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# Comments from UCSF Program on Reproductive Health and the Environment on the Supplemental Draft Risk Evaluation for 1,4-Dioxane

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

We appreciate the opportunity to provide written comments on the draft supplemental risk evaluation and risk determination for 1,4-dioxane ("*Draft Supplement*" and "*Draft Revised Risk Determination"*) issued under EPA's Toxic Substances Control Act (TSCA),[1] which requires EPA to evaluate chemical risks based on the "best available science," and "adequate information".[2] 1,4-dioxane is a potent carcinogenic solvent used in myriad industrial processes, such as the production of polyethylene terephthalate ("PET") plastic. Its widespread industrial use and use in numerous consumer and commercial products, like adhesives, detergents, and paints, has resulted in high levels of drinking water contamination across the country.

Our comments on EPA's 2020 1,4-dioxane risk evaluation highlighted how the Agency ignored key exposure pathways, failed to identify susceptible subpopulations, and used a flawed systematic review methodology.[3] For example, almost 30 million people in the U.S. receive drinking water with 1,4-dioxane levels above the reference concentration for a 1-in-1,000,000 cancer risk of 0.35 µg/L,[4,5] however EPA's original Risk Evaluation for 1,4-dioxane excluded the drinking water pathway asserting that it was managed under the Safe Drinking Water Act (SDWA), even though EPA has not established a National Primary Drinking Water Regulation under SDWA for 1,4-dioxane[6] and has not decided whether one is necessary.[7]

We support the Agency's decision to conduct additional analysis in the *Draft Supplement* to better characterize risks from 1,4-dioxane, and to issue draft revisions to the risk determination for 1,4-dioxane based on the additional analyses. The *Draft Supplement* evaluates risks for exposure pathways and conditions of use that were improperly excluded from the original risk evaluation, including occupational exposure to 1,4-dioxane in certain industrial and consumer products, and general population exposure to 1,4-dioxane from drinking water and air. Among the important findings are:

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[1] US EPA (2023) Draft Supplement to the Risk Evaluation for 1,4-Dioxane . Available: https://www.regulations.gov/document/EPA-HQ-OPPT-2022-0905-0032

[2] 15 USC §2625 (h)-(i) and 15 USC §2601 (b)(1)

[3] US EPA. (2019). Toxic Substances Control Act (TSCA) Science Advisory Committee on Chemicals Review of Risk Evaluation for 1, 4 Dioxane. Comment submitted by Swati Rayasam, Science Associate, Program on Reproductive Health and the Environment, Department of Obstetrics, Gynecology and Reproductive Sciences, University of California, San Francisco et al. Available: https://www.regulations.gov/comment/EPA-HQ-OPPT-2019-0238-0056

[4] McElroy, A.; Hyman, M.; Knappe, D. 1,4-Dioxane in drinking water: emerging for 40 years and still unregulated. Current Opinion in Environmental Science & Health 2019, 7, 117– 125, DOI: 10.1016/j.coesh.2019.01.003

[5] US EPA. (2010). IRIS Assessment Summary – 1,4-Dioxane. Available: https://cfpub.epa.gov/ncea/iris2/chemicallanding.cfm?substance_nmbr=326

[6] US EPA. (2021). Announcement of Final Regulatory Determinations for Contaminants on the Fourth Drinking Water Contaminant Candidate List, 86 FR 12272. Available: https://www.federalregister.gov/documents/2021/03/03/2021-04184/announcement-of-final-regulatory-determinations-for-contaminants-on-the-fourth-drinking-water

[7] 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

- occupational cancer risks as high as 2-in-100 for both inhalation and dermal exposures;[8]
- drinking water cancer risks to the general population from industrial releases as high as 2.5-in-100;[9]
- drinking water cancer risks to the general population from down-the-drain releases of 1,4-dioxane in consumer and commercial products as high as 6-in-100,000;[10] and
- ambient air cancer risks to the general population as high as 1-in-10,000.[11]

The *Draft Supplement* thus provides critical information that was omitted from the 2020 Risk Evaluation. However, there are still significant flaws in the *Draft Supplement* that continue EPA's pattern of underestimating the health and environmental impacts of 1,4-dioxane. In addition, the *Draft Revised Risk Determination* fails to include all conditions of use that are contributors to the unreasonable risk posed by 1,4-dioxane to the general population.

Our comments address the following main issues:

1. **EPA should apply existing methods to generate quantitative estimates of non-cancer risks from 1,4-dioxane exposures.**
2. **EPA has not adequately assessed aggregate 1,4-dioxane exposures**
    a. **EPA has partially incorporated aggregate exposure estimation into its modeling of risks from surface waters**
    b. **EPA's risk estimates for air emissions of 1,4-dioxane continue to rely on data for a single year and for individual facilities, without incorporating aggregate exposure**
    c. **EPA does not consider combinations of inhalation, oral and dermal exposures**
    d. **EPA does not consider combinations of occupational, consumer and fenceline/general population exposures**
    e. **EPA relies on a single study with flawed assumptions about residential occupancy to estimate lifetime exposure risk**
3. **EPA's revised risk determination inappropriately excludes some key contributors to unreasonable risk.**
    a. **EPA should consider down-the-drain releases from consumer and commercial products as contributors to unreasonable risks to the general population**
    b. **EPA should consider air releases from industrial and commercial sources as contributors to unreasonable risks to the general population**
    c. **EPA should further revise its unreasonable risk determination to take into account aggregate exposures that is has failed to model**
4. **EPA has not appropriately identified PESS as required by TSCA**

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

Sincerely,

[8] US EPA (2023) Draft Supplement to the Risk Evaluation for 1,4-Dioxane. p 21. Available: https://www.regulations.gov/document/EPA-HQ-OPPT-2022-0905-0032

[9] US EPA (2023) Draft Supplement to the Risk Evaluation for 1,4-Dioxane. p 23. Available: https://www.regulations.gov/document/EPA-HQ-OPPT-2022-0905-0032

[10] US EPA (2023) Draft Supplement to the Risk Evaluation for 1,4-Dioxane. Table 5-4. Available: https://www.regulations.gov/document/EPA-HQ-OPPT-2022-0905-0032

[11] US EPA (2023) Draft Supplement to the Risk Evaluation for 1,4-Dioxane. p 24. Available: https://www.regulations.gov/document/EPA-HQ-OPPT-2022-0905-0032

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## DETAILED COMMENTS

### 1. EPA should apply existing methods to generate quantitative estimates of non-cancer risks from 1,4-dioxane exposures.

The *Draft Supplement* continues to rely on the deficient methods for non-cancer dose-response analysis and risk characterization employed in the original 1,4-dioxane risk evaluation and other TSCA risk evaluations. EPA's methods for non-cancer risk evaluation do not provide a quantitative estimate of risk. Instead, they rely on calculation of a margin of exposure ("MOE"), defined as:

> Margin of Exposure = Non-cancer point of departure / Human exposure.[12]

The MOE approach is a scientifically inappropriate approach 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").[13] Use of the MOE, which relies on a point of departure ("POD") with no extrapolation to lower doses, is a simplistic approach that only compares the POD to the exposure level and judges whether this ratio "is interpreted as indicating a human health risk" or if "risk is not indicated."[14] 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

[12] US EPA (2023) Draft Supplement to the Risk Evaluation for 1,4-Dioxane . p 136. Available: https://www.regulations.gov/document/EPA-HQ-OPPT-2022-0905-0032
[13] 15 USC §2602 (12) and 2625 (h)-(i)
[14] US EPA (2023) Draft Supplement to the Risk Evaluation for 1,4-Dioxane . p 136. Available: https://www.regulations.gov/document/EPA-HQ-OPPT-2022-0905-0032

exposure can be identified for a diverse exposed population.[15, 16] The National Academies[17] and the World Health Organization ("WHO")[18] have outlined superior methods for risk estimation that have been demonstrated in published case studies.[19, 20, 21, 22]

We applied the WHO methodology to estimate risks of adverse effects from chronic inhalation and oral exposure of 1,4-dioxane at doses relevant to the *Draft Supplement*. Our analysis finds that the risks of adverse effects to the olfactory epithelium (a nasal tissue involved in detecting odors) at inhalation exposure levels reported in the *Draft Supplement* and risks of non-cancer liver effects at oral exposure levels reported in the *Draft* Supplement are very high, as multiple COUs have estimated exposures well in excess of the level associated with 0.1% (1-in-1000) incidence of effects.

Our analysis (see Technical Appendix for details) found that:

- 0.05 ppm is the lower bound (95% confidence) chronic human dose (continuous inhalation exposure) at which olfactory epithelium effects are expected in 1% of the population,
- 0.02 ppm is the lower bound (95% confidence) chronic human dose (continuous inhalation exposure) at which olfactory epithelium effects are expected in 0.1% of the population,
- 0.01 ppm is the lower bound (95% confidence) chronic human dose (continuous inhalation exposure) at which olfactory epithelium effects are expected in 0.01% (1-in-10,000) of the population,
- 0.2 mg/kg-d is the lower bound (95% confidence) chronic human oral dose at which liver toxicity is expected in 1% of the population,
- 0.06 mg/kg-d is the lower bound (95% confidence) chronic human oral dose at which liver toxicity is expected in 0.1% of the population, and
- 0.02 mg/kg-d is the lower bound (95% confidence) chronic human oral dose at which liver toxicity is expected in 0.01% (1-in-10,000) of the population.

