteria for health effects evidence that inappropriately excluded important toxicity endpoints.**
    c. **EPA inappropriately excluded at least 37 PECO-relevant health effects studies from evidence integration.**
    d. **EPA's methods for evaluation of study quality need to incorporate further improvements that have been recommended by the National Academies.**
    e. **EPA continues to use unclear terminology regarding evidence synthesis and integration.**
    f. **EPA released an incomplete draft systematic review protocol for 1,3-butadiene that was not made publicly available in advance of the draft risk evaluation.**
    g. **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.**

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

8. **EPA did not conduct a cumulative risk assessment. Failure to do so will underestimate risk, especially to potentially exposed or susceptible sub-populations.**

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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Detailed Comments:

1. **EPA appropriately affirmed the mutagenic mode of action but underestimates cancer risks because of failure to account for prenatal susceptibility of pregnant workers and pregnant people in fenceline communities, failure to account for risks of breast and bladder cancers, and reliance on inaccurate exposure estimates in the calculation of inhalation unit risk (IUR).**

Consistent with decades of data from *in vitro*, cellular, animal and human studies, as well as other authoritative assessments, EPA confirms that 1,3-butadiene has a mutagenic mode of action, specifically that it "is carcinogenic through metabolism into direct-acting mutagens."[13]

As such, EPA appropriately applies age-dependent adjustment factors for children less than 16 years old.[14] However, there is significant evidence that the prenatal life stage is also susceptible to carcinogens. California EPA reviewed the evidence on differential susceptibility to carcinogens based on age and life stage and derived age adjustment values for carcinogens which include the prenatal period, proposing "a default Age-Sensitivity Factor of 10 for the third trimester until age 2 years."[15] EPA should also apply an adjustment factor of 10 for pregnant people in fenceline communities, as well as pregnant workers.

EPA should apply an additional adjustment factor to account for increased risks of breast and bladder cancers. EPA made an overall judgement of "indeterminate/ no effect" for mammary tumors based on human evidence.[16] However, one of the key studies relied on, Sathiakumar et al. 2019, had several scientific issues.[17] The standardized mortality results compared workers to the general population, which does not account for the healthy worker effect; instead, workers should have been compared to an internal control worker population. The analysis focused on workers who were ever exposed to 1,3-butadiene, but should also have been done for workers exposed to different levels of 1,3-butadiene. Finally, the study had low power, with a small number of deaths from breast cancer. The animal data shows species concordance with increases in mammary tumors in mice and rats with 1,3-butadiene exposures, indicating a significant concern for breast cancers.[18]

EPA states that "Overall, although an association between 1,3- butadiene exposure and exposure-related increase in bladder cancer mortality was observed in styrene-butadiene rubber workers,

[13] U.S. EPA (2024). Draft Risk Evaluation for 1,3-Butadiene, p. 60.
[14] U.S. EPA (2024). Draft Human Health Hazard Assessment for 1,3-Butadiene. p. 88.
[15] California EPA (2009). California Environmental Protection Agency, Office of Environmental Health Hazard Assessment. Technical Support Document for Cancer Potency Factors: Methodologies for derivation, listing of available values, and adjustments to allow for early life stage exposures, p. 50. http://oehha.ca.gov/media/downloads/crnr/tsdcancerpotency.pdf.
[16] U.S. EPA (2024). Draft Human Health Hazard Assessment for 1,3-Butadiene. p.132.
[17] Sathiakumar, Nalini MD; Tipre, Meghan DrPH; Leader, Mark BFA; Brill, Ilene MPH; Delzell, Elizabeth SD. Mortality Among Men and Women in the North American Synthetic Rubber Industry, 1943 to 2009. Journal of Occupational and Environmental Medicine 61(11):p 887-897, November 2019. | DOI: 10.1097/JOM.0000000000001688.
[18] U.S. EPA (2024). Draft Human Health Hazard Assessment for 1,3-Butadiene. pp. 132-133.

the absence of smoking data may limit the interpretation of these findings."[19] But the EPA IRIS assessment noted that data on smoking was available: "Workers are not allowed to smoke in the plants because of the explosive potential of 1,3-butadiene; therefore, the workers may have had lower cigarette consumption."[20] EPA should reconsider the bladder cancer data in light of this information.

As 1,3-butadiene has a mutagenic mode of action, EPA appropriately used a linear cancer assessment approach. However, the inhalation unit risk (IUR) EPA derived is about 10-fold lower (less potent) than the value calculated by EPA in its 2002 Integrated Risk Information System (IRIS) assessment.[21] EPA notes this is primarily due to using revised, higher exposure estimates from Macaluso et al. 2004: "when comparable exposure-response models are used, differences in key parameter estimates are due primarily to changes in exposure estimates for the SBR [styrene-butadiene rubber] cohort."[22]

EPA inappropriately used overestimated modeled exposure estimates rather than the actual measured exposures for the primary occupational health study. EPA states that the exposure estimates in Macaluso, et al.2004 "were revised upward by as much as an order of magnitude," compared to the EPA IRIS assessment.[23] This is accurate. The EPA IRIS assessment incorporated measured exposure data from NIOSH. EPA also states that "Macaluso et al. (2004) revised the exposure estimates for 1,3-butadiene that incorporated additional information, including historical industrial hygiene surveys by NIOSH."[24] It is not accurate that Macaluso et al. 2004 incorporated historical industrial hygiene surveys by NIOSH. Macaluso only compared their modeled estimates of 1,3-butadiene levels to actual measured 1,3-butadiene levels collected by NIOSH. In almost all cases, Macaluso's modeled estimates are higher, sometimes quite significantly, than NIOSH measurements (see Table 1).

[19] U.S. EPA (2024). Draft Human Health Hazard Assessment for 1,3-Butadiene. p. 43.
[20] US EPA (2002). Integrated Risk Information System: 1,3-Butadiene, p. 17. https://iris.epa.gov/static/pdfs/0139_summary.pdf.
[21] US EPA (2002). Integrated Risk Information System: 1,3-Butadiene. https://iris.epa.gov/static/pdfs/0139_summary.pdf.
[22] U.S. EPA (2024). Draft Human Health Hazard Assessment for 1,3-Butadiene, p. 67; Macaluso M, Larson R, Lynch J, Lipton S, Delzell E. Historical estimation of exposure to 1,3-butadiene, styrene, and dimethyldithiocarbamate among synthetic rubber workers. J Occup Environ Hyg. 2004 Jun;1(6):371-90. doi: 10.1080/15459620490452004. PMID: 15238328.
[23] U.S. EPA (2024). Draft Human Health Hazard Assessment for 1,3-Butadiene. p. 66.
[24] U.S. EPA (2024). Draft Human Health Hazard Assessment for 1,3-Butadiene. p. 65.

Table 1. *Data from Table VIII of Macaluso et al. 2004. Job Group-Specific 1,3-Butadiene (BD) Time-Weighted Average (TWA) Exposure Measurements from NIOSH Surveys and Estimates from Macaluso, 2004.*

	1,3-butadiene TWA (ppm)			
	NIOSH measurements		**Macaluso, 2004 modeled estimates**	
Job group	**Mean (SD)**	**Range**	**Mean**	**90% uncertainty interval**
Tank farm operator	2 (4)	0–24	13	2–113
Reactor operator	1.8 (4)	0–25	4	0–28
Recovery operator	No data			
Finishing operator	0.35 (1)	0–7	0	—
Maintenance, skilled	1.8 (7)	0–43	3.8	0–22
Maintenance, unskilled	No data			
Laboratory technician	3 (7)	0–38	5	0–58
All workers	1.1 (4)	0–43	2	2–2

There is little rationale presented in Macaluso et al. 2004 as to why modeled exposure estimate would be more reliable than the measurements taken by NIOSH.

There are clear financial conflicts of interest in both Macaluso et al. 2004 and Sathiakumar et al. 2021, the key studies EPA relied on for derivation of the new IUR: funding from the trade group that promotes chemical manufacturer's interests, the American Chemistry Council (formerly the Chemical Manufacturers' Association). The acknowledgement from Macaluso et al. 2004 says:

> This study was funded by the International Institute of Synthetic Rubber Producers and the Olefins Panel of the Chemical Manufacturers' Association.[25]

The funding statement from Sathiakumar et al. 2021 says:

> International Institute of Synthetic Rubber Producers, American Chemistry Council (Olefins Panel) and Styrene Information and Research Center. The sponsors were given an opportunity to provide comments on a draft of this paper. However, the contract between the University of Alabama at Birmingham and the sponsors stipulated that the academic investigators should independently carry out the design, conduct and reporting of the study. Accordingly, the authors made all decisions about the contents of this paper.[26]

[25] Macaluso M, Larson R, Lynch J, Lipton S, Delzell E. Historical estimation of exposure to 1,3-butadiene, styrene, and dimethyldithiocarbamate among synthetic rubber workers. J Occup Environ Hyg. 2004 Jun;1(6):371-90. doi: 10.1080/15459620490452004. PMID: 15238328.

[26] Sathiakumar N, Bolaji BE, Brill I, Chen L, Tipre M, Leader M, Arora T, Delzell E. 1,3-Butadiene, styrene and lymphohaematopoietic cancers among North American synthetic rubber polymer workers: exposure-response analyses. Occup Environ Med. 2021 Dec;78(12):859-868. doi: 10.1136/oemed-2020-107197. Epub 2021 Jun 9. PMID: 34108254; PMCID: PMC8606437.

EPA should calculate the IUR for 1,3-butadiene with the original exposure information used in its 2002 IRIS assessment which are based on measured data rather than biased modeled estimates, and incorporate updated information for the cohort to include women as well as men and a longer timeline. While EPA states that "differences in key parameter estimates are due primarily to changes in exposure estimates"[27] it is important for it to demonstrate this transparently with the updated data set.

2. EPA underestimates non-cancer risks because it inappropriately excludes the most sensitive non-cancer endpoint, ovarian atrophy, without appropriate scientific justification.

EPA inappropriately relies on a hypothesized mechanism of action (MOA) proposed in Kirman et al. 2012 to dismiss ovarian atrophy in its assessment for non-cancer hazard identification.[28] EPA adopts the proposed Kirman MOA with slight modification and uses it to suggest "there may be greatly reduced sensitivity in humans" to ovarian toxicity from 1,3-butadiene.[29] This is not supported by the scientific evidence.

First, the MOA hypothesized by Kirman and by EPA does not have supporting evidence in the critical key event, follicle depletion (which EPA calls Key Event 3). EPA acknowledges that "the mechanism for how 1,3-butadiene metabolites lead to follicle depletion is unclear."[30] Thus EPA is making a scientific decision based on an unsubstantiated hypothesis.

