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# Comments from Academics, Scientists and Clinicians on the Draft Risk Evaluation for 1-Bromopropane

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

We appreciate the opportunity to provide written comments on the draft risk evaluation for 1-bromopropane, issued under EPA's Toxic Substances Control Act (TSCA), as amended by the Frank R. Lautenberg Chemical Safety for the 21st Century Act ("amended TSCA").[1] 1-bromopropane is a solvent with widespread household and industrial uses, including degreasers, spot cleaners and stain removers with significant potential for inhalation and dermal exposures to consumers and workers. EPA's draft risk evaluation indicates that 1-bromopropane has myriad adverse effects, including carcinogenicity and reproductive, developmental, and neurological toxicity.

Despite flaws in its evaluation that result in underestimating risks, EPA found that multiple uses of 1-bromopropane present unreasonable risks of cancer, reproductive and/ or developmental toxicity to consumers and workers, and to people in the vicinity (bystanders and occupational non-users). Some of the risks (developmental effects such as reduced litter size and post-implantation loss) raise high concern as they "may result from a single exposure during a critical window of development."[2] EPA must take prompt action to protect the public from the serious risks posed by 1-bromopropane.

In fact, EPA has not accurately identified all the risks of concern for 1-bromopropane, as methodological problems in the draft risk evaluation led to risk underestimation. For example, EPA excluded studies showing possible widespread exposures to 1-bromopropane in pregnant women and did not consider documented inhalation exposure for the general population. It is highly likely that additional consumer and industrial uses pose unreasonable risks, and that other populations, including susceptible sub-populations, face unreasonable risks from 1-bromopropane (such as children who were inadequately considered and the general population who EPA excluded from the current evaluation).

EPA's risk determinations have been and will continue to be inadequate until the methodological, scientific and technical problems we and many other commenters identified are consistent with current and best scientific principles for systematic reviews, assessing population susceptibility, and exposure assessment. The law requires EPA to make decisions about chemical risks based on the "best available science, "adequate information" and "weight of the scientific evidence,"[3] which EPA regulation defined as "…a systematic review method, applied in a manner suited to the nature of the evidence or decision, that uses a pre-established protocol to comprehensively, objectively, transparently, and consistently

[1] US EPA (2019) 1-Bromopropane (1–BP); Draft Toxic Substances Control Act (TSCA) Risk Evaluation. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0235-0022

[2] Id. Page 185.

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

identify and evaluate each stream of evidence, including strengths, limitations, and relevance of each study and to integrate evidence as necessary and appropriate based upon strengths, limitations, and relevance.''[4]

We are concerned that the current evaluation does not follow these mandates, leaving public health at risk.

**Our comments address the following main issues:**

1. **EPA's TSCA systematic review methodology for identifying and evaluating the evidence continues to have serious scientific flaws; this pattern of methodological change is not evidence-based, lacks transparency, and is likely to have resulted in a biased evidence base for the 1-bromopropane draft risk evaluation.**
    a. **EPA must address the comments from the SACC on Pigment Violent 29 and incorporate the recommended changes to its systematic review prior to finalizing the 1-bromopropane evaluation and for future TSCA risk evaluations.**
    b. **EPA continues to rely on "key/ supporting/ influential information," the qualifications of which are still not clearly articulated, and also fails to detail its approach using the "hierarchy of preferences" to exclude relevant studies.**
2. **EPA incorrectly draws conclusions based on ECHA "robust summaries," which comprise the majority of aquatic toxicity data.**
3. **EPA's draft risk determinations are not protective of potentially exposed or susceptible subpopulations.**
    a. **EPA's refusal to consider documented inhalation exposure for the general population due to its potential listing as a hazardous air pollutant (HAP) has no basis.**
    b. **EPA excludes from consideration data from the National Health and Nutrition Examination Survey (NHANES) and National Children's Study (NCS) which suggest widespread exposure to 1-bromopropane, including pregnant women in the general population.**
    c. **EPA does not adequately account for children's potential exposures to 1-bromopropane.**
    d. **EPA inappropriately excludes studies with relevant data on workers and underestimates worker risks through its scientifically unsupported assumptions about use of personal protective equipment (PPE).**
    e. **EPA is underestimating exposures by failing to aggregate dermal and inhalation exposure.**
4. **EPA's misuse of risk assessment elements like NOAEL / LOAEL and Uncertainty Factors could lead to an underestimation of risk.**

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

Sincerely,

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[4] 40 CFR 702.33

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**DETAILED COMMENTS**

**1. EPA's TSCA systematic review methodology for identifying and evaluating the evidence continues to have serious scientific flaws; this pattern of methodological change is not evidence-based, lacks transparency, and is likely to have resulted in a biased evidence base for the 1-bromopropane draft risk evaluation.**