The implications of these risk benchmarks can be understood by comparison with the exposure levels considered by EPA to represent negligible risk (i.e., an MOE greater than the EPA-designated benchmark), and by comparison with EPA's modeled drinking water and air exposures.

EPA's non-cancer risk characterization for continuous chronic inhalation exposure to 1,4-dioxane uses 0.846 ppm as the point of departure, and a benchmark MOE of 30.[23] This means that EPA concludes

[15] 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. Environ Health, 21(Suppl 1), 132. https://doi.org/10.1186/s12940-022-00930-3

[16] 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

[17] National Research Council. (2009). Toward a unified approach to dose-response assessment. In Science and decisions: Advancing risk assessment. https://doi.org/10.17226/12209

[18] 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

[19] 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

[20] 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

[21] 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

[22] 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. https://doi.org/10.1080/15287394.2012.670895

[23] US EPA (2023) Draft Supplement to the Risk Evaluation for 1,4-Dioxane. Table 5-1. Available: https://www.regulations.gov/document/EPA-HQ-OPPT-2022-0905-0032

"risk is not indicated".[24] for any chronic continuous exposure less than 0.846 ppm / 30 = 0.028 ppm. Our analysis indicates that an exposure of 0.028 ppm is substantially greater than the lower bound dose for the 1-in-1000 risk level.

EPA's non-cancer risk characterization for chronic oral exposure to 1,4-dioxane uses 2.6 mg/kg-d as the point of departure, and a benchmark MOE of 30.[25] This means that EPA concludes "risk is not indicated".[26] for any chronic oral exposure less than 2.6 mg/kg-d / 30 = 0.09 mg/kg-d. Our analysis indicates that an exposure of 0.09 mg/kg-d is substantially greater than the lower bound dose for the 1-in-1000 risk level.

Comparison of selected exposures estimated in the *Draft Supplement* to these risk benchmarks to exposures demonstrates the importance of these methods.

EPA's exposure modeling indicates that there are extensive adult average daily doses via drinking water in excess of the level posing non-cancer risk as high as 1-in-1000, i.e., 0.06 mg/kg-d. For example, two COUs (1,4-dioxane manufacturing and PET manufacturing) have 95$^{th}$ percentile doses of 0.06 mg/kg-d or greater, and six COUs have maximum doses exceeding the 1-in-1000 level, including one COU (ethoxylation byproduct) with a maximum estimated dose 10 times the 1-in-1000 level. For reasons detailed below, EPA's exposure estimates are likely to underestimate drinking water exposures to 1,4-dioxane, thus the risks suggested by these comparisons are similarly expected to also be underestimates.

Table 2-15 indicates that annual average ambient air concentrations of 1,4-dioxane from analysis of single-facility, single-year emissions can be as high as 0.02 ppm, which indicates fenceline community non-cancer risks of greater than 1-10,000. For reasons detailed below, the estimates in Table 2-15 are likely to underestimate air concentrations of 1,4-dioxane, thus this non-cancer risk estimate of greater than 1-in-10,000 is expected to also be an underestimate.

EPA should apply these analyses utilizing probabilistic dose-response methods in the *Draft Supplement* to better inform its risk determinations and to provide the necessary analyses for use in the risk management process. More generally, EPA should use this type of analysis in the TSCA program to inform its unreasonable risk determinations, the analysis of benefits of regulatory alternatives, and (when workplace chemical protections are proposed for uses that are not prohibited) to determine the level of an Existing Chemical Exposure Limit ("ECEL"). EPA's analyses of the anticipated effects of its proposed TSCA rules for methylene chloride and perchloroethylene did not include quantitative estimates of the nonfatal non-cancer health benefits of the risk management actions. EPA should remedy this deficiency in its forthcoming TSCA risk management actions by applying available methods, which constitute the "best available science," to estimate baseline risks and risk reductions of non-cancer effects.

**2. EPA has not adequately assessed aggregate 1,4-dioxane exposures.**

Computing aggregate exposure in TSCA risk evaluations is necessary for estimation of the total exposure and risk to individuals who are exposed to a single chemical in multiple ways, such as exposure in the workplace and at home. EPA's 2017 risk evaluation framework rule defines aggregate exposure and important related terms as:

[24] US EPA (2023) Draft Supplement to the Risk Evaluation for 1,4-Dioxane. p 136. Available: https://www.regulations.gov/document/EPA-HQ-OPPT-2022-0905-0032

[25] US EPA (2023) Draft Supplement to the Risk Evaluation for 1,4-Dioxane. Table 5-1. Available: https://www.regulations.gov/document/EPA-HQ-OPPT-2022-0905-0032

[26] US EPA (2023) Draft Supplement to the Risk Evaluation for 1,4-Dioxane. p 136. Available: https://www.regulations.gov/document/EPA-HQ-OPPT-2022-0905-0032

> *Aggregate exposure* means the combined exposures to an individual from a single chemical substance across multiple routes and across multiple pathways.
>
> *Pathways* means the mode through which one is exposed to a chemical substance, including but not limited to: Food, water, soil, and air.
>
> *Routes* means the particular manner by which a chemical substance may contact the body, including absorption via ingestion, inhalation, or dermally (integument).[27]

The definition of aggregate exposure is incomplete, as aggregate exposure estimation includes consideration of multiple sources, facilities, and conditions of use, as well as the critical elements of multiple routes and multiple pathways. The *Draft Supplement* has incorporated some important aspects of aggregate exposure estimation, but EPA's approach is too limited and fails to aggregate all the various combinations of exposure that may be experienced by many individuals, such as combinations of occupational, consumer and general population exposures.

a. <u>EPA has partially incorporated aggregate exposure estimation into its modeling of risks from surface waters</u>

EPA used a probabilistic modeling approach to estimate surface water concentrations of 1,4-dioxane. The results are reported by COU, and represent a combination of:

> modeled water concentrations predicted downstream of release sites using aggregate probabilistic modeling that incorporates direct releases from facilities, indirect releases via POTWs, down-the drain releases, and other upstream sources (represented as the distribution of available surface water monitoring data).[28]

EPA estimated cancer risks from drinking water exposure as high as 0.025, or 2.5 cancer cases per 100 people exposed.[29] This modeling approach represents progress in estimating aggregate exposures by combining several sources of 1,4-dioxane in surface waters, including facility effluents, down-the-drain releases from commercial and consumer products, and other contributors to "background" concentrations of 1,4-dioxane in receiving waters. However, there is no indication in the methodology or results that EPA has considered whether multiple facilities (from the same COU or different COUs) may have releases to the same body of water. If there are surface waters that receive 1,4-dioxane-containing effluents from more than one facility, and these sources have not been combined, then EPA has artificially constrained its method of calculating aggregate exposures in a manner that will underestimate exposure and risk. In addition, it is unclear from EPA's methodology if its approach to determining background concentrations of 1,4-dioxane in receiving waters captures all potential sources of 1,4-dioxane and appropriately characterizes potential variability in background concentrations across geographic locations.

b. <u>EPA's risk estimates for air emissions of 1,4-dioxane continue to rely on data for a single year and for individual facilities, without incorporating aggregate exposure</u>

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[27] US Environmental Protection Agency. (2017). Procedures for Chemical Risk Evaluation under the Amended Toxic Substances Control Act (Final) 40 CFR 702.33.

[28] U.S. EPA (2023). Science Advisory Committee on Chemicals (SACC) Peer Review of 2023 Draft Supplement to the 1,4-Dioxane Risk Evaluation. 1,4-Dioxane Draft RE - File Drinking Water Exposure and Risk Estimates for 1,4-Dioxane Surface Water Concentrations Predicted with Probabilistic Modeling - public release - July 2023. Aggregate Model Exposure & Risk. Available: https://www.regulations.gov/document/EPA-HQ-OPPT-2022-0905-0028

[29] US EPA (2023) Draft Supplement to the Risk Evaluation for 1,4-Dioxane. pp 142. Available: https://www.regulations.gov/document/EPA-HQ-OPPT-2022-0905-0032

EPA states that it has implemented steps to assess aggregate exposure from air releases of 1,4-dioxane that go beyond what was presented in the 2022 *Draft Fenceline Screening Methodology*:

> EPA expanded upon the methods described in the 2022 Fenceline Report in response to SACC comments/recommendations by evaluating potential aggregate concentrations from multiple facilities.[30]

EPA's presentation of its methods and results in the *Draft Supplement* is unclear regarding how it has estimated aggregate air concentrations of 1,4-dioxane. For example, Figure 2-18, entitled "Brief Description of Methodologies and Analyses Used to Estimate Ambient Air Concentrations and Exposures" does not mention aggregate concentrations or combined modeling of emissions from more than one facility.

EPA reports modeling results separately for each of 11 occupational exposure scenarios (OES). EPA identified 21 facilities with emissions posing a cancer risk greater than 1-in-1,000,000, and risks as high as 1-in10,000.[31] In these results, EPA has clearly not aggregated concentrations from multiple OES, thus concentrations for communities with facilities in more than one OES will be underestimated.