It is for exactly this reason, that in 2013, one year after the Kirman study was published, the California Office of Environmental Health Hazard Assessment (OEHHA) found "There is currently no accepted mode of action for the acute or chronic effects of butadiene exposure noted in this document," including ovarian atrophy.[31] Further, OEHHA found that humans are very likely *more* sensitive to ovotoxic effects, noting "Humans differ substantially from mice in lifespan and in the time available for chronic exposure to effect ovotoxicity which is far longer in humans, and the generally greater robustness of the mouse reproductive system relative to the human."[32]

Further, the conflict of interest statement for Kirman states that the American Chemistry Council provided funding for the work, yet EPA does not consider this financial conflict of interest in assessing the quality of the Kirman study and evaluating its conclusions in comparison to the

[27] U.S. EPA (2024). Draft Human Health Hazard Assessment for 1,3-Butadiene, p. 67.
[28] U.S. EPA (2024). Draft Human Health Hazard Assessment for 1,3-Butadiene, p. 22; C.R. Kirman, R.L. Grant, Quantitative human health risk assessment for 1,3-butadiene based upon ovarian effects in rodents, Regulatory Toxicology and Pharmacology, Volume 62, Issue 2, 2012, Pages 371-384, ISSN 0273-2300, https://doi.org/10.1016/j.yrtph.2011.11.001.
[29] U.S. EPA (2024) Draft Human Health Hazard Assessment for 1,3-Butadiene, p. 27.
[30] U.S. EPA (2024) Draft Human Health Hazard Assessment for 1,3-Butadiene, p. 24.
[31] California Office of Environmental Health Hazard Assessment (2013) 1,3-Butadiene reference exposure levels. p. 30. https://oehha.ca.gov/media/downloads/crnr/072613bentcrel.pdf.
[32] California Office of Environmental Health Hazard Assessment (2013) 1,3-Butadiene reference exposure levels. p. 35. https://oehha.ca.gov/media/downloads/crnr/072613bentcrel.pdf.

conclusions from OEHHA's assessment.[33] The NASEM and SACC have both recommended that EPA account for the bias that can result from financial conflicts of interest when assessing the quality of studies (see more in comment 6d below).[34]

EPA is not using the best available science when it discounts the ovarian atrophy endpoint and is instead using a hypothetical scenario with insufficient data to bolster a weak MOA analysis that other independent, authoritative sources rejected. Ovarian atrophy is the most sensitive non-cancer health hazard and there is sufficient relevant, high-quality data for EPA to use this endpoint in its non-cancer dose-response assessment.

3. EPA must apply best available methods to generate quantitative estimates of noncancer risks for varying levels of exposure to 1,3-butadiene].

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" and to ensure protection of "potentially exposed and susceptible subpopulations" (PESS).[35]

Use of the MOE, which relies on a point of departure (POD) with no extrapolation to lower doses, is a simplistic and inappropriate approach that only compares the POD to the exposure level and judges whether this ratio "is interpreted as a human health risk of concern"[36] or is interpreted as representing no concern. 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.[37]

The National Academies[38] and the World Health Organization[39] (WHO) have outlined more robust methods for risk estimation that more accurately account for variability and vulnerability

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[33] UCSF Program on Reproductive Health and the Environment. We Need the Best Science Free of Conflicts of Interest so Environmental Health Decision-Making Can Protect Public Health. https://prhe.ucsf.edu/sites/g/files/tkssra341/f/wysiwyg/UCSF%20PRHE%20EPA%20COI%20v1.pdf.
[34] National Research Council. Review of EPA's Integrated Risk Information System (IRIS) Process, p. 79. Washington, DC: National Academies Press; 2014.
[35] 15 U.S.C. § 2602(12).
[36] U.S. EPA (2024). Draft Risk Evaluation for 1,3-Butadiene, p. 53.
[37] 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; 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.
[38] National Research Council (2009). Science and Decisions: Advancing Risk Assessment, Chapter 5.
[39] 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.

across the human population and have been demonstrated in published case studies.[40] We applied the WHO methodology to the 1,3-butadiene chronic inhalation endpoint of decreased fetal weight, using the POD reported by EPA, to estimate risk-specific doses for several levels of incidence (e.g. 1%, 0.1%, etc.).

Based on application of the WHO methodology to 1,3-butadiene chronic inhalation exposures (see Technical Appendix for details), we found that:

- 0.20 ppm is the lower bound (95% confidence) chronic human inhalation dose at which reduced fetal weight is expected in 1% of the population.
- 0.14 ppm is the lower bound (95% confidence) chronic human inhalation dose at which reduced fetal weight is expected in 0.5% of the population.
- 0.07 ppm is the lower bound (95% confidence) chronic human inhalation dose at which reduced fetal weight is expected in 0.1% of the population.
- 0.03 ppm is the lower bound (95% confidence) chronic human inhalation dose at which reduced fetal weight is expected in 0.01% (1-in-10,000) of the population.
- 0.01 ppm is the lower bound (95% confidence) chronic human inhalation dose at which reduced fetal weight is expected in 0.001% (1-in-100,000) of the population.
- EPA's POD for chronic inhalation exposure to 1,3-butadiene is 2.5 ppm, and the benchmark MOE is 30.[41] This means that EPA concludes that any chronic inhalation exposure less than 2.5 ppm / 30 = 0.084 ppm is not of concern. Our analysis finds that the upper bound risk at a chronic inhalation exposure of 0.084 ppm is 0.17%, equivalent to 17-in-10,000 or approximately 1-in-600.

EPA should apply the WHO framework to the reduced fetal weight endpoint to better inform its risk characterization and risk determination for 1,3-butadiene. EPA should also apply the WHO framework to additional noncancer outcomes, including ovarian atrophy, other reproductive and developmental outcomes, and hematological effects.

4. EPA's determination of unreasonable risk in occupational settings inappropriately discounts and disregards exposure levels of 50% of workers, including high-end exposures, without justification and violates TSCA's requirement to assess risks to groups with greater exposures.

[40] 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; 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; 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; 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.

[41] U.S. EPA (2024). Draft Risk Evaluation for 1,3-Butadiene, p. 53.

EPA's risk characterization for 1,3-butadiene clearly supports its determination of unreasonable risk to workers, but EPA has underestimated risks to workers because there are significant flaws in the exposure assumptions it used. The use of high-end exposure estimates to inform risk characterization is consistent with the best available science, EPA's practice in previous TSCA risk evaluations, and with the statutory requirements of TSCA. However, in the 1,3-butadiene Draft Risk Evaluation, EPA failed to use high-end exposure estimates to inform unreasonable risk determinations for workers for chronic non-cancer and cancer risks, effectively ignoring the higher-than-average risks that occur among 50% of workers.

EPA's use of central tendency estimates only for chronic exposure assumes that the exposure levels for all workers will generally fall near the "average exposures" over time. EPA inaccurately rationalizes the use of central tendency over high-end estimates:

> Central tendency is used for EPA's preliminary risk determination for chronic non-cancer and lifetime cancer estimates since longer-term average exposure (e.g., 250 days per working years or 78 years for cancer estimates) *would bias toward central tendency* (i.e., the more common risk estimates) vs. higher-end values (i.e., less common risk estimates or 95th percentile or value at which 95% of all measurements fall below it).[42]

This statement is simply the definition of the central tendency, which is representative of only typical or more common levels in the population, and not a rationale for disregarding chronic exposures and risks to workers with higher than typical chronic exposure levels. In choosing to rely on only the central tendency, EPA does not consider whether there is unreasonable risk to the 50% of the population with exposures greater than the central tendency. Further, it fails to meet its obligation under TSCA to identify any unreasonable risks to PESS, which include groups who "due to…greater exposure, may be at greater risk than the general population."[43] EPA's current approach fails to capture the risk for individuals with higher-than-average chronic exposures, such as those in the 99th percentile, who may be at much higher risk.

EPA assumes that central tendencies are more appropriate for chronic non-cancer and cancer risks "for longer-term average exposure."[44] This approach is misleading and assumes that **all** long-term exposure will align with the average of short-term measurements. EPA's approach incorrectly assumes that there is no variability across workplaces in long-term concentrations of 1,3-butadiene and that each day's concentration of 1,3-butadiene is independent of the levels in the same facility in previous days. In fact, different workplaces have different equipment and different procedures that are highly likely to result in consistent and highly-correlated day-to-day concentrations (a facility with high levels last month and last year is likely to have high levels today and tomorrow), and thus differences in chronic exposure concentrations. Long-term exposure estimates should consider not just average exposures, but also those workers who are exposed at higher levels over sustained periods of time. Relying on central tendency alone will underestimate the real-world exposure and potential harm to these workers.

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[42] U.S. EPA (2024). Draft Risk Evaluation for 1,3-Butadiene, p. 112 (Emphasis added).
[43] 15 U.S.C. §2602(12).
[44] U.S. EPA (2024). Draft Risk Evaluation for 1,3-Butadiene, p. 112.

Moreover, EPA inappropriately uses single-day averages from monitoring data as a basis for the risk estimates without additional adjustments to account for the limitations of the data. The use of single-day averages will very likely miss days with high peak concentrations, underestimating the risk to more highly exposed workers. Furthermore, the available monitoring data is not fully representative of the full range of facilities that produce or process 1,3-butadiene. It is reasonably foreseeable that there are facilities where exposures could be much higher than indicated by the available measurements.

EPA's failure to use high-end exposure estimates results in an understatement of unreasonable risks to workers. For a number of COUs EPA considered high-end exposure estimates only for intermediate (30-day) non-cancer risks, while considering only central tendency exposure estimates in the determination of chronic (longer than 30 days) non-cancer and cancer unreasonable risks. This results in underestimating chronic unreasonable risks.

For example, EPA found that the COU Manufacturing – Infrastructure/ Distribution Operations contributed to unreasonable risk from intermediate non-cancer *only*. However, EPA should have also found that this COU contributed to unreasonable risk for both chronic non-cancer and cancer impacts. EPA's calculated high-end risk estimates (which were disregarded in the unreasonable risk determination) for both chronic non-cancer and cancer were at levels that it considers unreasonable for central tendency estimates (non-cancer MOE = 11 and cancer risk = 3.4E-04).

It is unclear why EPA is not considering the risk estimates it has already calculated based on high-end exposures in its determinations of unreasonable risk.

According to Table 5-4, all of the following COUs should be considered as contributing to unreasonable risks for chronic non-cancer or cancer impacts, based on risk estimates using high-end exposures:

- Manufacturing – Infrastructure/ Distribution Operations – for chronic non-cancer and cancer risks
- Manufacturing – Instrument and Electrical – for 8-hour and 12-hour TWA cancer risks
- Manufacturing – Laboratory Technician – for chronic non-cancer and cancer risks
- Manufacturing – Machinery and Specialists – for chronic non-cancer and cancer risks
- Manufacturing – Maintenance – for chronic non-cancer and cancer risks
- Manufacturing – Maintenance – Turnaround – for chronic non-cancer and cancer risks
- Manufacturing – Operations Onsite – for chronic non-cancer and cancer risks
- Manufacturing – Safety Health and Engineering – for chronic non-cancer and cancer risks
- Processing – Processing as a Reactant – Intermediate – Infrastructure/ Distribution Operations – for chronic non-cancer and cancer risks
- Processing – Processing as a Reactant – Intermediate – Instrumental and Electrical – for cancer risks
- Processing – Processing as a Reactant – Monomer used in polymerization process – Worker – for chronic non-cancer and cancer risks

- Processing – Processing as a Reactant – Monomer used in polymerization process – ONU (12-hr TWA) – for cancer risks
- Processing – Incorporation into Formulation, Mixture, or Reaction Product – Infrastructure/ 2210 Distribution Operations – for chronic non-cancer and cancer risks
- Processing – Incorporation into Formulation, Mixture, or Reaction Product – Instrument and Electrical (8-hr and 12-hr TWA) – for cancer risks
- Processing – Incorporation into Formulation, Mixture, or Reaction Product – Laboratory Technician – for chronic non-cancer and cancer risks
- Processing – Incorporation into Formulation, Mixture, or Reaction Product – Machinery and Specialists – for chronic non-cancer and cancer risks
- Processing – Incorporation into Formulation, Mixture, or Reaction Product – Maintenance – for chronic non-cancer and cancer risks
- Processing – Incorporation into Formulation, Mixture, or Reaction Product – Maintenance – Turnaround – for chronic non-cancer and cancer risks
- Processing – Incorporation into Formulation, Mixture, or Reaction Product – Operations Onsite – for chronic non-cancer and cancer risks
- Processing – Incorporation into Formulation, Mixture, or Reaction Product – Safety Health and Engineering – for chronic non-cancer and cancer risks
- Processing – Incorporation into Article – Other: Polymer in: Rubber and plastic product manufacturing (Worker) – for chronic non-cancer and cancer risks

Furthermore, Table 5-4 presents the risk estimates in a way that is unclear and difficult for readers to interpret accurately. There is a noticeable omission of data for the COU "Processing--Processing as a Reactant – Intermediate." Table 5-4 should be revised in the final risk evaluation to improve clarity, include the missing data, and enhance overall transparency.