**a. EPA must address the comments from the SACC on Pigment Violent 29 and incorporate the recommended changes to its systematic review prior to finalizing the 1-bromopropane evaluation and for future TSCA risk evaluations.**

EPA's systematic review method developed under TSCA (hereafter referred to as the "TSCA method")[5] fails to accurately evaluate the evidence on 1-bromopropane. We commented on the scientific flaws in the TSCA method previously as summarized in a recent peer-reviewed commentary published in the *American Journal of Public Health*.[6,7,8]

The other draft risk evaluations released by EPA demonstrate the TSCA method's fundamental deficiencies, which the Science Advisory Committee on Chemicals (SACC) further highlighted in its peer review of the Draft Risk Evaluation of C.I. Pigment Violet 29 (PV29).[9]

The SACC made critical recommendations necessary to improve the TSCA method, but EPA has not addressed these in the draft 1-bromopropane evaluation, therefore the scientific flaws in the TSCA

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

[6] US EPA (2018). **Problem Formulations for Risk Evaluations To Be Conducted Under Toxic Substances Control Act, and General Guiding Principles To Apply Systematic Review in TSCA Risk Evaluations**. Comment submitted by Veena Singla, Associate Director, Science and Policy, Program on Reproductive Health and the Environment, University of California, San Francisco et al. Available: **https://www.regulations.gov/document?D=EPA-HQ-OPPT-2018-0210-0107**

[7] US EPA (2019). Draft Toxic Substances Control Act Risk Evaluations: Colour Index Pigment Violet 29. Comment submitted by Veena Singla, Associate Director, Science and Policy, Program on Reproductive Health and the Environment, University of California, San Francisco (UCSF) et al. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2018-0604-0014

[8] Singla V, Sutton P, Woodruff TW. (2019) The Environmental Protection Agency Toxic Substances Control Act Systematic Review Method May Curtail Science Used to Inform Policies, With Profound Implications for Public Health. Am J Public Health. doi: 10.2105/AJPH.2019.305068

[9] US EPA (2019) Peer Review of the Draft Risk Evaluation for Pigment Violet 29 (PV29). Available: https://www.regulations.gov/docket?D=EPA-HQ-OPPT-2018-0604 D=EPA-HQ-OPPT-2018-0604

method persist. Below, we highlight the areas of most concern raised by the SACC that remain unaddressed.

> *"The Agency rationale for developing the TSCA SR should include a comparison to other SR approaches and describe the rationale for major differences."* [10]

The 1-bromopropane draft evaluation does not contain a rationale for departing from well established, scientifically valid systematic review approaches that have already been implemented in environmental health assessments and decision-making such as the Navigation Guide[11] and the Office of Health Assessment and Translation (OHAT).[12] Currently the World Health Organization utilizes the Navigation Guide methodology to assess the global burden of work-related injury and disease.[13] If EPA conducted a comparison of these approaches as suggested, it would demonstrate that the TSCA method implemented in the 1-bromopropane draft evaluation is inconsistent with these aforementioned methods and does not follow best practices for systematic review.

> *"The Committee discussed the need to publish peer reviewed pre-established protocols for each of the Agency's reviews prior to performing the actual risk assessment. The protocol for PV29 was created concurrently with the review, which is contrary to best practices for systematic reviews."*[14]

This critical methodological step is again absent in 1-bromopropane draft evaluation. The use of pre-established protocols minimizes bias in the evidence base by explicitly defining question formulation, the conduct of searches, and study evaluation, *a priori*.[15] Most importantly, decision-making transparency throughout the systematic review process is fundamental to the integrity of evidence-based evaluations.[16] The EPA's 2017 framework rules mandate that the agency use "a pre-established protocol" to conduct risk assessments. Further, in its review of the EPA IRIS program's proposed systematic review methods, the National Academies of Science (NAS) stated that "Completing the literature search as part of protocol development is inconsistent with current best practices for systematic review, and the IRIS program is encouraged to complete the public-comment process and finalize the protocol before initiating the systematic review."

> *"The Committee noted that the TSCA SR weighted scoring system may be inappropriate if there is disagreement in the weighting of different metrics. For example, a certain study characteristic*

[10] US EPA (2019) Peer Review of the Draft Risk Evaluation for Pigment Violet 29 (PV29). Page 26. Available: https://www.regulations.gov/docket?D=EPA-HQ-OPPT-2018-0604 D=EPA-HQ-OPPT-2018-0604

[11] Woodruff TJ, Sutton P. The Navigation Guide systematic review methodology: a rigorous and transparent method for translating environmental health science into better health outcomes. Environ Health Perspect. 2014;122(10):1007-1014.

[12] National Toxicology Program (NTP). Handbook for Conducting a Literature-Based Health Assessment Using OHAT Approach for Systematic Review and Evidence Integration. Research Triangle Park, NC: National Toxicology Program; 2015.