Following presentation of its air dispersion modeling results, EPA says:

> Based on the air concentrations estimated through the Ambient Air: Single Year Methodology, EPA also estimated potential aggregate air concentrations resulting from the combined releases of multiple facilities in proximity to each other. Details of the methods used to aggregate exposure and corresponding risk are presented in Appendix J.4.[32]

However, no further detail is provided on the modeling of multiple facilities and no results from this modeling are provided in the main text of the *Draft Supplement*, so it appears that EPA assigns this aggregate exposure modeling no importance in informing the risk characterization or risk determination.

In addition to the lack of aggregate exposure model estimates, there are other important deficiencies in EPA's analysis of the air pathway. It is unclear why modeling of air concentrations with AERMOD continues to use only one year of emissions data, rather than six years, as applied elsewhere, to address SACC recommendations. EPA has conducted analysis with multiple years of emissions data using only the Integrated Indoor/Outdoor Air Calculator (IIOAC). EPA acknowledges significant limitations of IIOAC, including the inability to model concentrations at distances less than 100 meters, and a lack of local meteorology data. In addition, it does not appear that the IIOAC modeling incorporates any aspect of aggregate exposure, such as multiple facilities affecting the same community. The utility of the IIOAC analysis is unclear since its results are not presented in the *Draft Supplement*.

EPA's presentation of results from AERMOD single-year modeling in Table 2-15 is unclear. EPA has summarized the distribution of annual average concentrations at specified distances from the facilities with emissions. For each distance, there is presumably an annual average for 16 receptor points times the number of facilities, which produces a distribution of air concentrations at each distance, which may be summarized with statistics such as the minimum, median, mean, 95$^{th}$ percentile and maximum concentration. However, EPA's labeling of the table suggests that it has first determined the 95$^{th}$

[30] US EPA (2023) Draft Supplement to the Risk Evaluation for 1,4-Dioxane . p 83. Available: https://www.regulations.gov/document/EPA-HQ-OPPT-2022-0905-0032

[31] US EPA (2023) Draft Supplement to the Risk Evaluation for 1,4-Dioxane. Table 5-8. Available: https://www.regulations.gov/document/EPA-HQ-OPPT-2022-0905-0032

[32] US EPA (2023) Draft Supplement to the Risk Evaluation for 1,4-Dioxane . p 88. Available: https://www.regulations.gov/document/EPA-HQ-OPPT-2022-0905-0032

percentile annual average concentrations, and then reported minimum, median, mean, and maximum 95th percentile concentrations. The steps in the set of summary calculations are unclear; for example, from what set of values is the 95th percentile concentration determined, and how can there be a minimum and maximum 95th percentile of the annual average concentration? EPA should clearly state the steps in calculating the values presented in Table 2-15.

c. EPA does not model aggregate exposure considering combinations of inhalation, oral and dermal exposures

EPA says that it "considered aggregating cancer risks across inhalation, oral, and/or dermal routes of exposure,"[33] but chose not to for reasons that are unclear.

EPA states:

> There is uncertainty around the extent to which cancer risks across routes are additive for 1,4-dioxane. Liver tumors are the primary site of cancer risk from oral exposures. Inhalation exposure in rats is associated with multiple tumor types, including liver. The IUR used to calculate inhalation cancer risk reflects combined risks from multiple tumor types. While EPA concluded that nasal cavity lesions are likely to be primarily the result of systematic [*sic*] delivery (as discussed on p.192 of the 2020 RE), there is uncertainty around the degree to which those effects could be partially due to portal of entry effects following inhalation exposure. It is therefore unclear the extent to which it is appropriate to quantitatively aggregate cancer risks based on the IUR with liver tumor risks associated with oral or dermal exposures. EPA considers the potential aggregate cancer risk across routes to be a source of uncertainty for 1,4-dioxane cancer risk estimates.[34]

This passage provides no cogent scientific rationale for EPA's failure to add inhalation cancer risks to oral or dermal exposure cancer risks. It discusses uncertainty regarding whether nasal cavity lesions are due to systemic delivery or portal of entry effects but draws no connection between this uncertainty and the questions of adding inhalation cancer risks to the risks from other routes of exposure. Existing EPA guidance encourages the addition of cancer risks that may occur independently. EPA's 2020 *Supplementary Guidance for Conducting Health Risk Assessment of Chemical Mixtures* discusses the application of response addition to components of a chemical mixture that act independently of one another, saying that this approach is "used extensively for cancer."[35] If varied cancer outcomes can be combined via response addition for different chemicals, then outcomes that vary for a single chemical, such as 1,4-dioxane, can be combined in the same manner.

d. EPA does not model aggregate exposure considering combinations of occupational, consumer and fenceline/general population exposures

EPA's SACC review of the *Draft Fenceline Screening Methodology* highlighted EPA's lack of consideration of multiple ways that residents of fenceline communities may exposed. The SACC said that EPA should:

[33] US EPA (2023) Draft Supplement to the Risk Evaluation for 1,4-Dioxane. p 164. Available: https://www.regulations.gov/document/EPA-HQ-OPPT-2022-0905-0032

[34] US EPA (2023) Draft Supplement to the Risk Evaluation for 1,4-Dioxane. p 164. Available: https://www.regulations.gov/document/EPA-HQ-OPPT-2022-0905-0032

[35] US EPA (2020). Supplementary Guidance for Conducting Health Risk Assessment of Chemical Mixtures, p. 30. Available: https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=20533

> Include aggregate and cumulative exposures from populations exposed at work who live in the community, or who may also be exposed to multiple facility emissions.[36]
>
> Overall, the SACC generally agrees that aggregate and cumulative exposures should be considered. In many fenceline communities, members of the community also work at the polluting facility and so may have occupational exposures that also contribute to cumulative body burden of the contaminant and thereby potential toxicological risks. The current screening approach excludes occupational exposure assessments, but an improved version of the screening tool focused on cumulative impacts would ideally take a more holistic view of the lived experience of fenceline community members for chemical risk assessment and would better serve the logic of a useful screening approach.[37]

EPA acknowledges that some individuals may be subject to combinations of occupational exposures, consumer exposures, and general population exposures, but it does not explain its choice to disregard these combinations:

> EPA also considered potential for aggregate exposures across groups. For example, there may be some individuals who are exposed at work as well as through general population air and drinking water pathways or through consumer product use. This as a source of uncertainty. These types of aggregate risks were not quantified and risks for individual exposure scenarios should be interpreted with an appreciation for potential aggregate exposures and risks.[38]

EPA only states that it did not consider these combinations of exposures and provides no rationale for this decision and no indication of the potential importance of combined exposures. Only by aggregating workplace, consumer, and general population exposures, by all routes of exposure, can EPA's risk evaluations treat an exposed individual as a "whole person." Instead, EPA's exposure construct subdivides an individual's exposure and risk into multiple separate components, without ever bringing these components together to estimate the individual's **total** exposure and risk. As a result, EPA is underestimating exposure to populations who are exposed in multiple ways, which will particularly result in underestimation of both cancer and non-cancer risk to PESS, and a potential failure to eliminate unreasonable risk to PESS as required by TSCA.

e. <u>EPA relies on a single study with flawed assumptions about residential occupancy to estimate lifetime exposure risk</u>

EPA calculates a Lifetime Average Daily Dose (LADD) and Lifetime Average Daily Concentration (LADC) to estimate lifetime exposures to 1,4-dioxane from various sources, such as disposal to landfills, drinking water, air, and down-the-drain releases. These estimates are critical to the Agency's understanding and management of chronic exposure to 1,4-dioxane, particularly for PESS.

As a component of calculating the LADD and LADC in the *Draft Supplement,* EPA states that:

[36] US EPA (2023) Draft Supplement to the Risk Evaluation for 1,4-Dioxane . p 18. Available: https://www.regulations.gov/document/EPA-HQ-OPPT-2022-0905-0032

[37] US EPA (2023) Draft Supplement to the Risk Evaluation for 1,4-Dioxane . pp 48-49. Available: https://www.regulations.gov/document/EPA-HQ-OPPT-2022-0905-0032

[38] US EPA (2023) Draft Supplement to the Risk Evaluation for 1,4-Dioxane . p 164. Available: https://www.regulations.gov/document/EPA-HQ-OPPT-2022-0905-0032

> To estimate lifetime exposures through drinking water, EPA calculated a Lifetime Average Daily Dose (LADD) based on 33 years of exposure starting from birth or 33 years of exposure as an adult, averaged over a 78-year lifetime.[39]

and

> To estimate potential lifetime exposures [through air], EPA calculated LADCs based on 33 years of exposure.[40]

EPA then goes on to state in a footnote that this use of 33 years is based on the "95$^{th}$ percentile residential occupancy period" in EPA's Exposure Factors Handbook.[41]

EPA's Exposure Factors Handbook often contains guidance based on limited or no evidence that does not consider real-world behaviors or uses of products and often fails to identify highly exposed populations.[42] As a result, guidance from the Exposure Factors Handbook often results in an underestimate of exposures. The Exposure Factors Handbook only uses one citation to justify its claim of 33 years of "residential occupancy," a study by Johnson and Capel from 1992 using data from 1987.[43] EPA must assume a lifetime exposure to air and drinking water of 78 years, in alignment with the Agency's typical practice.