Overall, the use of central tendency estimates in the unreasonable risk determination does not ensure that workers with greater than the median exposure level (half of workers) are adequately protected. By prioritizing use of high-end chronic exposure and risk estimates for determining unreasonable risk and addressing exposures at the 95th or 99th percentiles, EPA would better reflect the risks to workers who are at greater risk, fulfilling its mandate to protect worker health.

5. EPA underestimates risks to fenceline communities because it did not consider real-world exposures, increased susceptibility, and cumulative exposures.

EPA's risk characterization for 1,3-butadiene clearly supports its determination of unreasonable cancer risks for communities living near facilities manufacturing and processing 1,3-butadiene.[45] However, EPA also inappropriately disregards some risks of concern to fenceline communities, citing "conservative" assumptions—but in reality, EPA is underestimating risks.[46]

EPA's analysis underestimates risks to communities because it failed to consider aggregate exposures, reasonably available chemical release data, increased susceptibility, and cumulative

[45] U.S. EPA (2024). Draft Risk Evaluation for 1,3-Butadiene, p. 119.
[46] U.S. EPA (2024). Draft Risk Evaluation for 1,3-Butadiene, p. 121.

exposures. The best available scientific protocols and methodologies for conducting risk assessments require consideration of all exposure pathways, accounting for aggregate and cumulative exposures, as well as increased susceptibility to harm.[47] Residents of fenceline communities must be considered a "potentially exposed or 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.

a. EPA did not adequately evaluate real world exposures to 1,3-butadiene.

EPA acknowledges that communities are exposed to 1,3-butadiene from all sources - those related to TSCA conditions of use, and those not related to TSCA conditions of use (COUs). However, it declines to consider aggregate (total) exposure to 1,3-butadiene in its risk evaluation "because TSCA only provides authority to regulate exposures resulting from TSCA COUs and does not provide authority to regulate beyond TSCA COUs."[48] Whether or not the exposure comes from a TSCA condition of use, it will contribute to overall exposure and to risk. EPA must consider all sources of 1,3-butadiene exposures in its general population risk evaluation.

EPA did not consider all relevant and available chemical release data in its fenceline exposure assessment. We support EPA's use of Toxics Release Inventory data from multiple reporting years, and we also support EPA's stated intent to incorporate data from the National Emissions Inventory in the final risk evaluation ("EPA intends to incorporate exposures and risks analyses based on the 2017 and 2020 NEI reported releases for the finalized draft risk evaluation").[49] However, chemical incidents and releases also result in exposures to fenceline communities and as these events are "known" and "reasonably foreseen" consequences of chemical manufacturing, transportation, use, and disposal, they must be considered under TSCA.[50] For example, the Chemical Safety and Hazard Investigation Board released a report detailing a 2019 explosion and fire at a facility in Texas with large releases of 1,3-butadiene.[51] Additionally, facility start up, shut down and malfunction conditions also result in releases of 1,3-butadiene and exposures to fenceline communities which must be included in EPA's assessment.[52] In January of 2024, a winter storm in Texas resulted in "upset" events, with facilities reporting multiple chemical releases, including thousands of pounds of 1,3-butadiene, to the Texas Commission on Environmental Quality.[53]

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[47] 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.

[48] U.S. EPA (2024). Draft General Population Exposure for 1,3-Butadiene, p. 26.

[49] U.S. EPA (2024). Draft General Population Exposure for 1,3-Butadiene, p. 8.

[50] 15 U.S.C. § 2602(4).

[51] Chemical Safety and Hazard Investigation Board (2022). Investigation report: TPC Group Chemical Plant Butadiene Unit. https://www.csb.gov/tpc-port-neches-explosions-and-fire/.

[52] 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).

[53] Environment Texas (2024). Texas emissions events during January 2024 winter storm. https://environmentamerica.org/texas/center/resources/texas-emissions-events-during-january-2024-winter-storm/;

b. EPA did not account for increased susceptibility of fenceline communities.

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.[54] These factors can include biological traits like age, genetic makeup, and pre-existing health conditions, which are collectively considered *intrinsic* factors.[55]

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, food insecurity, or extreme weather.[56] 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.[57]

The Texas Tribune (2024). Texas companies reported releasing 1 million pounds of excess pollution during recent cold snap. https://www.texastribune.org/2024/01/26/texas-pollution-emissions-cold-weather-upsets/.

[54] 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.

[55] 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.

[56] 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; 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 Exposures for Cumulative Environmental Health Risk Assessment. International journal of environmental research and public health, 15(12), 2797. https://doi.org/10.3390/ijerph15122797; 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.7074l; 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; 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; 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.

[57] 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; 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.

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 exposures.[58] EPA does not 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,"[59] and understates the risks posed to fenceline communities. It is well established in the scientific literature that both intrinsic and extrinsic factors can increase susceptibility and thus must be taken into consideration when evaluating risks to "potentially exposed or susceptible subpopulations,"[60] including fenceline communities.

Further, 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.[61] 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.[62] The SACC further recommended that EPA could apply safety factors to account for factors like co-occurrence of multiple chemical and non-chemical stressors.[63]

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 1,3-butadiene as a result of intrinsic and extrinsic susceptibility factors. EPA should apply additional adjustment factors to account for fenceline communities' increased susceptibility. 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

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[58] 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.

[59] 15 U.S.C. § 2625(h).

[60] 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; 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; 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 Exposures for Cumulative Environmental Health Risk Assessment. International journal of environmental research and public health, 15(12), 2797. https://doi.org/10.3390/ijerph15122797.

[61] 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.

[62] 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.

[63] 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.

EPA.[12] 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.[64] Application of this expanded adjustment factor will more adequately capture human variability in the response to 1,3-butadiene exposures, including in highly exposed or susceptible subpopulations, and is consistent with recommendations made by scientific experts.[65]

c. EPA did not consider cumulative risk of exposures to multiple chemicals sharing common adverse outcomes with 1,3-butadiene.

EPA fails to consider communities' cumulative exposures to other chemicals, in addition to 1,3-butadiene, from a variety of sources and pathways (see more in Comment 8, cumulative risk assessment, below). In doing so, EPA is ignoring the real-world exposures and risks faced by many fenceline communities**.** EPA's failure to consider cumulative exposures is particularly problematic for chemicals that contribute to common adverse health outcomes, which could increase the likelihood of harm to communities exposed to 1,3-butadiene.[66] For EPA to assess fenceline communities' risks without considering cumulative exposures is not "consistent with the best available science,"[67] 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.[68] TSCA requires EPA to use scientifically supported approaches and methodologies to "integrate and assess available information on hazards and exposures," including those that contribute to

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[64] WHO IPCS (2017). Guidance Document on Evaluating and Expressing Uncertainty in Hazard Characterization. Available: http://www.inchem.org/documents/harmproj/harmproj/harmproj11.pdf.

[65] 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.

[66] 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; 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; 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; 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; 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.

[67] 15 U.S.C. § 2625(h).

[68] 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; 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.

cumulative risks in fenceline communities.[69] 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.[70] Consistent with recommendations made by scientific experts,[71] EPA could apply additional adjustment factors to account for any cumulative risks to fenceline communities that are exposed to 1,3-butadiene and to other chemicals with common adverse outcomes.

6. EPA did not apply the best available science to identify and evaluate relevant and useful health effects studies for 1,3-butadiene.

a. EPA did not conduct a comprehensive and up-to-date literature search.

The need for transparent, consistent and comprehensive approaches to identifying health effects literature has been a key driver for increased adoption of systematic review methods in environmental health assessments over the past 15 years.[72] EPA's assessment of 1,3-butadiene is a concerning step backwards in this area, as the approach to identifying evidence is not clear, consistent or comprehensive. Based on the inconsistent procedures applied, it is unlikely that EPA would have identified and included all relevant health effects studies. This indicates critical deficiencies in the EPA systematic review protocol and the 1,3-butadiene Draft Risk Evaluation.

The 1,3-butadiene Draft Risk Evaluation relies on a literature search that was conducted in 2019 and has not been updated since. As stated in EPA's systematic review protocol for 1,3-butadiene:

> The search for peer-reviewed and gray literature relevant references was completed in September and May 2019, respectively.[73]

EPA has therefore not conducted a comprehensive search for studies relevant to the 1,3-butadiene Draft Risk Evaluation in the five-plus years prior to its release for public comment. EPA indicates that studies published after its 2019 literature search were considered if they were

[69] 15 U.S.C. § 2605(b)(4)(F)(i).
[70] 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.
[71] 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.
[72] National Research Council (2011). Review of the Environmental Protection Agency's Draft IRIS Assessment of Formaldehyde; Woodruff TJ, Sutton P; Navigation Guide Work Group. An evidence-based medicine methodology to bridge the gap between clinical and environmental health sciences. Health Affairs 2011 May;30(5):931-7; Rooney AA, Boyles AL, Wolfe MS, Bucher JR, Thayer KA. 2014. Systematic review and evidence integration for literature-based environmental health science assessments. Environ Health Perspect 122:711–718.
[73] U.S. EPA (2024). Draft Systematic Review Protocol for 1,3-Butadiene, p. 8.

identified in public comments or otherwise came to the attention of EPA staff.[74] This is not a comprehensive approach to identifying relevant evidence and is not consistent with the best available science.

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

PECO (population, exposure, comparator, and outcome) 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 1,3-butadiene Draft Hazard Assessment and Draft Protocol do not provide the PECO statement that was used to identify relevant health effects studies. A PECO statement was provided in the broader 2021 TSCA Draft Systematic Review Protocol, which EPA has never revised to address public comments and more than 200 SACC recommendations. The PECO statement for 1,3-butadiene is deficient and excludes a broad range of important toxicity outcomes from consideration in the draft risk evaluation.