[13] Mandrioli, D., Schlünssen, V., Ádám, B., Cohen, R. A., Colosio, C., Chen, W., … Scheepers, P. T. J. (2018, October 1). WHO/ILO work-related burden of disease and injury: Protocol for systematic reviews of occupational exposure to dusts and/or fibres and of the effect of occupational exposure to dusts and/or fibres on pneumoconiosis. Environment International, Vol. 119, pp. 174–185. https://doi.org/10.1016/j.envint.2018.06.005

[14] US EPA (2019) Peer Review of the Draft Risk Evaluation for Pigment Violet 29 (PV29). Page 27. Available: https://www.regulations.gov/docket?D=EPA-HQ-OPPT-2018-0604 D=EPA-HQ-OPPT-2018-0604

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

[16] Institute of Medicine Committee on Standards for Systematic Reviews of Comparative Effectiveness Research. Finding What Works in Health Care: Standards for Systematic Reviews J Eden, L Levit, A Berg, S Morton (Eds.), National Academies Press (US) Copyright 2011 by the National Academy of Sciences, Washington (DC) (2011)

> *that may be a "fatal flaw" would be weighted equally to other more minor elements. The "Agency should provide justification for using a weighted scoring system and the rationale for the specific metrics used for differential weighting in its evaluation of studies."*[17]

EPA needs to assess the studies underpinning its regulatory decisions with transparent and scientifically accepted methods. The use of weighted quality scores lacks both empirical and statistical justification and such scores are not able to distinguish between studies with a high and low risk of bias in meta-analyses.[18,19,20] Further, in its review of the EPA's IRIS program the NAS strongly recommended using a methodology that did not incorporate quantitative scoring of a study.[21] Therefore, although the use of such scores is not recommended, EPA has again used scoring in the 1-bromopropane draft risk evaluation without justification or rationale for the specific metrics applied for differential weighting in its evaluation of studies. Additionally, as the SACC highlights, the use of this weighted scoring system may lead to the exclusion of a study, due to one 'fatal flaw'; and these 'fatal flaws' are not necessarily related to the quality of the study. EPA's scoring system includes many such 'fatal flaws' that are not related to bias, but rather to reporting. Thus, EPA could be excluding important studies that are of sufficient quality based on a single limitation that is reflective of poor reporting. This is not consistent with the EPA's 2017 regulation that requires consideration of all relevant science while accounting for "strengths and limitations." Instead, review authors should attempt to request the missing information required to make the determination from the study authors.[22] If the missing information cannot be identified, a potential bias could then be considered. However, the study should not be rated as having 'high risk of bias' or 'fatal flaw'.

> *"Regarding data integration, the Committee discussed the benefits of including a more thorough and inclusive data integration discussion in the TSCA SR for PV29… there is a need in the Evaluation for a thorough description and outline for how all evidence and data are integrated into a final weight of evidence conclusion"*[23]

The 1-bromopropane draft risk evaluation fails to clearly pre-specify the method for integrating two or more streams of evidence. We recommend an approach that has been successfully used by the NAS[24],

[17] US EPA (2019) Peer Review of the Draft Risk Evaluation for Pigment Violet 29 (PV29). Page 26-7. Available: https://www.regulations.gov/docket?D=EPA-HQ-OPPT-2018-0604 D=EPA-HQ-OPPT-2018-0604

[18] Juni P, Witschi A, Bloch R, Egger M. The hazards of scoring the quality of clinical trials for meta-analysis. *Jama.* 1999;282(11):1054-1060

[19] Higgins J, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions. Chichester: The Cochrane Collaboration and Wiley-Blackwell; 2008.

[20] Herbison P, Hay-Smith J, Gillespie WJ. Adjustment of meta-analyses on the basis of quality scores should be abandoned. J Clin Epidemiol. *2006 Dec; 59(12):1249-56.*

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

[22] Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019). Chpt 5.2.3 Correspondence with investigators. Cochrane, 2019. Available from www.training.cochrane.org/handbook

[23] US EPA (2019) Peer Review of the Draft Risk Evaluation for Pigment Violet 29 (PV29). Page 27. Available: https://www.regulations.gov/docket?D=EPA-HQ-OPPT-2018-0604 D=EPA-HQ-OPPT-2018-0604

[24] NAS. (2017). Application of Systematic Review Methods in an Overall Strategy for Evaluating Low-Dose Toxicity from Endocrine Active Chemicals. Washington, D.C.: The National Academies Press; 2011

International Agency for Research on Cancer (IARC),[25] OHAT[26] and Navigation Guide[27] consisting of an overall rating in the confidence of the body of evidence, for each specified outcome. The overall rating should then be translated into a conclusion on the level of evidence for a health effect, and then finally into a hazard identification conclusion. Human and animal evidence when available should be integrated, while mechanistic data may be used to help inform the final conclusions. The ad hoc nature of the process outlined in the 1-bromopropane draft risk evaluation is not consistent with best practice methods of systematic review developed, endorsed or used by the aforementioned organizations.