First, this study does not represent the "best available science." as its dataset is overly narrow (as noted below) and is nearly 36 years old.

Second, there are several named limitations in the study that impact is generalizability and its ability to be applied to future scenarios. For example, Johnson and Capel state that their study estimates:

> "1) refer to elapsed time in the residence rather than to total occupancy period, 2) omit persons living in rental housing, 3) apply to entire households rather than to individuals and 4) are based on data which may be out of date." [44]

The omission of renting populations, which are disproportionately Black, brown, and Indigenous and/or lower income, limits the applicability of this study's findings to the diverse general population. Additionally, the study only considers age and gender as relevant demographics to assess, overlooking the import of racial and economic demographics in housing data. This is contrary to current a National Academies of Sciences, Engineering and Medicine report finding:

[39] US EPA (2023) Draft Supplement to the Risk Evaluation for 1,4-Dioxane . p 102. Available: https://www.regulations.gov/document/EPA-HQ-OPPT-2022-0905-0032

[40] US EPA (2023) Draft Supplement to the Risk Evaluation for 1,4-Dioxane . p 103. Available: https://www.regulations.gov/document/EPA-HQ-OPPT-2022-0905-0032

[41] US EPA (2023) Draft Supplement to the Risk Evaluation for 1,4-Dioxane . p 102; footnote 15. Available: https://www.regulations.gov/document/EPA-HQ-OPPT-2022-0905-0032

[42] 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

[43] Johnson T and Capel J. (1992). A Monte Carlo Approach to Simulating Residential Occupancy Periods and Its Application to the General US Population – Prepared by International Technology Air Quality Services for US Environmental Protection Agency; Office of Air Quality Planning and Standards.

[44] Johnson T and Capel J. (1992). A Monte Carlo Approach to Simulating Residential Occupancy Periods and Its Application to the General US Population. pp 2. – Prepared by International Technology Air Quality Services for US Environmental Protection Agency; Office of Air Quality Planning and Standards.

> the combination of social policies and the persistence of segregation has led to these severe racial inequalities in neighborhood environments. The persistence of spatial inequality by race is directly linked with prospects for economic mobility.[45]

People with lower social and/or economic mobility, such as people of color and low-income people, have historically had higher residential mobility due to lower homeownership and higher likelihood of renting, in part because of discriminatory housing practices.[46, 47] In addition, while people of color and low-income people are more likely to move, they're also more likely to move within the same neighborhoods, meaning their exposure to toxic chemicals would remain consistent, despite their change in residence.

> …the especially high levels of local pollution experienced by black householders appear to be maintained by both a relatively lower likelihood of escaping the highly polluted neighborhoods in which they originate and a tendency to relocate to destinations with higher levels of proximate industrial pollution than those experienced by mobile white householders. The fact that these differences in mobility destinations and overall hazard proximity levels persist even with controls for income, education, and a wide range of other sociodemographic characteristics is consistent with the argument that discriminatory real estate practices restrict residential options for members of at least some minority groups and that these restrictions are especially virulent in limiting opportunities for black householders. Furthermore, whereas white householders of all economic strata are able to avoid highly polluted neighborhoods, high levels of income appear to be especially important in determining residential outcomes for both black and Latino householders. Yet, even the highest-income black and Latino householders tend to end up in neighborhoods with higher levels of pollution than those experienced by even low-income whites, a finding consistent with at least one variant of the discrimination/stratification perspective.[48]

This issue is also generational, as the NASEM found that "about half of Black Americans in the United States have lived in the poorest quarter of U.S. neighborhoods for multiple, consecutive generations."[49]Additionally, research analyzing census data has found that "80% of young adults migrate less than 100 miles from where they grew up. 90% migrate less than 500 miles. Migration distances are shorter for Black and Hispanic individuals and for those from low-income families."[50]

Johnson and Capel also uplift a concerning assumption regarding the applicability of their methods to people with varying histories of mobility, saying:

> In the Monte Carlo procedure, a man aged 55 who has lived in his current residence for 30 years is given the same probability of not moving as a man of the same age who has lived in his current residence for only 5 years. This probability is based on the average behavior of 55-year-old males as determined by a survey questionnaire administered by the BOC to a sample of persons in this age group.

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[45] National Academies of Sciences, Engineering, and Medicine. 2022. Research and Data Priorities for Improving Economic and Social Mobility: Proceedings of a Workshop. pp 39-40. Washington, DC: The National Academies Press. https://doi.org/10.17226/26598.

[46] DeLuca, S., Wood, H., Rosenblatt, P. (2019). Why Poor Families Move (And Where They Go): Reactive Mobility and Residential Decisions. City & Community, 18(2), 556–593. https://doi.org/10.1111/cico.12386

[47]Brookings Institute. (2021). Homeownership, racial segregation, and policy solutions to racial wealth equity. Available: https://www.brookings.edu/articles/homeownership-racial-segregation-and-policies-for-racial-wealth-equity/

[48] Crowder K, Downey L. Interneighborhood migration, race, and environmental hazards: modeling microlevel processes of environmental inequality. AJS. 2010 Jan;115(4):1110-49. doi: 10.1086/649576. PMID: 20503918; PMCID: PMC2908425.

[49] National Academies of Sciences, Engineering, and Medicine. 2022. Research and Data Priorities for Improving Economic and Social Mobility: Proceedings of a Workshop. pp 39-40. Washington, DC: The National Academies Press. https://doi.org/10.17226/26598.

[50] Sprung-Keyser B, Hendren N, Porter S. (2022). The Radius of Economic Opportunity: Evidence from Migration and Local Labor Markets. Working Paper CES 22-27. U.S. Census Bureau, Center for Economic Studies. Available: https://www.census.gov/library/working-papers/2022/adrm/CES-WP-22-27.html

> Intuitively, one would expect that a person who has lived in his current residence for an extended period of time is more tied to his home than another person who has lived in his current residence for a relatively brief period of time. The former person is less likely to move in the coming year; the latter person is more likely to move. **If this pattern holds for the general population, then the Monte Carlo process proposed here will tend to underestimate the occurrence of very large occupancy periods**.[51] (emphasis added)

The study's inability to effectively assess "very large occupancy periods" is precisely what EPA is required to consider under TSCA, as this represents a PESS, similar to those with lower social or economic mobility. In addition to EPA's problematic general assumptions about residential occupancy, the *Draft Supplement* applies the same study, and thus the same flawed and outdated assumptions around residential occupancy, to fenceline community exposure:

> For fenceline communities, all exposure estimates assume continuous exposure (24 hours/day) throughout the duration of exposure. The exposure duration used to calculate the LADC is based on the 95$^{th}$ percentile of the expected duration at a single residence, 33 years (U.S. EPA, 2011) and the averaging time is based on a 78-year lifetime.[52]

This series of methodological limitations, including 1) limiting the study population to homeowners, 2) failing to consider racial or economic demographics, and 3) using a methodology that underestimates highly exposed populations makes this study inappropriate to inform the calculations in the *Draft Supplement* as it will severely underestimate risk. To effectively account for the duration of residence in fenceline communities, EPA must assume a lifetime exposure to air and drinking water of 78 years, in alignment with the Agency's typical practice.

**3. EPA's revised risk determination inappropriately excludes some key contributors to unreasonable risk.**

EPA has appropriately proposed to revise the risk determination for 1,4-dioxane to include "General Population via discharges to surface water sources of drinking water"[53] as a contributor to unreasonable risk for COUs including manufacturing, processing, two industrial uses (intermediate and processing aid), and disposal. However, EPA has inappropriately chosen not to designate other general population exposures as contributors to the unreasonable risk from 1,4-dioxane.

a. <u>EPA should designate down-the-drain releases from consumer and commercial products as contributing to unreasonable risks to the general population</u>

EPA's risk evaluation estimates down-the-drain (DTD) releases of 1,4-dioxane to surface waters from consumer and commercial product use in the aggregate and finds that these appear to pose cancer risks in excess of 1-in-1,000,000, and therefore unreasonable risks:

> plausible DTD release scenarios may present risk greater than 1 in 1 million in the absence of industrial releases.[54]

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[51] Johnson T and Capel J. (1992). A Monte Carlo Approach to Simulating Residential Occupancy Periods and Its Application to the General US Population – Prepared by International Technology Air Quality Services for US Environmental Protection Agency; Office of Air Quality Planning and Standards. pp 30-31.