The outcome component of the PECO statement for 1,3-butadiene health effects evidence provides the following criteria for inclusion and exclusion of studies:

> **Human:** All health outcomes (cancer and non-cancer) at the organ level or higher.
> **Animal and Plants:** All apical biological effects (effects measured at the organ level or higher) and bioaccumulation from laboratory studies with concurrently measured media and/or tissue concentrations. Apical endpoints include but are not limited to reproduction, survival, and growth.
>
> **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.[75] (emphasis added)

By limiting the relevant human and animal studies to those with "apical" effects or those with effects at the "organ level or higher," 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 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

[74] U.S. EPA (2024). Draft Systematic Review Protocol for 1,3-Butadiene, p. 12; U.S. EPA (2024). Draft Human Health Hazard Assessment for 1,3-Butadiene, p. 13.
[75] U.S. EPA (2021). Draft Systematic Review Protocol Supporting TSCA Risk Evaluations for Chemical Substances, Table_Apx H-19.

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."[76] 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,"[77] and identified "tumors, birth defects, and neurologic impairments"[78] as examples. No biochemical measures or early biological changes were mentioned among the examples.

The definition of an apical effect appears to be narrower than the definition of an adverse effect provided by the EPA IRIS program: "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."[79] The definition of adverse effect includes, for example, "a biochemical change;" such effects appear to be excluded from the 1,3-butadiene Draft Risk Evaluation as they would likely be considered cellular-level effects rather than organ-level or apical effects.

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)[80]
- reduced thyroid hormone levels (2020 TSCA risk evaluation of HBCD; 2021 toxicity assessment of PFBS) [81]
- decreased erythrocyte counts and hemoglobin (2020 TSCA risk evaluation of perchloroethylene)[82]

[76] U.S. EPA (2021). Draft Systematic Review Protocol Supporting TSCA Risk Evaluations for Chemical Substances, Table_Apx H-19.
[77] National Research Council (2007). Toxicity Testing in the 21st Century: A Vision and a Strategy, p. 38.
[78] National Research Council (2007). Toxicity Testing in the 21st Century: A Vision and a Strategy, p. 177.
[79] U.S. EPA. IRIS Glossary. https://www.epa.gov/iris/iris-glossary.
[80] 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; 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; 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.
[81] U.S. EPA (2020). Risk evaluation for cyclic aliphatic bromide cluster (HBCD); 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.
[82] U.S. EPA (2020). Risk Evaluation for Percholorethylene (Ethene, 1,1,2,2-Tetrachloro-).

- measures of immune function, such as increases in immunoglobulin E, lymphocytes, natural killer cells, and interlukin-4 levels (2020 TSCA risk evaluation of perchloroethylene)[83]
- 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)[84]
- acetylcholinesterase inhibition (numerous assessments of pesticides, including cumulative risk assessments of organophosphate and carbamate pesticides)[85]

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 1,3-butadiene Draft Risk Evaluation, or provide a justification for why these outcomes should not be considered as potential hazards of 1,3-butadiene.

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"[86] (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.[87] 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

[83] U.S. EPA (2020). Risk Evaluation for Percholorethylene (Ethene, 1,1,2,2-Tetrachloro-).
[84] U.S. EPA (2020). Risk Evaluation for Trichloroethylene; U.S. EPA (2020). Risk Evaluation for Percholorethylene (Ethene, 1,1,2,2-Tetrachloro-); 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; 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.
[85] U.S. EPA (2006). Organophosphorus cumulative risk assessment. https://www.regulations.gov/document/EPA-HQ-OPP-2006-0618-0002; U.S. EPA (2008). Revised N-methyl carbamate cumulative risk assessment. https://www.regulations.gov/document/EPA-HQ-OPP-2008-0347-0029.
[86] U.S. EPA (2021). Draft systematic review protocol supporting TSCA risk evaluations for chemical substances, p. 345.
[87] 15 U.S.C. § 2625(h).

the TSCA risk evaluations toward inclusion of industry-funded guidelines studies that are generally focused on apical endpoints.

c. EPA inappropriately excluded at least 37 PECO-relevant health effects studies from evidence integration.

In the first 10 TSCA risk evaluations completed in 2020-2021, EPA's practice was to exclude some health effects studies from consideration based on study quality evaluations; studies could be excluded based on a single perceived methodological shortcoming. EPA's draft systematic review protocol for 1,3-butadiene says that, in response to recommendations from the NASEM, SACC and public comments, all relevant studies are included:

> One main clarification is that *all references that undergo systematic review are considered for use in the risk evaluation*, even those that do not meet the various discipline and sub-discipline screening criteria or those that are categorized as supplemental information at title and abstract (TIAB) or full-text screening.[88] (emphasis in original)

This would be a welcome improvement to EPA's practice in TSCA risk evaluations; however, full consideration of EPA's systematic review procedures, as outlined in the draft protocol and hazard assessment, indicates that PECO-relevant health effects studies of 1,3-butadiene can in fact be excluded from or disregarded in the risk evaluation.

First, the draft systematic review protocol says EPA applied "further filtering" procedures to PECO-relevant health effects studies:

> References that met the PECO screening criteria and were categorized as having epidemiology information and/or animal toxicity information for the evaluation of human health hazard went through a fit-for-purpose further filtering step to determine which studies would move forward to data quality evaluation and data extraction.[89]

> To streamline the identification of studies containing dose-response data, modifications were implemented to the process described in the 2021 Draft Systematic Review Protocol (U.S. EPA, 2021). Following PECO-based screening, references that met PECO screening criteria for epidemiology underwent a further filtering process to identify the subset of potentially relevant references that proceeded to data quality evaluation and extraction.[90]

The protocol does not provide any explanation for why the application of the PECO was insufficient for determining studies to include in the risk evaluation or why this "further filtering" process (which was not included in the 2021 TSCA draft systematic review method) was applied.

[88] U.S. EPA (2024). Draft Systematic Review Protocol for 1,3-Butadiene, p. 5.
[89] U.S. EPA (2024). Draft Systematic Review Protocol for 1,3-Butadiene, p. 20.
[90] U.S. EPA (2024). Draft Systematic Review Protocol for 1,3-Butadiene, p. 20.

EPA states that one purpose of the further filtering step was to remove studies that were included in EPA's 2002 Integrated Risk Information System (IRIS) assessment of 1,3-butadiene but were not used for dose-response assessment:

> References that were included in the IRIS assessment but weren't used to determine points of departure (POD) for dose-response in the IRIS assessment didn't proceed to the remaining questions on the further filtering form and didn't proceed to data quality evaluation and extraction.[91]

EPA provides no explanation for why studies relevant to characterizing the health effects of 1,3-butadiene and previously cited by EPA were not further considered in the 1,3-butadiene Draft Risk Evaluation. EPA later states that 16 PECO-relevant epidemiology studies were not advanced to study quality evaluation or data extraction because they were cited in the IRIS assessment but not included in that assessment's dose-response analysis.[92]

EPA also used the further filtering process to exclude epidemiology studies that it judged to have inadequate data for dose-response analysis. It is not clear why, even if true that these studies did not have sufficient dose-response data, the studies should not be included in the Draft Risk Evaluation for consideration in drawing evidence integration conclusions. EPA later states that 21 PECO-relevant epidemiology studies were not advanced to study quality evaluation or data extraction because they lacked sufficient dose-response data.[93]

After excluding 37 epidemiology studies through the further filtering process, EPA asserts that these studies were all "included in hazard identification and evidence integration,"[94] but this statement is not plausible, as there is no mechanism for studies lacking quality evaluation and data extraction to be considered in evidence integration; assessors conducting the hazard identification and evidence integration do not have access to the same information for studies that were filtered out as they have for the studies that met EPA's further filtering criteria.

Implementation of the further filtering step is also unclear. EPA provides a further filtering form for epidemiology studies that includes a series of questions regarding the methods of a study. The form concludes with the Yes/No question "Should this reference move on to data quality extraction and evaluation?"[95] but no instructions are given for how the assessor is to answer this question.

Second, studies that EPA assigned an overall quality determination (OQD) of "uninformative" were not advanced to data extraction. The protocol states the EPA has continued its practice of excluding some studies based on study quality evaluations:

> data wasn't extracted from Uninformative evaluations.[96]

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[91] U.S. EPA (2024). Draft Systematic Review Protocol for 1,3-Butadiene, p. 20.
[92] U.S. EPA (2024). Draft Systematic Review Protocol for 1,3-Butadiene, p. 26.
[93] U.S. EPA (2024). Draft Systematic Review Protocol for 1,3-Butadiene, p. 26.
[94] U.S. EPA (2024). Draft Systematic Review Protocol for 1,3-Butadiene, p. 27.
[95] U.S. EPA (2024). Draft Systematic Review Protocol for 1,3-Butadiene, p. 26.
[96] U.S. EPA (2024). Draft Systematic Review Protocol for 1,3-Butadiene, p. 56.

EPA's choice not to conduct data extraction for some studies based on the overall quality determination is equivalent to excluding these studies from the risk evaluation, again contradicting EPA's claim that all relevant studies are considered in the risk evaluation.

EPA never explains, in either the draft systematic review protocol or the draft hazard assessment, how an OQD is derived from the study quality metrics. A statement at the end of the data quality evaluation forms for both epidemiology and toxicology studies indicates that EPA uses an automatic calculation of the OQD:

> Specify which OQD you would give this paper (either confirm the auto calculated judgement OR suggest a new one based on your professional judgement)?[97]

However, there is no other mention of "auto calculated judgement" in the protocol or hazard assessment. Further, there is no guidance given on when and with what basis an OQD not based on auto-calculation may be assigned. It is therefore unclear the basis on which the disqualifying label of "Uninformative" (or alternately, determinations of High, Medium or Low) is assigned to a study.

These examples demonstrate that EPA has not implemented procedures consistent with its claim that "all references that undergo systematic review are considered for use in the risk evaluation."[98] The TSCA systematic review method needs substantial revisions to correct a process that continues to exclude relevant evidence.

d. EPA's methods for evaluation of study quality need to incorporate further improvements that have been recommended by the National Academies.

The 1,3-butadiene Draft Risk Evaluation incorporates two recently-implemented critical improvements to the assessment of study quality that were applied in other recent TSCA risk evaluations: quantitative scoring of study quality is no longer used; and study quality domains for evaluation of health effects studies have been aligned with the domains used by EPA's Integrated Risk Information System (IRIS). These changes respond to important recommendations of the NASEM and the SACC.

EPA needs to incorporate two further improvements to study quality evaluation recommended by the NASEM.

First, EPA should incorporate assessment of financial conflict of interest (COI) as a risk of bias domain for evaluating studies. Industry sponsorship can bias research through various mechanisms, including how a study is designed and conducted, selective reporting of the results, skewed or incomplete analyses of study data, misleading or selective presentation of conclusions, and signaling of preferred outcomes in framing the questions to be investigated.[99]

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[97] U.S. EPA (2024). Draft Systematic Review Protocol for 1,3-Butadiene, pp. 64 and 76.
[98] U.S. EPA (2024). Draft Systematic Review Protocol for 1,3-Butadiene, p. 5.
[99] Odierna DH, Forsyth SR, White J, Bero LA. The cycle of bias in health research: a framework and toolbox for critical appraisal training. Account Res. 2013;20(2):127-141; Fabbri A, Lai A, Grundy Q, Bero LA. The influence of

The NASEM has highlighted the "large body of evidence showing that financial COIs lead to systemic biases in research"[100] and recommended that "funding sources should be considered in the risk-of-bias assessment conducted for systematic reviews that are part of an IRIS assessment."[101] To ensure that EPA assessments account for the possible bias in the evidence base, industry sponsorship and author financial COI should incorporated as a study quality evaluation domain that could affect the validity of a study's findings and conclusions.