As "The SACC serves as a primary scientific peer review mechanism of the EPA, Office of Pollution Prevention and Toxics (OPPT), and is structured to provide balanced expert assessment of chemicals and chemical-related matters facing the Agency,"[28] it is critical that EPA address the SACC's comments through changes to its systematic review prior to finalizing the 1-bromopropane evaluation, and implement such changes for future TSCA risk evaluations.

**b. EPA continues to rely on "key/ supporting/ influential information," the qualifications of which are still not clearly articulated, and also fails to detail its approach using the "hierarchy of preferences" to exclude relevant studies.**

In our previous comments on 1,4-dioxane and HBCD we outlined critiques regarding EPA's new approach of relying on "key and supporting/ influential information" and we reiterate these critiques for 1-bromopropane.[29] This approach was not previously published nor peer-reviewed, it has not gone through a public comment period, does not meet the requirements of EPA's regulation, and raises serious concerns about bias in the evidence base of these evaluations. These methodological problems are significant enough that EPA's risk conclusions are highly likely to be biased.

In the draft risk evaluation, EPA states:

> *"EPA used previous chemical assessments to quickly identify relevant key and supporting information as a pragmatic approach to expedite the quality evaluation of the data sources, but many of those data sources were already captured in the comprehensive literature as explained above. EPA also considered newer information not taken into account by previous chemical assessments as described in the Strategy for Conducting Literature Searches for 1-Bromopropane (1-BP): Supplemental Document to the TSCA Scope Document (U.S. EPA, 2017e)."*[30]

[25] IARC Monographs on the Evaluation of Carcinogenic Hazards to Humans. Lyon (FR): International Agency for Research on Cancer; 2019 Available from:https://monographs.iarc.fr/wp-content/uploads/2019/07/Preamble-2019.pdf

[26] National Toxicology Program Office of Health Assessment and Translation. Handbook for Conducting a Literature-Based Health Assessment Using OHAT Approach for Systematic Review and Evidence Integration. National Institute of Environmental Health Sciences; 2015

[27] Woodruff TJ, Sutton P. The Navigation Guide systematic review methodology: a rigorous and transparent method for translating environmental health science into better health outcomes. Environ Health Perspect. 2014;122(10):1007-1014

[28] US EPA (2019) Peer Review of the Draft Risk Evaluation for Pigment Violet 29 (PV29). Page 2. Available: https://www.regulations.gov/docket?D=EPA-HQ-OPPT-2018-0604 D=EPA-HQ-OPPT-2018-0604

[29] US EPA (2019). Draft Toxic Substances Control Act (TSCA) Risk Evaluations and TSCA Science Advisory Committee on Chemicals (SACC) Meetings; Cyclic Aliphatic Bromide Cluster (HBCD) and 1,4-Dioxane; Notice of Availability and Public Meetings. Comment submitted by Swati Rayasam, Science Associate, Program on Reproductive Health and the Environment, Department of Obstetrics, Gynecology and Reproductive Sciences, University of California, San Francisco et al. Available: **https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0237-0059** and **https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0238-0056**

[30] US EPA (2019) 1-Bromopropane (1–BP); Draft Toxic Substances Control Act (TSCA) Risk Evaluation. Page 43. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0235-0022

Echoing our previous comments, [31] the supplemental documents EPA references do not contain the phrasing "key and supporting information," and on page 142 of the draft risk evaluation, EPA describes its approach to identify key and supporting information as "including information supporting key analyses, arguments, and/or conclusions in the risk evaluation," which again requires knowing what the "key analyses, arguments, and/ or conclusions" are first, and then identifying the supporting information. [32] This approach is likely to bias a review and does not abide by the clear guidance of using a systematic review process as described in the framework rules. The fundamental purpose of a systematic review is to evaluate the evidence base of all science relevant to the review question and determine conclusions from the body of evidence as a whole. EPA's method is not consistent with established methods for systematic review and is missing critical pieces- including pre-established protocols that are necessary to avoid bias.

EPA states that it excluded 37 sources based on its hierarchy of preferences – which we have previously critiqued as a new methodology that the Agency introduced in these recent risk evaluations. To reiterate, the hierarchy of preferences is not part of the TSCA systematic review method document, nor in the 1-bromopropane scope or problem formulation documents, and it has not been subject to peer-review or public comment.