[52] US EPA (2023) Draft Supplement to the Risk Evaluation for 1,4-Dioxane . p 478. Available: https://www.regulations.gov/document/EPA-HQ-OPPT-2022-0905-0032

[53] US EPA (2023) 1,4-Dioxane Draft Revised Unreasonable Risk Determination July 2023 p 1. Available: https://www.regulations.gov/document/EPA-HQ-OPPT-2016-0723-0104

[54] US EPA (2023) Draft Supplement to the Risk Evaluation for 1,4-Dioxane . p 152. Available: https://www.regulations.gov/document/EPA-HQ-OPPT-2022-0905-0032

EPA's risk estimates (as shown in Table 5-4 of the *Draft Supplement*) are actually up to 60 times higher than 1-in-1,000,000, at 6-in-100,000. EPA's revised risk determination for 1,4-dioxane, however, concludes that down-the-drain releases do not contribute to unreasonable risk:

> Assuming no dilution between the point of release and the drinking water intake, the estimated risks range from $2.04\times10^{-11}$ to $6.11\times10^{-5}$, with the risks increasing as population increases and stream flow decreases (Table 5-4, Ref. 1). Overall confidence in risk estimates for drinking water exposures resulting from DTD releases is medium. Based on this analysis, EPA proposes to find that general population exposures to drinking water contaminated with 1,4-dioxane from DTD releases do not contribute to the unreasonable risk from 1,4-dioxane.[55]

EPA does not provide any explanation for this proposed finding. General population cancer risks of greater than 1-in-1,000,000 should be designated as a contributor to unreasonable risk. In this case, risks are up to 60 times greater.

b. <u>EPA should designate air releases from industrial and commercial sources as a contributor to unreasonable risks to the general population</u>

EPA modeled exposure and risk to the general population for air releases of 1,4-dioxane from 11 COUs, including manufacture, processing, industrial and commercial use, and disposal. EPA identified 26 facilities posing cancer risks greater than 1-in-1,000,000 to the general population, and risks as high as 1-in-10,000.

EPA's *Draft Revised Risk Determination* did not conclude that air emissions contributed to unreasonable risk for any COU, including COUs with many facilities at estimated cancer risk above 1-in-100,000. EPA says:

> For the screening level analysis locations where lifetime cancer risk is estimated to be within the benchmark range of $1\times10^{-6}$ to $1\times10^{-4}$, EPA evaluated land use patterns to determine whether fenceline community exposures are reasonably anticipated. Based on this characterization of land use patterns, fenceline community exposures for the screening level analysis are reasonably anticipated at 50 percent of facilities where cancer risk is within the benchmark range based on modeled air concentrations.
> EPA's confidence in the risk estimates for ambient air exposures for those COUs identified in the previous paragraph is medium to high...Based on the risk estimates for cancer, acute effects, and non-cancer chronic effects, the fact that the risk estimates are within the applicable benchmark range, and EPA's confidence in the risk estimates, EPA does not find that fenceline community exposure to 1,4-dioxane in ambient air from releases from industrial conditions of use, including hydraulic fracturing and industrial laundry facilities, and institutional laundry facilities contributes to the unreasonable risk from 1,4-dioxane.[56]

EPA does not provide a clear rationale for its conclusion that air releases of 1,4-dioxane do not contribute to unreasonable risk and seems to imply that it would determine unreasonable risk only for cancer risks greater than 1-in-10,000. This is not a health-protective standard, especially for fenceline communities

[55] US EPA (2023) 1,4-Dioxane Draft Revised Unreasonable Risk Determination July 2023 p 17. Available: https://www.regulations.gov/document/EPA-HQ-OPPT-2016-0723-0104

[56] US EPA (2023) 1,4-Dioxane Draft Revised Unreasonable Risk Determination July 2023 pp 19-21. Available: https://www.regulations.gov/document/EPA-HQ-OPPT-2016-0723-0104

that are exposed to multiple other carcinogenic air toxics in addition to 1,4-dioxane. Further, the results used in the risk determination considered only the releases from single facilities. EPA identified five locations in the U.S. where two or three 1,4-dioxane emitters are in close proximity. EPA conducted only a cursory analysis of aggregate air concentrations in these five locations, concluding that there were not large increments of exposure relative to the single-facility analysis. As a result, EPA did not consider estimated air concentrations of 1,4-dioxane for communities with two or three emitting facilities in the risk determination. In addition, EPA's AERMOD analysis that is used for risk characterization is based on only one year's worth of emissions data, disregarding the likelihood that other years may have greater emissions. Finally, EPA has not considered whether some individuals in communities where air pathway risks exceed 1-in-100,000 might also have incremental exposures from drinking water, consumer products or workplace exposures that could result in aggregate exposures with risks exceeding 1-in-10,000. It is very likely that some members of communities with relatively high risks from air releases also have drinking water, workplace, and/or consumer product exposures that should be assessed in an aggregate exposure analysis. Since EPA has not conducted that aggregate exposure analysis, it should qualitatively consider the total risks to communities with relatively high risks from air releases that would result from non-air pathways.

c. <u>EPA should further revise its unreasonable risk determination to take into account aggregate exposures that is has failed to model</u>

EPA's *Draft Revised Risk Determination* does not incorporate any consideration of aggregate exposures that were not modeled in the *Draft Supplement*. The *Draft Supplement* says, for example, that combinations of occupational, consumer, and general population exposures and risks should be considered in interpreting the quantitative risk estimates:

> EPA also considered potential for aggregate exposures across groups. For example, there may be some individuals who are exposed at work as well as through general population air and drinking water pathways or through consumer product use. This as a source of uncertainty. **These types of aggregate risks were not quantified and risks for individual exposure scenarios should be interpreted with an appreciation for potential aggregate exposures and risks**. (emphasis added).[57]

EPA seems to acknowledge that its failure to aggregate exposures should be considered in the risk determination by saying that its risk estimates "should be should be interpreted with an appreciation for potential aggregate exposures and risks," but the *Draft Revised Risk Determination* makes no mention of aggregate exposure across workplace, consumer, and general population exposures, and there is no indication that combinations of these exposures were considered in interpreting the reported quantitative results from the risk evaluation. For example, EPA decided that some COUs or pathways with cancer risks greater than 1-in-100,000 do not contribute to unreasonable risk, implicitly requiring a 1-in-10,000 risk for an unreasonable risk determination. However, it is very likely that some members of communities with relatively high risks from air releases also have drinking water, workplace, and/or consumer product exposures that should be assessed in an aggregate exposure analysis. Since EPA has not conducted that aggregate exposure analysis, it should qualitatively consider the total risks to communities from the combination of air releases and non-air pathways in making the final risk determination.

[57] US EPA (2023) Draft Supplement to the Risk Evaluation for 1,4-Dioxane . p 164. Available: https://www.regulations.gov/document/EPA-HQ-OPPT-2022-0905-0032

4. **EPA has not appropriately identified PESS as required by TSCA**

A critical aspect of conducting risk evaluation under TSCA is to identify potentially exposed or susceptible subpopulations for each chemical assessed. Amended 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.[58]

In the final 2017 TSCA risk evaluation framework rule, EPA defined PESS (using the statutory definition) as:

> a group of individuals within the general population identified by the Administrator who, due to either greater susceptibility or greater exposure, may be at greater risk than the general population of adverse health effects from exposure to a chemical substance or mixture, such as infants, children, pregnant women, workers, or the elderly.[59]

EPA has not employed a consistent or structured approach in identifying PESS in its TSCA risk evaluations, including scope documents for ongoing risk evaluations, to date. EPA's approach and terminology for identifying PESS varied considerably in the first 10 risk evaluations.[60] Among the inconsistencies are differences in whether health conditions related to a chemical's hazards were considered and whether fenceline communities were included.[61, 62] For example, fenceline communities were identified as PESS for hexabromocyclododecane (HBCD), but not for 1,4-dioxane, 1-bromopropane (1-BP), or C.I. Pigment Violet 29 (PV-29); children were identified as PESS for 1-BP and HBCD, but not for 1,4-dioxane or PV-29.[63] 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.[64]

EPA has not yet proposed such a methodology. However, the consideration of PESS in Table 5-11 of the risk evaluation supplement is a useful initial step towards developing a consistent, structured approach to identifying PESS in TSCA risk evaluations. The table gives explicit consideration to each of the following: lifestage, pre-existing disease, lifestyle activities, occupational exposures, geographic factors, socio-demographic factors, nutrition, genetics, unique activities, aggregate exposures, other chemical and non-chemical stressors.

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[58] 15 USC §2605(b)(4)(A)

[59] US Environmental Protection Agency. (2017). Procedures for Chemical Risk Evaluation under the Amended Toxic Substances Control Act (Final) 40 CFR 702.

[60] 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

[61] 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

[62] McPartland, J., Shaffer, R. M., Fox, M. A., Nachman, K. E., Burke, T. A., Denison, R. A. (2022). Charting a Path Forward: Assessing the Science of Chemical Risk Evaluations under the Toxic Substances Control Act in the Context of Recent National Academies Recommendations. Environmental health perspectives, 130(2), 25003. https://doi.org/10.1289/EHP9649

[63] 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. Table-S3 Environmental science & technology, 56(17), 11969–11982. https://doi.org/10.1021/acs.est.2c02079

[64] 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

EPA, however, has not appropriately considered each of the relevant factors in identifying populations groups that, as the statute requires, "due to either greater susceptibility or greater exposure, may be at greater risk than the general population of adverse health effects."