Importantly, including funding as a risk of bias domain does not mean excluding industry-sponsored studies from EPA's hazard and risk assessment; it only means documenting funding as one of many domains of potential bias and evaluating its impact on the overall quality of the body of evidence.

Second, EPA has continued to apply an overall quality determination (OQD) of High, Medium, Low, or Uninformative to each study. To adhere to best practices in systematic review, EPA should not derive an overall study rating, and instead implement the domain-based approach of the Navigation Guide.[102] This was a recommendation of the National Academies for TSCA systematic review:

> There are many tools for assessing risk of bias, such as those used by the Navigation Guide, OHAT, and the IRIS Program, and there is no consensus on the best tool for risk-of-bias analysis. However, there are best practices. For example, tools are preferred that rely on the evaluation of individual domains rather than the creation of overall quality scores (Eick et al. 2020). Such tools provide a structured framework within which to make qualitative decisions on the overall quality of studies and to identify potential sources of bias. Overall quality scores may not adequately distinguish between studies with high and low risk of bias in meta-analyses (Herbison et al. 2006). Importantly, there is also a lack of empirical evidence on the use of quality scores (Jüni et al. 1999).[103]

One aspect of the significant problems raised in applying an overall study rating is illustrated by EPA's evaluation of study quality for oral toxicity studies of formaldehyde.

EPA identified gastrointestinal effects as the most sensitive endpoint for oral exposure to formaldehyde. However, EPA classified the chronic oral exposure studies (by Til *et al*. and Tobe *et al*.) for gastrointestinal effects as "Uninformative." After further consideration, EPA decided

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industry sponsorship on the research agenda: a scoping review. Am J Public Health. 2018;108(11):e9-e16; Psaty BM, Prentice RL. Minimizing bias in randomized trials: the importance of blinding. JAMA. 2010;304(7):793-794; Psaty BM, Kronmal RA. Reporting mortality findings in trials of rofecoxib for Alzheimer disease or cognitive impairment: a case study based on documents from rofecoxib litigation. JAMA. 2008;299(15):1813-1817.

[100] National Academies of Sciences, Engineering, and Medicine (2023). Sponsor Influences on the Quality and Independence of Health Research: Proceedings of a Workshop, p. 9.

[101] National Research Council (2014). Review of EPA's Integrated Risk Information System (IRIS) Process, p. 79.

[102] Lam, J., Koustas, E., Sutton, P., Padula, A. M., Cabana, M. D., Vesterinen, H., Griffiths, C., Dickie, M., Daniels, N., Whitaker, E., & Woodruff, T. J. (2021). Exposure to formaldehyde and asthma outcomes: A systematic review, meta-analysis, and economic assessment. PloS one, 16(3), e0248258. https://doi.org/10.1371/journal.pone.0248258.

[103] National Academies of Sciences, Engineering, and Medicine (2021). The Use of Systematic Review in EPA's Toxic Substances Control Act Risk Evaluations, p. 36.

that these studies actually are informative, and that the Til *et al*. study should be used for dose-response analysis:

> Taken together, the three drinking water studies demonstrate a consistent pattern of gastrointestinal effects at comparable dose levels…While limitations in the two chronic drinking water studies resulted in OPPT data quality ratings of "uninformative for dose response" for the individual studies, the body of evidence across all three studies in combination increases the overall confidence in both the nature of the effects observed and the levels of formaldehyde exposure associated with those effects.[104]

> The three oral studies were selected to inform dose-response because they comprise the best available data on oral exposure to formaldehyde…when considered in conjunction with the other two studies, Til et al. 1989 contributes meaningful information to the WOE and dose-response despite the OPPT data quality rating of "uninformative."[105]

EPA's own analysis of its study quality ratings procedures therefore indicated that an overall study quality rating can be highly misleading and that labeling studies as "Uninformative" or excluding studies based on the rating for a single study quality metric could erroneously lead to disregarding studies that constitute the best available science.

Accordingly, EPA must revise its approach to TSCA study quality evaluation to avoid disregarding studies based on pre-assigned labels that are unwarranted. By replacing the overall study quality determination with a domain- or metric-based approach, as the NASEM recommended for the TSCA program in 2021,[106] risk assessors can evaluate the ratings for each study in each domain at the evidence synthesis step to reach conclusions across the body of evidence, informed by the strengths and limitations of all relevant studies. These improved procedures should be applied to 1,3-butadiene and are necessary for consistency with EPA's claim that all relevant studies are considered in the risk evaluation.

EPA should immediately implement the NASEM recommendation to use a domain-based approach instead of an overall quality determination.

e. EPA continues to use unclear terminology regarding evidence synthesis and integration.

EPA's use of unclear terminology for evidence synthesis and integration is an additional scientific shortcoming of the approach to systematic review for 1,3-butadiene. The NASEM has recommended the use of the term "evidence synthesis" for assembling the evidence and drawing conclusions from a single evidence stream (e.g. toxicology, epidemiology), and "evidence integration" for the subsequent process of drawing conclusions considering all evidence

[104] U.S. EPA (2024). Draft Human Health Hazard Assessment for Formaldehyde, pp. 30-31.
[105] U.S. EPA (2024). Draft Human Health Hazard Assessment for Formaldehyde, p. 32.
[106] NASEM (2021). The Use of Systematic Review in EPA's Toxic Substances Control Act Risk Evaluations, p. 36.

streams.[107] The SACC review of EPA's 2021 Draft TSCA Method document reiterated this recommendation:

> The EPA did not follow the recommendation of NASEM to separate evidence synthesis from evidence integration. To quote NASEM: "Evidence synthesis deals with more homogeneous data within a single stream, and evidence integration deals with more heterogeneous data from multiple streams."[108]
>
> The EPA could improve the clarify, transparency, and efficiency of its process by adopting the NASEM recommendation to use "synthesis" for drawing conclusions separately for each evidence stream (i.e., human, animal, and mechanistic evidence) and use 'integration' for drawing conclusions considering all evidence streams in combination – in context of the risk evaluation process/needs.[109]

In the 1,3-butadiene Draft Risk Evaluation, however, EPA disregards the advice of both the NASEM and the SACC by continuing to use the term "evidence integration" for both steps.[110]

This is one more area in which EPA's approach differs from best practices in systematic review, violating the best available science requirement under TSCA.[111] In addition, failing to adopt consistent and vetted terminology decreases the clarity of the risk evaluation and creates confusion for peer reviewers and the public regarding the procedures applied to drawing conclusions from a single stream of evidence.

f. EPA released an incomplete draft systematic review protocol for 1,3-butadiene that was not made publicly available in advance of the draft risk evaluation.

Along with the 1,3-butadiene Draft Risk Evaluation, EPA released a draft chemical-specific systematic review protocol. Publication of a chemical-specific protocol is consistent with best available scientific methods in systematic review and responds to recommendation of the NASEM and the SACC. However, the comments above demonstrate many flaws and deficiencies in the protocol and the procedures applied to conducting the risk evaluation. Public release of the protocol for public comment and peer review in advance of conducting the risk evaluation would have provided an opportunity for early identification and correction of the many critical deficiencies described above. For future TSCA risk evaluations, EPA must publish a chemical-specific systematic review protocol for public comment before completing the draft

[107] NASEM (2021). The Use of Systematic Review in EPA's Toxic Substances Control Act Risk Evaluations, p. 45.
[108] U.S. EPA (2022). Meeting Minutes and Final Report for the Science Advisory Committee on Chemicals Virtual Meeting "Draft Systematic Review Protocol Supporting TSCA Risk Evaluations for Chemical Substances Version 1.0" held on April 19-21, 2022, p. 83.
[109] U.S. EPA (2022). Meeting Minutes and Final Report for the Science Advisory Committee on Chemicals Virtual Meeting "Draft Systematic Review Protocol Supporting TSCA Risk Evaluations for Chemical Substances Version 1.0" held on April 19-21, 2022, p. 88.
[110] U.S. EPA (2024). Draft Systematic Review Protocol for 1,3-Butadiene, pp. 79-80; U.S. EPA (2024). Draft Human Health Hazard Assessment for 1,3-Butadiene, Figure 2-1.
[111] 15 U.S.C. § 2625(h).

risk evaluation, as recommended by the Institute of Medicine and the NASEM as a best practice for systematic review.[112]

The TSCA program should follow the established procedures of EPA's IRIS program, which makes a draft protocol for each assessment 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.[113] EPA should apply the same approach for all TSCA risk evaluations.

g. 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 deeply flawed 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 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.

7. 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) in the 1,3-butadiene Draft Risk Evaluation.[114] EPA excluded multiple potential groups that are PESS for 1,3-butadiene and among the PESS identified, EPA did not apply a transparent methodology for quantifying the risk of harm to each identified PESS using the best available science. This omission is consistent with previous risk evaluations where EPA regularly underestimated the risk to PESS due to a lack of adequate identification and consideration of PESS. By not adequately considering PESS, EPA is violating TSCA's requirements. EPA, therefore, must adopt a consistent framework for identifying and quantifying the risk of harm to PESS from 1,3-butadiene exposures.

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[112] Institute of Medicine (2011). Finding what works in health care: Standards for systematic reviews; National Research Council (2014). Review of EPA's Integrated Risk Information System (IRIS) process.
[113] 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).
[114] 15 U.S.C. §2605(b)(4)(A).

Identification and consideration of PESS for each chemical assessed is a critical aspect of conducting risk evaluation under TSCA, as 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.[115]

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 from exposure to a chemical substance or mixture, such as infants, children, pregnant women, workers, the elderly, or overburdened communities.[116]

EPA needs to develop and apply a consistent approach to identify all PESS. To date, EPA has not employed a consistent or structured approach to identifying PESS in its TSCA risk evaluations, including scope documents for ongoing risk evaluations. EPA's approach and terminology 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.[117] To remedy the problem of 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.[118]

EPA has not yet proposed such a methodology. While the listing of potential PESS factors in Table 5-8 and Appendix G of the draft risk evaluation and in Table 7-1 of the draft human health risk assessment are useful initial steps towards developing a consistent, structured approach to identifying PESS in TSCA risk evaluations, EPA's evaluation and application of uncertainty factors aimed at protecting PESS falls short at every step. The evaluation of PESS factors is inconsistent across the tables, failing to give consideration to several groups that should be considered PESS. Table 5-8 gives explicit consideration to each of the following: lifestage, pre-existing disease, occupational and consumer exposures, geographic/site-specific factors, socio-demographic factors, genetics/epigenetics, and aggregate exposures, yet EPA fails to fully

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[115] 15 U.S.C. §2605(b)(4)(A).
[116] U.S. EPA (2024). Procedures for Chemical Risk Evaluation Under the Toxic Substances Control Act, § 702.33.
[117] 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.
[118] 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.

consider all PESS within each category identified. EPA says that factors such as lifestyle activities, nutrition, unique activities, and other chemical and non-chemical stressors that have previously been included as PESS factors in risk evaluations were not further analyzed in this table due to a lack of "direct evidence available."[119] Furthermore, the uncertainty factors identified by EPA are insufficient for protecting PESS.