Additionally, and new to the 1-bromopropane draft risk evaluation, is the lack of explanation of what the hierarchy of preferences means. The 1-bromopropane draft risk evaluation only mentions the hierarchy of preferences once in a footnote of the literature flow diagram for environmental release and occupational exposure data on page 45 with no further explanation:

*"EPA's approach uses a hierarchy of preferences that guide decisions about what types of data/information are included for further analysis, synthesis and integration into the environmental release and occupational exposure assessments. EPA prefers using data with the highest rated quality among those in the higher level of the hierarchy of preferences (i.e. data>modeling>occupational exposure limits or release limits)."*
EPA is not being clear about what sources of information the Agency is relying on and which sources they exclude, going against the tenants of transparency and consistency within systematic review processes.

There have been major differences between the three released draft risk evaluations in terms of process and information. The risk evaluation for 1,4-dioxane provided a table of key studies, while both HBCD and 1-bromopropane have provided no such table, so it is not possible to determine what evidence and studies were evaluated as key information and what was excluded based on the hierarchy of preferences. EPA labelled the literature flow diagrams for all three draft assessments differently, with HBCD and 1,4-dioxane being labelled as "Engineering Releases and Occupational Exposure Data sources" while 1-bromopropane is labelled "Environmental Release and Occupational Exposure data sources."

[31] US EPA (2019). Draft Toxic Substances Control Act (TSCA) Risk Evaluations and TSCA Science Advisory Committee on Chemicals (SACC) Meetings; Cyclic Aliphatic Bromide Cluster (HBCD) and 1,4-Dioxane; Notice of Availability and Public Meetings. Comment submitted by Swati Rayasam, Science Associate, Program on Reproductive Health and the Environment, Department of Obstetrics, Gynecology and Reproductive Sciences, University of California, San Francisco et al. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0237-0059 and https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0238-0056

[32] US EPA (2019) 1-Bromopropane (1–BP); Draft Toxic Substances Control Act (TSCA) Risk Evaluation. Page 142. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0235-0022

Additionally, while both 1,4-dioxane and HBCD outlined the hierarchy of preferences in detail, [33] EPA only provides the brief definition above for 1-bromopropane. These types of inconsistencies indicate that EPA is not adhering to rigorous and systematic evaluation of the literature, and thus there cannot be confidence in the risk assessment.

To meet TSCA's scientific mandates, EPA should not use the approach of "key/ supporting/ influential information" and the "hierarchy of preferences" and conduct an systematic review using a scientifically valid method referenced above.

**2. EPA incorrectly draws conclusions based on ECHA "robust summaries," which comprise the majority of aquatic toxicity data.**

In considering the evidence base for environmental hazards and aquatic toxicity in the 1-bromopropane draft risk evaluation, EPA states:

> ***"****a total of one on-topic environmental hazard study (acute fish study; (Geiger et al., 1988)) was identified and reviewed according to the systematic review criteria… In addition to this study, five robust data summaries were identified in the European Chemicals Agency (ECHA) Database and were used to characterize the environmental hazards of 1-BP to aquatic receptors (ECHA, 2017)."* [34]

Based on a single fish study and five "robust summaries" not subject to internal nor external review, EPA determined that 1-bromopropane presented low to moderate hazard to aquatic environmental receptors. It is important to note that the summaries in the ECHA database are written by the chemical manufacturer, not ECHA, and that ECHA does not peer review or validate these summaries. That EPA is evaluating aquatic toxicity using an evidence base over 80% comprised of industry dossiers, which are neither full studies nor government documents that have been evaluated for quality or reliability, is deeply concerning. Based on its mandate under TSCA to utilize the "adequate information" and "best available science," EPA cannot reliably determine that 1-bromopropane poses no environmental risk using this evidence base. [35]

**3. EPA's draft risk determinations are not protective of potentially exposed or susceptible subpopulations.**

**a. EPA's refusal to consider documented inhalation exposure for the general population due to its potential listing as a hazardous air pollutant (HAP) has no basis.**

Due to the volatile nature of 1-bromopropane, EPA acknowledges that inhalation is expected to be the primary route of exposure. However, in the 1-bromopropane draft risk evaluation, EPA decided not to consider the inhalation exposure pathway for the general population, indicating that because 1-bromopropane **will be** listed as a hazardous air pollutant (HAP) the Clean Air Act will effectively manage risk. [36]

[33] US EPA (2019) EPA – HBCD Draft Risk Evaluation for Cyclic Aliphatic Bromide Cluster, pages 175-176. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0237-0002

[34] US EPA (2019) 1-Bromopropane (1–BP); Draft Toxic Substances Control Act (TSCA) Risk Evaluation. Page 138. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0235-0022

[35] 15 USC §2625 (h)-(i) and 15 USC §2601 (b)(1)

[36] US EPA (2019) 1-Bromopropane (1–BP); Draft Toxic Substances Control Act (TSCA) Risk Evaluation. Page 27. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0235-0022