Lifestage. EPA says that it "qualitatively described the potential for biological susceptibility due to lifestage differences and developmental toxicity but did not identify quantitative evidence of lifestage-specific susceptibilities to 1,4-dioxane; A 10× UF was applied for human variability."[65] First, EPA has confused the identification of PESS with quantification. Enhanced susceptibility of infants, children, women of child-bearing 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. Second, EPA makes no adjustment to quantify the enhanced risks to these susceptible groups, instead applying the customary 10x human variability factor that is routinely applied in EPA risk assessments, and which is not sufficient to address variability across the range of TSCA chemicals.

Pre-existing disease. EPA says that it "qualitatively described the potential for pre-existing health conditions, such as liver disease, to increase susceptibility or alter toxicokinetics, but did not identify direct quantitative evidence."[66] Availability of quantitative evidence of increased susceptibility is not necessary to identify persons with pre-existing disease as PESS. Identified hazards of 1,4-dioxane include liver, kidney, neurological and respiratory effects. Therefore, EPA should identify individuals with liver, kidney, neurological and respiratory conditions as PESS.

Lifestyle activities. EPA identifies lifestyle activities to include smoking and physical activity. 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 1,4-dioxane due to higher breathing rates and should explicitly be identified as PESS, even if there is not direct chemical-specific evidence.

Occupational exposures. In addressing worker exposures as PESS, EPA failed to consider how consumer and general population exposures can add to workplace exposures and also failed to consider enhanced susceptibility from exposure to other chemicals and non-chemical stressors. People who have occupational exposure to other toxic chemicals (not 1,4-dioxane) can have enhanced susceptibility to the effects of 1,4-dioxane consumer and general population/fenceline exposures.

Geographic factors. EPA says that it has evaluated exposures to fenceline communities, but the fenceline exposure analysis is deficient in multiple respects, including a failure to fully consider aggregate exposures. EPA says it "did not identify geographic factors that increase biological susceptibility to 1,4-dioxane. This is a remaining source of uncertainty,"[67] but EPA has not considered the many characteristics that can enhance susceptibility to the effects of 1,4-dioxane and are common in fenceline communities, including pre-existing disease, co-exposures to other toxic chemicals, and a broad range of non-chemical stressors.

Socio-demographic factors. People experiencing poverty or racial discrimination can have enhanced susceptibility to the adverse effects of toxic chemicals, including 1,4-dioxane, and should be identified as PESS even if there is not direct chemical-specific evidence.

[65] US EPA (2023) Draft Supplement to the Risk Evaluation for 1,4-Dioxane . Table 5-11. Available: https://www.regulations.gov/document/EPA-HQ-OPPT-2022-0905-0032

[66] US EPA (2023) Draft Supplement to the Risk Evaluation for 1,4-Dioxane . Table 5-11. Available: https://www.regulations.gov/document/EPA-HQ-OPPT-2022-0905-0032

[67] US EPA (2023) Draft Supplement to the Risk Evaluation for 1,4-Dioxane . Table 5-11. Available: https://www.regulations.gov/document/EPA-HQ-OPPT-2022-0905-0032

Nutrition. People with food insecurity or lack of access to good nutrition can have enhanced susceptibility to the adverse effects of toxic chemicals, including 1,4-dioxane, and should be identified as PESS even if there is not direct chemical-specific evidence.

Genetics. EPA appropriately says that "Indirect evidence that genetic variants may increase susceptibility of the target organ,"[68] but it does not identify persons with those genetic variants as PESS. These groups should be identified as PESS even in the absence of direct evidence.

Unique activities. EPA primarily uses the designator unique activities in the *Draft Supplement* to describe cultural practices of tribes that may increase their exposure to 1,4-dioxane, such as sweat lodges, and also makes reference to subsistence fishers. Tribal populations practicing subsistence fishing and aquatic plant gathering may have increased exposure to 1,4-dioxane due to these traditional practices in addition to increased exposure from sweat lodges and should be identified as PESS even if there is not direct chemical-specific evidence.

Aggregate exposures. As detailed above, EPA has only partially accounted for aggregate exposure, but has not taken critical steps including aggregating across worker, consumer and general population/fenceline exposures.

Other chemical and non-chemical stressors. Consideration of how other chemical and non-chemical stressors can enhance susceptibility is critical not just for fenceline communities, as discussed above, but for other exposed groups including workers and people who use consumer products containing 1,4-dioxane. These factors should be considered in identifying PESS, even if there is not direct chemical-specific evidence.

EPA should expand its identification of PESS based on the factors described above and should expand on the approach of Table 5-11 to develop a comprehensive, consistent, and structured methodology for identifying PESS in all TSCA risk evaluations.

[68] US EPA (2023) Draft Supplement to the Risk Evaluation for 1,4-Dioxane . Table 5-11. Available: https://www.regulations.gov/document/EPA-HQ-OPPT-2022-0905-0032

**Technical Appendix: Analysis of 1,4-dioxane non-cancer risk using WHO/IPCS methodology**

In the TSCA 1,4-dioxane risk evaluation, EPA selected olfactory epithelium effects for estimation of risks from chronic inhalation exposures, and liver toxicity for estimation of risks from chronic oral exposures.

For risk characterization of non-cancer health effects, the TSCA risk evaluation calculates a "margin of exposure" (MOE) for each exposure scenario, which is the ratio of the point of departure (POD) to the exposure level. For olfactory epithelium effects (inhalation) and liver toxicity (oral) from 1,4-dioxane, the TSCA risk evaluation concluded that an MOE of 30 or more "indicated negligible concerns for adverse human health effects."[69] EPA's approach to risk characterization does not actually estimate risks of adverse effects in the population with chronic exposure to 1,4-dioxane, 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),[70] 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.[71, 72, 73, 74, 75]

We applied the IPCS approach for "quantal-deterministic" endpoints and the "approximate probabilistic" calculation (see IPCS report Fig 3.5, panel C)[76] to estimate risks of olfactory epithelium effects from chronic inhalation exposure to 1,4-dioxane and risks of liver toxicity from oral exposure to 1,4-dioxane. The analysis involved the following steps:

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

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 point of departure (POD) for quantal-deterministic endpoints. Since an $ED_{50}$ is not available from the EPA risk evaluation, we began with EPA's benchmark dose, lower confidence limit (BMDL) values and applied adjustments provided by the IPCS methodology. (To simplify the presentation of this analysis, we use the "BMD" and

[69] U.S. Environmental Protection Agency (2020). Final Risk Evaluation for 1,4-Dioxane, p. 213.
[70] World Health Organization. Guidance document on evaluating and expressing uncertainty in hazard characterization. IPCS harmonization project document; no. 11. 2014.
[71] 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
[72] 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
[73] 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
[74] 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
[75] 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
[76] World Health Organization. Guidance document on evaluating and expressing uncertainty in hazard characterization. IPCS harmonization project document; no. 11. 2014.

"BMDL" notation for both inhalation and oral values, instead of using "BMC" and BMCL" for inhalation values.) At the same time, we incorporated quantitative uncertainties for each of these adjustments.

EPA used a benchmark response (BMR) of 10% to derive the BMDL values. The chronic non-cancer $BMDL_{10}$ values provided in Table 4-1[77] of the *Draft Supplement* are:

- Inhalation (continuous) (olfactory epithelium effects): 0.846 ppm
- Oral (liver toxicity): 2.6 mg/kg-d

For inhalation, we conducted this analysis with the POD for continuous exposure rather than occupational exposure, given the emphasis of the *Draft Supplement* on assessing general population exposure. All subsequent steps in the analysis are the same for either continuous or occupational exposure.

The first POD adjustment in the IPCS methodology is to convert the $BMDL_{10}$ to a $BMD_{10}$ as follows:

- $BMD_{10} = BMDL_{10} \times (BMD_{10} / BMDL_{10})$

This adjustment required computation of the $BMD_{10} / BMDL_{10}$ ratio. The necessary values for this ratio were obtained from the 2020 TSCA Risk Evaluation, Table 3-9 (inhalation) and Table 3-11 (oral).[78] Since $BMD_{10}$ values are available only before application of adjustments for exposure duration, units conversion and dosimetry, both the BMD and BMDL values prior to these adjustments were used in calculating these ratios:

- Inhalation: $BMD_{10} / BMDL_{10} = 6.47$ ppm / 4.74 ppm = 1.36
- Oral: $BMD_{10} / BMDL_{10} = 16.7$ mg/kg-d /9.57 mg/kg-d = 1.75

With these ratios, the $BMD_{10}$ in adjusted units can be calculated:

- Inhalation: $BMD_{10} = BMDL_{10} \times (BMD_{10} / BMDL_{10}) = 0.846$ ppm x 1.36 = 1.15 ppm
- Oral: $BMD_{10} = BMDL_{10} \times (BMD_{10} / BMDL_{10}) = 2.6$ mg/kg-d x 1.75 = 4.54 mg/kg-d

Uncertainty in the $BMD_{10}$ in the IPCS methodology, represented by the ratio of 95$^{th}$ percentile to 50$^{th}$ percentile (P95/P50), is provided by the same ratio of $BMD_{10} / BMDL_{10}$.