EPA rejected the application of uncertainty factors to account for the elevated risk to PESS. EPA quantitatively adjusted for differences in human susceptibility only with application of the standard 10-fold human variability uncertainty factor. The WHO and other authoritative bodies have demonstrated that the traditional 10X uncertainty factor is insufficient for fully accounting for the risk in sensitive groups and recommend the use of larger uncertainty factors.[120] EPA should increase the use of uncertainty factors to account for the wide range of vulnerability in the human population, as failure to do so will result in an underestimation of risk, particularly for PESS, and is not scientifically supported.

In addition, for many of the identified PESS, EPA concludes that, due to a lack of chemical specific data on the magnitude of increased susceptibility, no further adjustment is necessary. TSCA does not require chemical-specific quantitative data to identify or evaluate risk to PESS. Instead, TSCA requires EPA to rely on the "best available science" when evaluating risk 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.[121]

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[119] U.S. EPA (2024). Draft Human Health Hazard Assessment for 1,3-Butadiene, Table 7-1.

[120] 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.

[121] 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/.

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 to quantify risk for a susceptible subgroup. 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 generic adjustment factors (beyond the customary 10x factor for human variability) should be applied to ensure that risks to PESS are not underestimated.[122] Table 2 describes the PESS considerations listed in the 1,3-butadiene Draft Risk Evaluation, the gaps in PESS identification or consideration, and recommended science-based uncertainty factors for each group.

Table 2. PESS considerations and recommended uncertainty factors.

PESS Factor and Examples[a]	Greater Susceptibility or Exposure Addressed by EPA?[b]	EPA Proposed UF	PRHE Recommended UF
Lifestage Embryo/fetus, pregnant females, children, older adults	Identified potential PESS and applied ADAFs to the IUR for general population cancer risk characterization	ADAFs were applied for estimating cancer risk. No additional UFs beyond the 10X identified for general human variability for non-cancer risk	42X for general human variability and additional 10X for early life stages including pregnant women
Pre-existing disease Obesity, cardiovascular disease, diabetes	Identified potential PESS but failed to account for the full range of variability and vulnerability.	No additional UFs beyond the 10X identified for general human variability	42X and an additional 10X for pre-existing disease
Lifestyle activities Smoking, alcohol consumption, physical activity	Identified potential PESS but made no direct adjustment. Only included a "qualitative discussion"	No UF applied	42X and an additional 10X for non-chemical stressors
Geographic factors Fenceline, residence/school	Fenceline communities were "taken into consideration with	No UF applied for increased susceptibility	42X and an additional 10X for non-chemical stressors

[122] 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.

location, historical releases	modeled exposure concentrations"		
Socio-demographic factors Race/ethnicity, socioeconomic status, sex/gender, education	Identified potential PESS but made no direct adjustment. Race/ethnicity and socioeconomic status were only included as a "qualitative discussion"	No UF applied	42X and an additional 10X for non-chemical stressors
Nutrition Diet, malnutrition, subsistence fishing	Failed to adjust for nutrition factors	No UF applied	42X and an additional 10X for non-chemical stressors
Genetics/epigenetics Genetic polymorphisms	Did not sufficiently account for the genetic variability in human populations. EPA assumes that "linear low-dose cancer dose-response model should account for varying susceptibility" for cancer and 10X is sufficient for non-cancer risks	No additional UFs beyond the 10X identified for general human variability	42X
Unique Activities Open burning, sweat lodge/purification ceremonies (tribal)	EPA did not address this factor	No UF applied	42X and an additional 10X for non-chemical stressors
Other chemical and non-chemical stressors Stress, adverse childhood experiences, built environment, chemical co-exposures	Identified potential PESS but made no direct adjustment. Only included a "qualitative discussion"	No UF applied	42X and an additional 10X for multiple chemical stressors

[a] Examples are extracted from 1,3-butadiene Draft Risk Evaluation Appendix G and are not intended to be exhaustive.
[b] Quotations are extracted from Draft Human Health Hazard Assessment for 1,3-Butadiene Table 7-1.

EPA's identification of PESS has important gaps that are likely to result in underestimating risk for vulnerable groups

Lifestage.

EPA's approach to identifying susceptible lifestages is too narrow. In the 1,3-butadiene Draft Risk Evaluation, EPA has appropriately identified embryos, fetuses, infants, children, pregnant and lactating people, males of reproductive age, and older adults as PESS but continues to ignore other important lifestages. For example, EPA fails to identify women of reproductive age as a PESS.

EPA should also apply stronger uncertainty factors to account 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 these groups should be identified as PESS for each TSCA risk evaluation, regardless of whether there are chemical-specific data to quantify those differences. Instead, EPA applied only the standard 10x human uncertainty factor which, as discussed previously, is not sufficient to address human variability in response to chemical exposures.[123] While we agree with EPA's use of ADAFs to account for early life susceptibility for cancer, the factor alone does not fully address the increased cancer risk to 1,3-butadiene based on prenatal lifestage. As described in comment 1 above, a 10X adjustment factor should also be applied for prenatal susceptibility, as recommended by the California Office of Environmental Health Hazard Assessment (OEHHA). 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 in response to chemical exposure 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.[124] The WHO adjustment factors are based primarily on data for healthy adults and do not represent the increased susceptibility associated with life stage, which should be addressed with an additional human variability factor.

Pre-existing disease.

EPA did not identify any groups as PESS based on pre-existing disease or underlying health conditions. EPA identified blood and immune system disease as a likely hazard of 1,3-butadiene exposure but disregarded the prevalence of such diseases in the U.S.

[123] 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.
[124] 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.

population or the demographic distribution of blood or immune system disease as a vulnerability factor in its risk characterization. In prior risk evaluations, EPA has noted that co-exposure to other chemical or non-chemical stressors that increase the risk of identified hazards may increase susceptibility to the effects of the chemical in evaluation on the same health outcomes.[125] However, EPA has not consistently addressed this increased susceptibility. In the 1,3-butadiene Draft Risk Evaluation, EPA even acknowledges that "especially susceptible individuals may not be accounted for by standard approaches."[126] If standard approaches do not account for especially susceptible individuals EPA must increase its use of science-based uncertainty factors to account for the wide range of variability and vulnerability in the human population. EPA claims, without justification, that the 10X uncertainty factor for human variability is sufficient for characterizing this susceptibility. As discussed above, even an adjustment of 10X is not sufficient for accounting for the full range of human variability in response to chemical exposures.[127]

EPA should broaden its consideration of pre-existing disease as PESS to also include individuals with blood or immune system diseases and apply appropriate adjustments to the estimation of risks of each outcome for these groups.

Individual activities.

EPA identifies lifestyle activities to include smoking, alcohol consumption, and physical activity. EPA has indirect evidence of increased susceptibility to 1,3-butadiene for all the lifestyle activities identified but declined account for this increased susceptibility, due to a lack of direct evidence. EPA does not need chemical-specific data to account for these PESS groups; when such data are absent, the application of generic adjustment factors (beyond the customary 10x factor for human variability) should be applied to ensure that risks to PESS are not underestimated.[128] A failure to examine lifestyle factors as PESS will underestimate risk to susceptible subgroups. For example, people who engage in recreational exercise in fenceline communities (including non-residents of these communities), such as running, hiking, or playing outdoor sports, may have increased inhalation exposure to 1,3-butadiene and face greater health risks as a result.

EPA only mentions smoking as a lifestyle factor that could influence susceptibility to chemical exposures, but it chose not 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 1,3-butadiene, including as adverse effects on multiple organ systems. 1,3-butadiene has also been identified as having the highest

[125] U.S. EPA (2024). Unreasonable Risk Determination of the Draft Risk Evaluation for Formaldehyde, p. 107.
[126] U.S. EPA (2024). Draft Risk Evaluation for 1,3-Butadiene, Table 5-8.
[127] 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.
[128] 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.

cancer risk index per cigarette smoked per day compared to all other cigarette constituents. This elevated cancer risk due to greater exposure to 1,3-butadiene for cigarette smokers should be addressed by EPA.[129] Smokers should be considered as PESS even if there is no direct 1,3-butadiene-specific evidence. In addition, we recommend using the term "individual activities" instead of "lifestyle activities."

Geographic factors.

Some geographic factors were evaluated in the 1,3-butadiene Draft Risk Evaluation through the fenceline analysis, but EPA did not assess the increased susceptibility to 1,3-butadiene among PESS due to geographic factors. 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, extreme weather, racism, and poverty.[130] EPA is therefore required under TSCA to account for these enhanced susceptibilities when evaluating risks to fenceline communities. Furthermore, EPA should leverage the best available resources, including mandated reporting databased such as the Toxics Release Inventory (TRI), the National Emissions Inventory (NEI), and Discharge Monitoring Reports (DMR), as well as federal- and state-level environmental monitoring data and other data sources that could indicate chemical accidents, releases, or spills, to identify geographic areas linked with exposure to 1,3-butadiene (see more in comments section 5a above).

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[131] as well as their susceptibility to those exposures. For example, people experiencing poverty or racial discrimination may experience psychosocial stress that can enhance susceptibility to the

[129] Soeteman-Hernández LG, Bos PMJ, Talhout R. Tobacco smoke-related health effects induced by 1,3-butadiene and strategies for risk reduction. Toxicol Sci. 2013;136(2):566-580. doi:10.1093/toxsci/kft194.

[130] 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.

[131] 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.

adverse effects of toxic chemicals.[132] These groups must be identified as PESS, even if there is not direct chemical-specific evidence.

At a minimum, EPA should use the limited demographic analysis it has completed of populations living in proximity to sites with 1,3-butadiene releases to inform identification of PESS. EPA conducted such an analysis for the proposed TSCA risk management rule for trichloroethylene (TCE),[133] 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 general human variability) to account for enhanced susceptibility due to socio-demographic factors,[134] especially in scenarios where chemical-specific data is not available.

Nutrition.

In Table 7-1, EPA states that there was "no direct evidence available" to address susceptibility to 1,3-butadiene as a result of nutritional factors. However, EPA also states that:

> Micronutrient malnutrition can lead to multiple conditions that include birth defects, maternal and infant deaths, preterm birth, low birth weight, poor fetal growth, childhood blindness, and undeveloped cognitive ability.[135]

EPA acknowledges that nutritional factors, such as malnutrition, can lead to several conditions that can impact one's susceptibility to chemical exposures but does not address the impact of these factors. It has been documented that nutritional status can modify

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

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

[134] 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.

[135] U.S. EPA (2024). Draft Human Health Hazard Assessment for 1,3-Butadiene, Table 7-1.

susceptibility to chemical exposures.[136] People with food insecurity or lack of access to nutritious food can experience enhanced susceptibility to the adverse effects of toxic chemicals, including 1,3-butadiene, and should be identified as PESS. EPA must address nutrition as a PESS factor even if there is no direct chemical-specific evidence and adequately account for the elevated risks for this group by using scientifically-supported uncertainty factors.