First, EPA must evaluate inhalation exposures to the general population whether or not 1-bromopropane is listed as a HAP. As we detailed in our previous comments, established scientific principles for exposure assessment require that known exposures be included in the assessment, or exposure will not be accurately quantified and risk will be underestimated.[37] This is of particular concern for potentially exposed and susceptible subpopulations, as we outlined in our recent peer-reviewed commentary in *PLoS Biology*.[38]

Second, since publishing the list of HAPs in 1990, EPA has never added chemicals to the list. So despite inhalation being the primary route of exposure, and there being evidence of widespread exposure in the population and particularly in a susceptible subpopulation (see point below) EPA is excluding this known exposure assuming that regulatory action will take place on a petition that has been in limbo for nearly a decade. Additionally, under the legal requirements for the Clean Air Act, it would take EPA 8 years to evaluate *residual* risk to the population and, if necessary, create a stricter standard. [39] This clearly indicates that 1-bromopropane exposure risks to the general population should be assessed and will not be effectively managed under the Clean Air Act. TSCA requires a comprehensive assessment of exposures and by failing to do this, EPA will miss potentially exposed or susceptible sub-populations within the general population.

**b. EPA excludes from consideration data from the National Health and Nutrition Examination Survey (NHANES) and National Children's Study (NCS) which suggest widespread exposure to 1-bromopropane, including pregnant women in the general population.**

The draft risk evaluation references that a urinary metabolite of 1-bromopropane, BPMA, was detected in urine samples of adults in three separate NHANES cohorts. Another study reported a 99% detection of BPMA in the urine of 488 pregnant women in the National Children's Study suggesting "the possibility of low level but very widespread non-occupational exposures to 1-bromopropane," for this vulnerable population.[40] Despite describing this metabolite as "a valid biomarker for 1-BP exposure," EPA goes on to declare that based on questions around the specificity of the biomarker, it chose not incorporate these studies into the dose-response analysis, elaborating that its decision was based on a 2016 peer review panel for a prior 1-bromopropane risk assessment which had advised against using such data. [41] However, the 2016 review panel actually indicated that the committee *supported* the use of the biomarker out of an abundance of caution around overlooking a significant exposure scenario. This information was presented to EPA by Earthjustice in its public comments to the SACC for 1-bromopropane. [42]

[37] US EPA (2018). Problem Formulations for Risk Evaluations To Be Conducted Under Toxic Substances Control Act, and General Guiding Principles To Apply Systematic Review in TSCA Risk Evaluations. Comment submitted by Veena Singla, Associate Director, Science and Policy, Program on Reproductive Health and the Environment, University of California, San Francisco et al. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2018-0210-0107

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

[39] National Research Council. (2009). *Science and Decisions: Advancing Risk Assessment*. Page 52. Retrieved from https://www.nap.edu/catalog/12209/science-and-decisions-advancing-risk-assessment

[40] US EPA (2019) 1-Bromopropane (1–BP); Draft Toxic Substances Control Act (TSCA) Risk Evaluation. Pages 148-49. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0235-0022

[41] Id.

[42] US EPA (2019) 1-Bromopropane (1–BP); Draft Toxic Substances Control Act (TSCA) Risk Evaluation and TSCA Science Advisory Committee on Chemicals (SACC) Meetings; Notice of Availability and Public Meetings. Comment submitted by Jonathan Kalmuss-Katz, Eve C. Gartner and Tosh Sargar, Earthjustice. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0235-0030

*" Given the possibility of overlooking a significant exposure scenario,* ***the inclusion of biomarker data could be useful****. Along these lines, the measurement of BPMA levels by Boyle et al. (2016) suggests the possibility of low level, but very widespread, non-occupational exposures to 1-BP…" [43](emphasis ours)*

This is especially pertinent considering that EPA indicates "the reproductive system is a target of concern for 1-BP exposure." [44] In fact, EPA found the target of impaired fetal development to be particularly sensitive, as evidenced by animal studies.

*Overall, the general consistency of findings indicative of impaired development across species, as reported in multiple studies from independent laboratories, is taken as evidence of a causative association between 1-BP exposure and developmental toxicity.[45]*

This outcome directly affects biologically susceptible populations such as pregnant women and fetuses. That EPA ignores this likely widespread exposure in the general population and exposures to the vulnerable subpopulations is scientifically inappropriate and indicates the draft risk evaluation will underestimate risks.

The inconsistencies in EPA's methodology are troubling. The Agency seems to have considered non-peer reviewed industry dossiers submitted to ECHA as reliable in its evaluation of aquatic toxicity while later excluding robust human data (NHANES and NCS) as inadequate for its dose-response analysis. If EPA needs additional data about the specificity of the 1-bromopropane biomarker, it should use its authorities to order the needed testing.