The second POD adjustment is to convert from the $BMD_{10}$ to an $ED_{50}$. The $ED_{50}$ and its uncertainty are determined 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 $(P95/P50)^2$."[79]

Combining these adjustments yields an $ED_{50}$ and composite uncertainty (P95/P50) for both the inhalation and oral PODs. In the IPCS approximate probabilistic calculation template, those values are entered as follows:

[77] US EPA (2023) Draft Supplement to the Risk Evaluation for 1,4-Dioxane . Table 4-1. Available: https://www.regulations.gov/document/EPA-HQ-OPPT-2022-0905-0032

[78] US EPA (2020) Final Risk Evaluation for 1,4-Dioxane. Available: https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/final-risk-evaluation-14-dioxane#riskevaluation

[79] 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 1,4-dioxane exposure | | | | |
|---|---|---|---|---|
| **Aspect** | **Inhalation (Continuous) Olfactory epithelium effects** | | **Oral Liver toxicity** | |
| | **P50** | **P95/P50** | **P50** | **P95/P50** |
| $BMD_{10}$ | 1.15 ppm | 1.36 | 4.54 mg/kg-d | 1.75 |
| $BMD_{10}$-to-$ED_{50}$ adjustment | 3 | 1.5 | 3 | 1.5 |
| **IPCS POD = $ED_{50}$** | **3.5 ppm** | **1.67[b]** | **13.6 mg/kg-d** | **1.99[c]** |

[a] Uncertainty is expressed as the ratio of the 95th percentile (P95) to the 50th percentile (P50)
[b] (Composite P95/P50) = $10^{[(\log 1.36)^2 + (\log 1.5)^2]^{0.5}} = 1.67$
[c] (Composite P95/P50) = $10^{[(\log 1.75)^2 + (\log 1.5)^2]^{0.5}} = 1.99$

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. Since the determination of the EPA $BMDL_{10}$ values incorporate dosimetric adjustments, no further adjustment for body size is necessary (P50 = 1). The uncertainty in the bodyweight scaling is not quantified in this analysis (P95/P50 = 1).

For the TK/TD differences remaining after bodyweight scaling, the IPCS report recommends a central estimate (P50) of 1 (i.e., no additional interspecies differences) and representing uncertainty with a P95/P50 factor of 3.[80] We incorporated these IPCS recommendations. These interspecies adjustments are the same for both inhalation and oral exposure. The interspecies adjustments are entered in the IPCS approximate probabilistic calculation template as follows:

| Interspecies adjustments for probabilistic dose-response analysis of chronic 1,4-dioxane exposure | | |
|---|---|---|
| **Aspect** | **P50** | **P95/P50** |
| $AF_{Interspecies\text{-}BS}$ | 1 | 1 |
| $AF_{Interspecies\text{-}TK/TD}$ | 1 | 3 |

[80] World Health Organization. Guidance document on evaluating and expressing uncertainty in hazard characterization. IPCS harmonization project document; no. 11. Table 4-3. 2014.

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 to lower levels of incidence. The IPCS report provides $AF_{intraspecies}$ for several incidence (I) values. As with the POD, the IPCS methodology uses the P50 as a central estimate and the P95/P50 as a measure of uncertainty for each value of I. $AF_{intraspecies}$ values provided by IPCS for several values of I, along with an additional value of I of interest for this analysis, are provided in the following table:

| Lognormal approximation of uncertainty distributions for intraspecies variability 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 |
| 0.1% (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

These interspecies adjustments are the same for both inhalation and oral exposure.

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" for inhalation exposure represents olfactory epithelium effects, and the "M" for oral exposure represents liver toxicity. The IPCS approach is a probabilistic method, so the $HD_M^I$ is a distribution; selected values from that distribution are presented as follows:

- P05: $5^{th}$ percentile estimate (lower confidence limit) of $HD_M^I$ (this value is shown in **bold**)
- P50: $50^{th}$ percentile estimate (median) of $HD_M^I$
- P95: $95^{th}$ percentile estimate (upper confidence limit) of $HD_M^I$

The following tables present the results for I = 1%, 0.5%, 0.1%, 0.01% and 0.001% using the POD, $AF_{interspecies}$ and $AF_{intraspecies}$ values shown above.

| Calculation of $HD_M^I$ from chronic 1,4-dioxane exposure (Incidence = 1%) | | | | |
|---|---|---|---|---|
| **Aspect** | **Inhalation (Continuous) Olfactory epithelium effects** | | **Oral Liver toxicity** | |
| | **P50** | **P95/P50** | **P50** | **P95/P50** |
| $BMD_{10}$ | 1.15 ppm | 1.36 | 4.54 mg/kg-d | 1.75 |
| $BMD_{10}$-to-$ED_{50}$ adjustment | 3 | 1.5 | 3 | 1.5 |
| **IPCS POD = $ED_{50}$** | **3.5 ppm** | **1.67** | **13.6 mg/kg-d** | **1.99** |
| $AF_{Interspecies-BS}$ | 1 | 1 | 1 | 1 |
| $AF_{Interspecies-TK/TD}$ | 1 | 3 | 1 | 3 |
| $AF_{Intraspecies\ (I=1\%)}$ | 9.69 | 4.32 | 9.69 | 4.32 |
| $HD_M^I$ | 0.36 ppm[a] | 6.68[b] | 1.40 mg/kg-d[a] | 7.06[c] |
| | **P05** | **P95** | **P05** | **P95** |
| $HD_M^{I\,(d)}$ | **0.05 ppm** | 2.39 ppm | **0.20 mg/kg-d** | 9.92 mg/kg-d |

[a] $HD_M^I$ (P50) = IPCS POD / ($AF_{Interspecies-BS}$ x $AF_{Interspecies-TK/TD}$ x $AF_{Intraspecies}$)
[b] (Composite P95/P50) = $10^{[(\log 1.67)^2 + (\log 1)^2 + (\log 3)^2 + (\log 4.32)^2]^{0.5}} = 6.68$
[c] (Composite P95/P50) = $10^{[(\log 1.99)^2 + (\log 1)^2 + (\log 3)^2 + (\log 4.32)^2]^{0.5}} = 7.06$
[d] $HD_M^I$ (P05) = $HD_M^I$ (P50) / (Composite P95/P50)
$HD_M^I$ (P95) = $HD_M^I$ (P50) x (Composite P95/P50)

| Calculation of $HD_M^I$ from chronic 1,4-dioxane exposure (Incidence = 0.5%) | | | | |
|---|---|---|---|---|
| **Aspect** | **Inhalation (Continuous) Olfactory epithelium effects** | | **Oral Liver toxicity** | |
| | **P50** | **P95/P50** | **P50** | **P95/P50** |
| $BMD_{10}$ | 1.15 ppm | 1.36 | 4.54 mg/kg-d | 1.75 |
| $BMD_{10}$-to-$ED_{50}$ adjustment | 3 | 1.5 | 3 | 1.5 |
| **IPCS POD = $ED_{50}$** | **3.5 ppm** | **1.67** | **13.6 mg/kg-d** | **1.99** |
| $AF_{Interspecies\text{-}BS}$ | 1 | 1 | 1 | 1 |
| $AF_{Interspecies\text{-}TK/TD}$ | 1 | 3 | 1 | 3 |
| $AF_{Intraspecies\ (I=0.5\%)}$ | 12.36 | 5.06 | 12.36 | 5.06 |
| $HD_M^I$ | 0.28 ppm [a] | 7.57 [b] | 1.10 mg/kg-d [a] | 7.97 [c] |
| | **P05** | **P95** | **P05** | **P95** |
| $HD_M^{I\,(d)}$ | **0.04 ppm** | 2.12 ppm | **0.14 mg/kg-d** | 8.78 mg/kg-d |

[a] $HD_M^I$ (P50) = IPCS POD / ($AF_{Interspecies\text{-}BS}$ x $AF_{Interspecies\text{-}TK/TD}$ x $AF_{Intraspecies}$)
[b] (Composite P95/P50) = $10^{[(\log 1.67)^2 + (\log 1)^2 + (\log 3)^2 + (\log 5.06)^2]^{0.5}} = 7.57$
[c] (Composite P95/P50) = $10^{[(\log 1.99)^2 + (\log 1)^2 + (\log 3)^2 + (\log 5.06)^2]^{0.5}} = 7.97$
[d] $HD_M^I$ (P05) = $HD_M^I$ (P50) / (Composite P95/P50)
$HD_M^I$ (P95) = $HD_M^I$ (P50) x (Composite P95/P50)

| Calculation of $HD_M^I$ from chronic 1,4-dioxane exposure (Incidence = 0.1%) | | | | |
|---|---|---|---|---|
| **Aspect** | **Inhalation (Continuous) Olfactory epithelium effects** | | **Oral Liver toxicity** | |
| | **P50** | **P95/P50** | **P50** | **P95/P50** |
| $BMD_{10}$ | 1.15 ppm | 1.36 | 4.54 mg/kg-d | 1.75 |
| $BMD_{10}$-to-$ED_{50}$ adjustment | 3 | 1.5 | 3 | 1.5 |
| **IPCS POD = $ED_{50}$** | **3.5 ppm** | **1.67** | **13.6 mg/kg-d** | **1.99** |
| $AF_{Interspecies\text{-}BS}$ | 1 | 1 | 1 | 1 |
| $AF_{Interspecies\text{-}TK/TD}$ | 1 | 3 | 1 | 3 |
| $AF_{Intraspecies\ (I=0.1\%)}$ | 20.42 | 6.99 | 20.42 | 6.99 |
| $HD_M^I$ | 0.17 ppm [a] | 9.89[b] | 0.67 mg/kg-d [a] | 10.35[c] |
| | **P05** | **P95** | **P05** | **P95** |
| $HD_M^{I\,(d)}$ | **0.02 ppm** | 1.68 ppm | **0.06 mg/kg-d** | 6.90 mg/kg-d |