Genetics.

EPA identifies several genetic polymorphisms that are associated with greater genotoxicity and mutations but fails to fully account for the resulting variability in human response to chemical exposures. EPA assumes that the positive mutation data from one cohort study done in Texas is sufficient to account for the full range of susceptibility across the human population. The cohort study includes data for 20,000 workers, however, data on these workers may not be sufficient to account for the foreseeable variability in response to chemical exposures from genetic factors across the entire population, let alone the combination of genetics and other susceptibility factors outlined in Table 7-1. 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 in the table, even though the NASEM and the WHO have both recommended that a larger factor is necessary to ensure public health protection. EPA must accordingly increase the uncertainty factor it uses to account for enhanced susceptibility to 1,3-butadiene based on genetic disorders and conditions to at least 42X.

Other chemical and non-chemical stressors.

Sixteen years ago, the NASEM recommended that EPA consider exposures to multiple chemical and non-chemical stressors in its risk assessments.[137] Yet, EPA continues to ignore the impact of combined chemical and non-chemical stressors in the majority of its risk assessments. In the 1,3-butadiene risk evaluation, EPA failed to address and quantify elevated risk among PESS groups that may be co-exposed to chemicals with shared adverse health outcomes or key characteristics. For example, there is extensive data that illustrates the co-exposure of 1,3-butadiene and formaldehyde, another known carcinogen, among fenceline communities in Texas.[138]

Despite the availability of data and NASEM recommendations to identify and consider co-exposures that can impact the susceptibility of communities and individuals exposed to 1,3-butadiene, EPA did not fully address this as a PESS consideration. As a result of the narrow consideration of PESS, EPA has ignored important factors that contribute to enhanced risk from 1,3-butadiene exposure. The relationship between co-exposures to

[136] Kordas K, Lönnerdal B, Stoltzfus RJ. Interactions between Nutrition and Environmental Exposures: Effects on Health Outcomes in Women and Children1,2. The Journal of Nutrition. 2007;137(12):2794-2797. doi:10.1093/jn/137.12.2794.

[137] National Research Council. (2009). Science and Decisions: Advancing Risk Assessment. National Academies Press (US). http://www.ncbi.nlm.nih.gov/books/NBK214630/.

[138] According to data obtained from the Toxics Release Inventory (TRI) and National Emissions Inventory (NEI) for cumulative 1,3-butadiene and formaldehyde releases in Houston, TX between the years of 2010-2020.

1,3-butadiene 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 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 1,3-butadiene 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 1,3-butadiene exposures.

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

8. EPA did not conduct a cumulative risk assessment. Failure to do so will underestimate risk, especially to potentially exposed or susceptible sub-populations.

EPA's traditional approach of conducting risk assessments on individual chemicals will not account for real-world exposures to 1,3-butadiene and other carcinogens and will underestimate risk posed to workers, the general population, and potentially exposed or susceptible subpopulations. 1,3-butadiene is recognized as a known human carcinogen by the International Agency for Research on Cancer (IARC)[139] and the National Toxicology Program (NTP).[140] The significant association between 1,3-butadiene and various types of lymphohematopoietic cancers has been confirmed by multiple agencies and authoritative bodies.[141] Despite acknowledging the carcinogenic nature of 1,3-butadiene, EPA has failed to consider the potential increased risk to the general population, workers, and potentially exposed or susceptible subpopulations when co-exposures to other carcinogens occur in the 1,3-butadiene Draft Risk Evaluation. When conducting risk evaluations, EPA is required to rely on "scientific information, technical procedures, measures, methods, protocols, methodologies, or models, employed in a manner consistent with the best available science."[142] It also must consider greater susceptibility or greater exposure of some populations, such as children and workers, to "mixture[s]" of chemicals.[143] TSCA further grants EPA broad authority to review "categories of chemicals" when conducting risk evaluations; TSCA states that "[a]ny action authorized or required to be taken by

[139] IARC (2012). Chemical agents and related occupations. IARC monographs on the evaluation of carcinogenic risk of chemicals to humans Volume 100F.
[140] NTP (National Toxicology Program). 2021. Report on Carcinogens, Fifteenth Edition. Research Triangle Park, NC: U.S. Department of Health and Human Services, Public Health Service.
[141] U.S. EPA. Health Assessment Of 1,3-Butadiene. U.S. Environmental Protection Agency, Office of Research and Development, National Center for Environmental Assessment, Washington Office, Washington, DC, EPA/600/P-98/001F, 2002.; NTP (National Toxicology Program). 2021. Report on Carcinogens, Fifteenth Edition. Research Triangle Park, NC: U.S. Department of Health and Human Services, Public Health Service.; IARC (2012). Chemical agents and related occupations. IARC monographs on the evaluation of carcinogenic risk of chemicals to humans Volume 100F.
[142] 15 U.S.C. § 2625(h).
[143] *Id.* § 2602(12).

[EPA] under any provision of [TSCA] with respect to a chemical substance or mixture may be taken by [EPA] in accordance with that provision with respect to a category of chemical *substances or mixtures.*"[144] In order to comply with TSCA, EPA should evaluate 1,3-butadiene and other relevant carcinogens as a class of chemicals and conduct a cumulative risk assessment.

1,3-butadiene is a ubiquitous contaminant with major environmental sources coming from chemical facilities, automobile exhaust, and tobacco smoke.[145] Assessment of 1,3-butadiene without considering other carcinogens for which co-exposure will occur in the human population will underestimate risk as co-exposures to 1,3-butadiene and multiple other carcinogens are prevalent in fenceline communities in the United States,[146] and co-exposures to these chemicals increases the likelihood of developing cancer.[147] The NASEM recommends that the best approach for quantifying cumulative risk posed by chemicals of the same class is to conduct a cumulative risk assessment when there is substantial evidence supporting multiple exposures and common adverse health outcomes.[148] Moreover, these methods do not require similarity of cancer endpoints in order to combine chemicals in a cumulative assessment.[149]

People are exposed to 1,3-butadiene and other known carcinogens, such as formaldehyde, from multiple sources and environments. Due to their high production volume and use in TSCA-regulated consumer products like plastics and rubber products, co-exposures to 1,3-butadiene and formaldehyde are likely. Moreover, these chemicals are co-released in high volumes in fenceline community areas. According to chemical release data reported to the Toxics Release Inventory (TRI) and the National Emissions Inventory (NEI), over **20 million** pounds of 1,3-butadiene and formaldehyde were released over a 10-year period in Houston, Texas.[150] In two of the fenceline neighborhoods in East Houston, more than 85 percent of the residents are Black or

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[144] *Id.* § 2625(c)(1) (emphasis added).
[145] Chen WQ, Zhang XY. 1,3-Butadiene: a ubiquitous environmental mutagen and its associations with diseases. Genes Environ. 2022;44:3. doi:10.1186/s41021-021-00233-y.
[146] Johnson GS, Washington SC, King DW, Gomez JM. Air Quality and Health Issues Along Houston's Ship Channel: An Exploratory Environmental Justice Analysis of a Vulnerable Community (Pleasantville). Race, Gender & Class. 2014;21(3/4):273-303.; 1. Mustafa H, Coogan M. Relationship Between Petroleum Chemical Plants and Environmental Justice Issues in Harris County, TX.
[147] NRC, Phthalates and Cumulative Risk Assessment at 5–6; Gina M. Solomon et al., Cumulative Environmental Impacts: Science and Policy to Protect Communities at 87-88, 37 Annual Rev. Public Health (2016), https://www.annualreviews.org/doi/pdf/10.1146/annurev-publhealth-032315-021807; UCSF Program on Reproductive Health and the Environment, Using the Best Available Science to Assess Hazards and Risks of Industrial Chemicals Will Ensure Better Public Health Decisions at 3, https://prhe.ucsf.edu/sites/g/files/tkssra341/f/wysiwyg/UCSF%20PRHE%20EPA%20Chemical%20Policy%20v1.pdf ; Woodruff TJ, Caldwell J, Cogliano VJ, Axelrad DA. Estimating cancer risk from outdoor concentrations of hazardous air pollutants in 1990. Environ Res. 2000 Mar;82(3):194-206. doi: 10.1006/enrs.1999.4021. PMID: 10702327.
[148] NRC, Phthalates and Cumulative Risk Assessment at 3–4; NRC broadly defines a cumulative risk assessment as an evaluation of "the risk posed by multiple chemicals and other stressors that cause varied health effects and to which people are exposed by multiple pathways and exposure routes and for varied durations."
[149] Woodruff TJ, Caldwell J, Cogliano VJ, Axelrad DA. Estimating cancer risk from outdoor concentrations of hazardous air pollutants in 1990. Environ Res. 2000 Mar;82(3):194-206. doi: 10.1006/enrs.1999.4021. PMID: 10702327.
[150] According to data obtained from the Toxics Release Inventory (TRI) and National Emissions Inventory (NEI) for cumulative 1,3-butadiene and formaldehyde releases in Houston, TX between the years of 2010-2020.

Latino.[151] The median household income across East Houston fenceline neighborhoods is more than 30 percent lower than that of the City of Houston, and over a quarter of the residents fall below the poverty level.[152] Most residents of these communities also experience food insecurity and healthcare inequity.[153]

Taken together with EPA's broad authority under TSCA to evaluate "categories of chemicals" when conducting risk evaluations and the mandate to use "best available science" including recommendations outlined by the NASEM, EPA must conduct a cumulative risk evaluation for 1,3-butadiene and other known carcinogens, including, at minimum, formaldehyde, which recently underwent risk evaluation under TSCA. In addition, due to EPA's requirement to evaluate risk to potentially exposed or susceptible subpopulations, EPA must consider non-chemical stressors, as described above, that increase an individual's susceptibility to harm from chemical exposures when conducting a cumulative risk assessment. A failure to evaluate the cumulative risk of these chemicals and other relevant non-chemical stressors is thus a failure to follow the mandates outlined by TSCA. In the long-term, conducting a cumulative chemical risk assessment poses several advantages, including: 1) gaining a deeper understanding of synergistic or additive toxicity resulting from multiple chemical exposures, and 2) most efficiently using EPA's limited risk evaluation resources by covering multiple, related chemicals in a single evaluation.[154]

[151] Heidi L. Bethel et al., A Closer Look at Air Pollution in Houston: Identifying Priority Health Risks, at 10 (2006), https://www3.epa.gov/ttn/chief/conference/ei16/session6/bethel.pdf; Union of Concerned Scientists & Tex. Env't Just. Advoc. Servs., Air Toxics and Health in the Houston Community of Manchester (June 2016), https://www.ucsusa.org/sites/default/files/attach/2016/06/ucs-manchester-air-toxics-and-health- factsheet-2016.pdf ("UCS Manchester Profile").

[152] Heidi L. Bethel et al., A Closer Look at Air Pollution in Houston: Identifying Priority Health Risks, at 10 (2006), https://www3.epa.gov/ttn/chief/conference/ei16/session6/bethel.pdf ("Report on Houston Air Pollution").

[153] Union of Concerned Scientists & Tex. Env't Just. Advoc. Servs., Air Toxics and Health in the Houston Community of Manchester (June 2016), https://www.ucsusa.org/sites/default/files/attach/2016/06/ucs-manchester-air-toxics-and-health- factsheet-2016.pdf.