**c. EPA does not adequately account for children's potential exposures to 1-bromopropane.**

Biological factors such as age can significantly affect health impacts from chemical exposure. For example, the prenatal life stage can be the most sensitive to developmental and reproductive toxicants, such as 1-bromopropane.[46,47] Despite considering the reproductive system a target of concern and EPA's assumption that a single exposure during a critical window of fetal development may be sufficient to produce adverse developmental effects, the 1-bromopropane risk evaluation fails to consider children, and particularly children of working-class families, in its exposure assessment, specifically when discussing dry cleaners. [48,49]

The only exposure consideration EPA gives children is to state they may be present for a 4-hour period after school, [50] but this presents two major problems:

[43] US EPA (2016) Minutes of the May 24-25, 2016 Chemical Safety Advisory Committee Meeting. Pg 14. Available: https://www.khlaw.com/Files/29464_Chemical_Safety_Advisory_Committee_Minutes.pdf.
[44] US EPA (2019) 1-Bromopropane (1–BP); Draft Toxic Substances Control Act (TSCA) Risk Evaluation. Page 155. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0235-0022
[45] Id. Page 160.
[46] Lanphear BP, Vorhees CV, Bellinger DC. Protecting Children from Environmental Toxins. PLoS Medicine. 2005;2(3).
[47] Bennett D, Bellinger DC, Birnbaum LS, Bradman A, Chen A, Cory-Slechta DA, et al. Project TENDR: Targeting Environmental Neuro-Developmental Risks The TENDR Consensus Statement. Environmental Health Perspectives. 2016;124(7).
[48] US EPA (2019) 1-Bromopropane (1–BP); Draft Toxic Substances Control Act (TSCA) Risk Evaluation. Page 155. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0235-0022
[49] Id. Page 145.
[50] Id. Page 90

1. Children in a family-owned dry cleaner are likely to spend their time outside of school in the dry-cleaning shop, and this time greatly eclipses their time spent in school, and
2. It does not consider children who are too young for school, who are biologically vulnerable, and who may be present in the dry-cleaning facility the same amount of time as their parent or guardian because of lack of ability to afford childcare.

According to EPA, dry cleaners are open 12 hours a day for 6 days a week equaling around 3,672 hours a year that the dry cleaner is open. [51] According to the National Center for Education Statistics, children **of school age** are in school around 1,195.2 hours total per year.[52] This means there are 2476.8 hours that school-age children spend NOT physically in school and likely in the business, representing a majority of children's time spent (67%) in the dry cleaner with the same exposure as occupational non-users and potentially more serious health impacts.

Additionally, children in family-owned dry-cleaning businesses are allowed to and likely do work for their family business, which are largely owned by working-class Korean families, as highlighted by a National Bureau of Economic Research working paper series.[53] According to the Fair Labor Standards Act,

> *"…a parent or a person standing in place of a parent may employ his own child or a child in his custody under the age of 16 years in any occupation other than the following: (a) Manufacturing; (b) mining; (c) an occupation found by the Secretary to be particularly hazardous or detrimental to health or well-being for children between the ages of 16 and 18 years."*[54]

Therefore, children employed in dry cleaners represent an allowable exemption under the FLSA.[55] Although chemicals like 1-bromopropane are developmental and reproductive toxicants, the exceptions to the FLSA based on hazardous work do not consider exposure to harmful chemicals.

The presence of children in a family-owned dry cleaning business, and especially their employment, would represent a chronic exposure over the child's life to age 18 (minimum), especially as it is likely that as children age, they will increase the amount they assist in the day to day business operations, and thus increase their exposure to 1-bromopropane.[56] Working in the business increases children's exposure and should represent a chronic exposure over biologically vulnerable life-stages. Despite this, EPA states that it does not consider exposures to children as chronic without providing any justification. EPA must adjust its exposure assumptions for children and assess risks under chronic exposure scenarios for occupational non-users in its final risk evaluation.

[51] US EPA (2019) 1-Bromopropane (1–BP); Draft Toxic Substances Control Act (TSCA) Risk Evaluation. Page 90. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0235-0022

[52] US Department of Education, National Center for Education Statistics. Schools and Staffing Survey (SASS), "Public School Data File," 2007-08. Available: https://nces.ed.gov/surveys/sass/tables/sass0708_035_s1s.asp

[53] National Bureau of Economic Research (Revised 2019) SOCIAL NETWORKS, ETHNICITY, AND ENTREPRENEURSHIP. Working Paper 21597. Available: https://www.nber.org/papers/w21597.pdf.

[54] 29 CFR §§570.126

[55] U.S. Department of Labor, Fair Labor Standards Act, Exemptions to the FLSA. Available: https://www.dol.gov/general/topic/youthlabor/exemptionsflsa

[56] Light I, Sabagh G, Bozorgmehr M, Der-Martirosian C. Beyond the Ethnic Enclave Economy. *Social Problems*. 1994; 41(1)pp 65–80, https://doi.org/10.2307/3096842.