[a] $HD_M^I$ (P50) = IPCS POD / ($AF_{Interspecies\text{-}BS}$ x $AF_{Interspecies\text{-}TK/TD}$ x $AF_{Intraspecies}$)
[b] (Composite P95/P50) = $10^{[(\log 1.67)^2 + (\log 1)^2 + (\log 3)^2 + (\log 6.99)^2]^{0.5}} = 9.89$
[c] (Composite P95/P50) = $10^{[(\log 1.99)^2 + (\log 1)^2 + (\log 3)^2 + (\log 6.99)^2]^{0.5}} = 10.35$
[d] $HD_M^I$ (P05) = $HD_M^I$ (P50) / (Composite P95/P50)
$HD_M^I$ (P95) = $HD_M^I$ (P50) x (Composite P95/P50)

| Calculation of $HD_M^I$ from chronic 1,4-dioxane exposure (Incidence = 0.01%) | | | | |
|---|---|---|---|---|
| **Aspect** | **Inhalation (Continuous) Olfactory epithelium effects** | | **Oral Liver toxicity** | |
| | **P50** | **P95/P50** | **P50** | **P95/P50** |
| $BMD_{10}$ | 1.15 ppm | 1.36 | 4.54 mg/kg-d | 1.75 |
| $BMD_{10}$-to-$ED_{50}$ adjustment | 3 | 1.5 | 3 | 1.5 |
| **IPCS POD = $ED_{50}$** | **3.5 ppm** | **1.67** | **13.6 mg/kg-d** | **1.99** |
| $AF_{Interspecies\text{-}BS}$ | 1 | 1 | 1 | 1 |
| $AF_{Interspecies\text{-}TK/TD}$ | 1 | 3 | 1 | 3 |
| $AF_{Intraspecies\ (I=0.01\%)}$ | 37.71 | 10.39 | 37.71 | 10.39 |
| $HD_M^I$ | 0.09 ppm [a] | 13.96[b] | 0.36 mg/kg-d [a] | 14.53[c] |
| | **P05** | **P95** | **P05** | **P95** |
| $HD_M^{I\ (d)}$ | **0.01 ppm** | 1.28 ppm | **0.02 mg/kg-d** | 5.24 mg/kg-d |

[a] $HD_M^I$ (P50) = IPCS POD / ($AF_{Interspecies\text{-}BS}$ x $AF_{Interspecies\text{-}TK/TD}$ x $AF_{Intraspecies}$)
[b] (Composite P95/P50) = $10^{[(\log 1.67)^2 + (\log 1)^2 + (\log 3)^2 + (\log 10.39)^2]^{0.5}} = 13.96$
[c] (Composite P95/P50) = $10^{[(\log 1.99)^2 + (\log 1)^2 + (\log 3)^2 + (\log 10.39)^2]^{0.5}} = 14.53$
[d] $HD_M^I$ (P05) = $HD_M^I$ (P50) / (Composite P95/P50)
$HD_M^I$ (P95) = $HD_M^I$ (P50) x (Composite P95/P50)

| Calculation of $HD_M^I$ from chronic 1,4-dioxane exposure (Incidence = 0.001%) | | | | |
|---|---|---|---|---|
| **Aspect** | **Inhalation (Continuous) Olfactory epithelium effects** | | **Oral Liver toxicity** | |
| | **P50** | **P95/P50** | **P50** | **P95/P50** |
| $BMD_{10}$ | 1.15 ppm | 1.36 | 4.54 mg/kg-d | 1.75 |
| $BMD_{10}$-to-$ED_{50}$ adjustment | 3 | 1.5 | 3 | 1.5 |
| **IPCS POD = $ED_{50}$** | **3.5 ppm** | **1.67** | **13.6 mg/kg-d** | **1.99** |
| $AF_{Interspecies-BS}$ | 1 | 1 | 1 | 1 |
| $AF_{Interspecies-TK/TD}$ | 1 | 3 | 1 | 3 |
| $AF_{Intraspecies\ (I=0.001\%)}$ | 64.25 | 14.65 | 64.25 | 14.65 |
| $HD_M^I$ | 0.05 ppm [a] | 19.02 [b] | 0.21 mg/kg-d [a] | 19.71 [c] |
| | **P05** | **P95** | **P05** | **P95** |
| $HD_M^{I\ (d)}$ | **0.003 ppm** | 1.03 ppm | **0.01 mg/kg-d** | 4.18 mg/kg-d |

[a] $HD_M^I$ (P50) = IPCS POD / ($AF_{Interspecies-BS}$ x $AF_{Interspecies-TK/TD}$ x $AF_{Intraspecies}$)
[b] (Composite P95/P50) = $10^{[(\log 1.67)^2 + (\log 1)^2 + (\log 3)^2 + (\log 14.65)^2]^{0.5}} = 19.02$
[c] (Composite P95/P50) = $10^{[(\log 1.99)^2 + (\log 1)^2 + (\log 3)^2 + (\log 14.65)^2]^{0.5}} = 19.71$
[d] $HD_M^I$ (P05) = $HD_M^I$ (P50) / (Composite P95/P50)
$HD_M^I$ (P95) = $HD_M^I$ (P50) x (Composite P95/P50)

Interpretation of results

Based on these calculations, for general population (continuous) inhalation exposures we find that:

- 0.05 ppm is the lower bound (95% confidence) human dose at which olfactory epithelium effects are expected in 1% of the population,
- 0.04 ppm is the lower bound (95% confidence) human dose at which olfactory epithelium effects are expected in 0.5% of the population,
- 0.02 ppm is the lower bound (95% confidence) human dose at which olfactory epithelium effects are expected in 0.1% of the population,
- 0.01 ppm is the lower bound (95% confidence) human dose at which olfactory epithelium effects are expected in 0.01% (1-in-10,000) of the population, and
- 0.003 ppm is the lower bound (95% confidence) human dose at which olfactory epithelium effects are expected in 0.001% (1-in,100,000) of the population.

EPA's non-cancer risk characterization for continuous chronic inhalation exposure to 1,4-dioxane uses 0.846 ppm as the point of departure, and a benchmark MOE of 30.[81] This means that EPA concludes "risk is not indicated"[82] for any chronic continuous exposure less than 0.846 ppm / 30 = 0.028 ppm. Our analysis indicates that an exposure of 0.028 ppm is substantially greater than the lower bound dose for the 1-in-1000 risk level.

For general population oral exposures we find that:

- 0.2 mg/kg-d is the lower bound (95% confidence) human dose at which liver toxicity is expected in 1% of the population,
- 0.14 mg/kg-d is the lower bound (95% confidence) human dose at which liver toxicity is expected in 0.5% of the population,
- 0.06 mg/kg-d is the lower bound (95% confidence) human dose at which liver toxicity is expected in 0.1% of the population,
- 0.02 mg/kg-d is the lower bound (95% confidence) human dose at which liver toxicity is expected in 0.01% (1-in-10,000) of the population, and
- 0.01 mg/kg-d is the lower bound (95% confidence) human dose at which liver toxicity is expected in 0.001% (1-in,100,000) of the population.

EPA's non-cancer risk characterization for chronic oral exposure to 1,4-dioxane uses 2.6 mg/kg-d as the point of departure, and a benchmark MOE of 30.[83] This means that EPA concludes "risk is not indicated"[84] for any chronic oral exposure less than 2.6 mg/kg-d / 30 = 0.09 mg/kg-d. Our analysis indicates that an exposure of 0.09 mg/kg-d is substantially greater than the lower bound dose for the 1-in-1000 risk level.

The estimates of $HD_M^I$ presented here were based entirely on input values available from the WHO/IPCS methodology document and from EPA's TSCA risk evaluation of 1,4-dioxane. 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.[85, 86, 87] 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.

[81] US EPA (2023) Draft Supplement to the Risk Evaluation for 1,4-Dioxane . Table 5-1. Available: https://www.regulations.gov/document/EPA-HQ-OPPT-2022-0905-0032

[82] US EPA (2023) Draft Supplement to the Risk Evaluation for 1,4-Dioxane . pp 136. Available: https://www.regulations.gov/document/EPA-HQ-OPPT-2022-0905-0032

[83] US EPA (2023) Draft Supplement to the Risk Evaluation for 1,4-Dioxane . Table 5-1. Available: https://www.regulations.gov/document/EPA-HQ-OPPT-2022-0905-0032

[84] US EPA (2023) Draft Supplement to the Risk Evaluation for 1,4-Dioxane . pp 136. Available: https://www.regulations.gov/document/EPA-HQ-OPPT-2022-0905-0032

[85] 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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