[154] NAS, *A Class Approach to Hazard Assessment of Organohalogen Flame Retardants* at 5–6 (Washington, DC: The National Academies Press) (2019), https://www.nap.edu/catalog/25412/a-class-approach-to-hazard-assessment-of-organohalogen-flame-retardants; UCSF Program on Reproductive Health and the Environment, *Using the Best Available Science to Assess Hazards and Risks of Industrial Chemicals Will Ensure Better Public Health Decisions* at 3.

Technical Appendix: Analysis of 1,3-butadiene non-cancer risk using IPCS methodology

In the *Draft Risk Evaluation for 1,3-Butadiene*, EPA selected decreased fetal weight in mice, for estimation of non-cancer risks from intermediate and chronic duration inhalation exposures. By adjusting doses from a study with intermittent dosing to continuous exposure and applying of benchmark dose (BMD) modeling, EPA derived a point of departure (POD) of 2.5 ppm.[155]

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 POD to the exposure level. For chronic inhalation exposures, the 1,3-butadiene *Draft Risk Evaluation* concludes that an MOE of less than 30 "is interpreted as a human health risk of concern,"[156] and MOEs of 30 or greater indicate no concern.

EPA's approach to risk characterization does not actually estimate risks of adverse effects in the population with chronic exposure to 1,3-butadiene, 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),[157] 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.[158,159,160,161,162]

We applied the IPCS approach for "quantal-deterministic" endpoints and the "approximate probabilistic" calculation (see IPCS report Fig 3.5, panel C)[163] to estimate risks of reduced fetal weight from chronic inhalation exposures to 1,3-butadiene. The analysis involved the following steps:

1. Derivation of IPCS POD and corresponding uncertainty adjustments
2. Application of interspecies adjustments

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[155] U.S. EPA (2024). Draft Risk Evaluation for 1,3-Butadiene, p. 53.
[156] U.S. EPA (2024). Draft Risk Evaluation for 1,3-Butadiene, p. 53.
[157] World Health Organization, International Programme on Chemical Safety (2017). Guidance document on evaluating and expressing uncertainty in hazard characterization, 2nd edition.
[158] 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.
[159] 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.
[160] 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.
[161] 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.
[162] 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.
[163] World Health Organization, International Programme on Chemical Safety (2017). Guidance document on evaluating and expressing uncertainty in hazard characterization, 2nd edition.

3. Application of intraspecies adjustments
4. Calculation of HD_M^I - the human dose (HD) of 1,3-butadiene associated with a particular magnitude of effect M (i.e., reduced fetal weight) 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. All POD and HD_M^I values presented in this analysis represent continuous exposure concentrations in parts per million (ppm).

We demonstrate each of these steps starting with the EPA POD to derive a set of 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 BMD modeling results and applied adjustments provided by the IPCS methodology. At the same time, we incorporated quantitative uncertainties for each of these adjustments.

EPA used a benchmark response (BMR) of 5% to derive the BMD and BMDL (lower confidence limit on the BMD) for decreased fetal weight from 1,3-butadiene inhalation exposure. The chronic inhalation non-cancer BMD_5 is 5.49 ppm, and the $BMDL_5$ is 2.52 ppm.[164] The IPCS framework uses the BMD as the P50 estimate. The P95/P50 ratio, representing uncertainty in the BMD, is equal to the BMD/BMDL ratio (5.49 ppm / 2.52 ppm = 2.18).

The ED_{50} and its uncertainty are then 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 $(P95/P50)^2$."[165]

The median (P50) estimate of the ED_{50} is then calculated by multiplying the BMD_5 by the IPCS adjustment factor (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:

[164] U.S. EPA (2024). Draft Human Health Hazard Assessment for 1,3-Butadiene, p. 146.
[165] 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.

Determination of point of departure (POD) and its uncertainty[a] for probabilistic dose-response analysis of chronic 1,3-butadiene inhalation exposure		
Aspect	**P50**	**P95/P50**
BMD_5[b]	5.49 ppm	2.18
BMD-to-ED_{50} adjustment[c]	3.0	1.5
IPCS POD = ED_{50}	**16.5 ppm**	**2.41**[d]

[a] Uncertainty is expressed as the ratio of the 95th percentile (P95) to the 50th percentile (P50)
[b] U.S. EPA (2024). Draft Human Health Hazard Assessment for 1,3-Butadiene, p. 146.
[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) = $10^{[(\log 2.18)^2 + (\log 1.5)^2]^{0.5}} = 2.41$

STEP 2: 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.

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.[166] 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.[167]

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.[168]

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

[166] U.S. EPA (2024). Draft Human Health Hazard Assessment for 1,3-Butadiene, p. 35.
[167] World Health Organization, International Programme on Chemical Safety (2017). Guidance document on evaluating and expressing uncertainty in hazard characterization, 2nd edition, Table 4.26.
[168] World Health Organization, International Programme on Chemical Safety (2017). Guidance document on evaluating and expressing uncertainty in hazard characterization, 2nd edition, Table 4.3.

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

STEP 3: Application of intraspecies (human variability) adjustments

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**
1%[a]	9.69	4.32
0.5%[a]	12.36	5.06
0.17%[b]	17.44	6.32
0.1% (1-in-1,000)[a]	20.42	6.99
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 4: 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 outcome of reduced fetal weight. The following tables present the HD_M^I results for I = 1%, 0.1% and 0.01% using the POD, $AF_{Interspecies}$, 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 $AF_{Intraspecies}$.

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 inhalation exposure to 1,3-butadiene: reduced fetal weight (Incidence = 1%)		
Aspect	**P50**	**P95/P50**
BMD_5	5.49 ppm	2.18
BMD-to-ED_{50} adjustment	3.0	1.5
IPCS POD = ED_{50}	**16.5 ppm**	**2.41**[d]
$AF_{Interspecies-BS}$	1	2
$AF_{Interspecies-TK/TD}$	1	3
$AF_{Intraspecies\ (I=1\%)}$	9.69	4.32
HD_M^I	1.70 ppm[a]	8.54[b]
	P50	**P95/P50**
$HD_M^{I\ (c)}$	**0.20 ppm**	14.5 ppm

[a] HD_M^I (P50) = IPCS POD / ($AF_{Interspecies-BS}$ x $AF_{Interspecies-TK/TD}$ x $AF_{Intraspecies}$)
[b] (Composite P95/P50) = $10^{[(\log 2.41)^2 + (\log 2)^2 + (\log 3)^2 + (\log 4.32)^2]^{0.5}} = 8.54$
[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 1,3-butadiene: reduced fetal weight (Incidence = 0.1%)		
Aspect	**P50**	**P95/P50**
BMD_5	5.49 ppm	2.18
BMD-to-ED_{50} adjustment	3.0	1.5
IPCS POD = ED_{50}	**16.5 ppm**	**2.41**[d]
$AF_{Interspecies\text{-}BS}$	1	2
$AF_{Interspecies\text{-}TK/TD}$	1	3
$AF_{Intraspecies\ (I=0.1\%)}$	20.42	6.99
HD_M^I	0.81 ppm[a]	12.16[b]
	P50	**P95/P50**
$HD_M^{I\ (c)}$	**0.07 ppm**	9.8 ppm

[a] HD_M^I (P50) = IPCS POD / ($AF_{Interspecies\text{-}BS}$ x $AF_{Interspecies\text{-}TK/TD}$ x $AF_{Intraspecies}$)
[b] (Composite P95/P50) = $10^{[(\log 2.41)^2 + (\log 2)^2 + (\log 3)^2 + (\log 6.99)^2]^{0.5}} = 12.16$
[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 1,3-butadiene: reduced fetal weight (Incidence = 0.01%)		
Aspect	**P50**	**P95/P50**
BMD_5	5.49 ppm	2.18
BMD-to-ED_{50} adjustment	3.0	1.5
IPCS POD = ED_{50}	**16.5 ppm**	**2.41**[d]
$AF_{Interspecies\text{-}BS}$	1	2
$AF_{Interspecies\text{-}TK/TD}$	1	3
$AF_{Intraspecies\ (I=0.01\%)}$	37.71	10.39
HD_M^I	0.44 ppm[a]	16.73[b]
	P50	**P95/P50**
$HD_M^{I\ (c)}$	**0.03 ppm**	7.3 ppm

[a] HD_M^I (P50) = IPCS POD / ($AF_{Interspecies\text{-}BS}$ x $AF_{Interspecies\text{-}TK/TD}$ x $AF_{Intraspecies}$)
[b] (Composite P95/P50) = $10^{[(\log 2.41)^2 + (\log 2)^2 + (\log 3)^2 + (\log 10.39)^2]^{0.5}} = 16.73$
[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.[169]
>
> 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.[170]

The WHO/IPCS said:

> 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).[171]

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).

Risk-specific dose estimates for chronic inhalation exposure to 1,3-butadiene: reduced fetal weight	
Incidence (I)	**HD_M^I lower -confidence limit (P05)**
1%[a]	0.20 ppm
0.5%	0.14 ppm
0.17%	0.084 ppm
0.1% (1-in-1,000)	0.07 ppm
0.01% (1-in-10,000)	0.03 ppm
0.001% (1-in-100,000)	0.01 ppm

[169] National Research Council (2009). Science and Decisions: Advancing Risk Assessment, p. 140.
[170] National Research Council (2009). Science and Decisions: Advancing Risk Assessment, p. 140.
[171] World Health Organization, International Programme on Chemical Safety (2017). Guidance document on evaluating and expressing uncertainty in hazard characterization, 2nd edition, p. 12.

Interpretation of results

Based on application of the WHO/IPCS methodology to 1,3-butadiene chronic inhalation exposures, we find that:

- 0.20 ppm is the lower bound (95% confidence) chronic human inhalation dose at which reduced fetal weight is expected in 1% of the population.
- 0.14 ppm is the lower bound (95% confidence) chronic human inhalation dose at which reduced fetal weight is expected in 0.5% of the population.
- 0.07 ppm is the lower bound (95% confidence) chronic human inhalation dose at which reduced fetal weight is expected in 0.1% of the population.
- 0.03 ppm is the lower bound (95% confidence) chronic human inhalation dose at which reduced fetal weight is expected in 0.01% (1-in-10,000) of the population.
- 0.01 ppm is the lower bound (95% confidence) chronic human inhalation dose at which reduced fetal weight is expected in 0.001% (1-in-100,000) of the population.
- EPA's POD for chronic inhalation exposure to 1,3-butadiene is 2.5 ppm, and the benchmark MOE is 30.[172] This means that EPA concludes that any chronic inhalation exposure less than 2.5 ppm / 30 = 0.084 ppm is not of concern. Our analysis finds that the upper bound risk at a chronic inhalation exposure of 0.084 ppm is 0.17%, equivalent to 17-in-10,000 or approximately 1-in-600.

The estimates of HD_M^I presented here were based entirely on input values and equations available from the WHO/IPCS methodology document and the related article by Chiu et al., and from EPA's draft risk evaluation documents for 1,3-butadiene. 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 population.[173,174,175] 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.

[172] U.S. EPA (2024). Draft Risk Evaluation for 1,3-Butadiene, p. 53.
[173] 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.
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[175] 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.