**d. EPA inappropriately excludes studies with relevant data on workers and underestimates worker risks through its scientifically unsupported assumptions about use of personal protective equipment (PPE).**

As highlighted during the SACC and in other comments, EPA selected points of departure and characterized 1-bromopropane's risks based solely on animal studies, even though there were human studies available for endpoints such as neurotoxicity,[57] carcinogenicity,[58]and hepatoxicity.[59] Troublingly, epidemiological data revealed neurological effects and cellular damage at much lower doses than the animal studies, and some of the epidemiological studies were specifically of worker populations. But while EPA scored these available human studies as acceptable under its TSCA systematic review, it justified their exclusion based on the possibility of exposure misclassification. [60]

Dr. Adam Finkel, a professor at the University of Michigan School of Public Health and expert in 1-bromopropane, wrote in his comments that "EPA invokes exposure misclassification without much foundation, and fails to mention that this would generally bias a study away from a significant positive finding." [61,62] This means that the excluded studies would *underestimate* the magnitude of the health effect in question.

Risk of exposure to 1-bromopropane while working in small or family owned dry cleaners is of particular concern as it is unlikely that businesses of this size have adequate worker protections in place. In the draft risk evaluation EPA models "assumed a separate worker unloads the dry-cleaning machine and finishes and presses the garments." [63] However, three pages later in the risk evaluation, the Agency appears to contradict their previous statement, indicating that "Workers at these shops often perform multiple activities; as such, a single worker who spot treats the garments using 1-BP may also load and unload the dry cleaning machines." [64] Risk estimates for workers in dry cleaners show some of the highest exposures; [65] and because of this and other potential faulty exposure model assumptions, the true risks are likely higher.

Page 59 of the supplemental information also points to the financial difficulty for small dry cleaning businesses to install engineering controls "such as local exhaust ventilation (LEV) located at or near the machine door [which] can reduce worker exposure during machine loading, machine unloading, and maintenance activities (NCDOL, 2013)… [which] may not be economically feasible for dry cleaning shops."[66] This is all brought full circle as, in the supplemental information on occupational exposure assessment, "EPA also acknowledges that dry cleaners do not fall under regulatory requirements with

[57] US EPA (2019) 1-Bromopropane (1–BP); Draft Toxic Substances Control Act (TSCA) Risk Evaluation. Page 156. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0235-0022

[58] Id. Page 158.

[59] Id. Page 154.

[60]Id. Page 349.

[61] Id.

[62] US EPA (2019) 1-Bromopropane (1–BP); Draft Toxic Substances Control Act (TSCA) Risk Evaluation and TSCA Science Advisory Committee on Chemicals (SACC) Meetings; Notice of Availability and Public Meetings. Comment submitted by Adam M. Finkel, Clinical Professor of Environmental Health Sciences, University of Michigan School of Public Health. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0235-0033

[63] US EPA (2019) 1-Bromopropane (1–BP); Draft Toxic Substances Control Act (TSCA) Risk Evaluation. Page 90. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0235-0022

[64] Id. Page 93.

[65] Id. Page 201. Tables 4-18, 4-19, 4-20.

[66] US EPA (2019) 1-BP SR Supplemental File: Supplemental Information on Occupational Exposure Assessment. Page 59 Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0235-0014

regard to engineering controls to protect their workers from 1BP." [67] Despite the high risk of worker exposure, EPA recognized that even the limited engineering controls are unlikely to be implemented by these businesses.

Finally, as in previous risk evaluations, [68] EPA has no scientific basis to assume that workers will use PPE, but despite this the Agency incorporates this assumption into its occupational scenarios, even though no OSHA standards exist for 1-bromopropane and "[f]ew literature sources indicate the use of respirators in 1-BP conditions of use." [69]

> *"MOE estimates for these respirator scenarios assume workers are properly trained and fitted on respirator use, and that they wear respirators for the entire duration of the work activity where there is potential exposure to 1-BP. For some occupational conditions of use, respirators with an APF of 50 do not reduce worker exposure to levels where the calculated MOE is greater than the benchmark MOE."* [70]

Even when making this assumption, EPA found that worker exposure was still below the benchmark MOE for some occupational scenarios where the Agency assumed the most protective PPE usage. EPA's assumption that workers will be trained to use respirators properly, will be properly fitted for PPE, or will utilize the provided PPE are not realistic on balance, and even with that assumption, PPE is still not protective of all workers. Use of PPE in the absence of a standard is a scientifically unsupported assumption, because even when an OSHA standard exists, it is not followed. [71]

EPA must revise its assumptions for occupational scenarios and re-evaluate worker risks; it is very likely that uses of 1-bromopropane that EPA determined did *not* pose unreasonable risks to workers in fact do pose risks when evidence-based scenarios are used.

**e. EPA is underestimating exposures by failing to aggregate dermal and inhalation exposure.**

Lastly, EPA does not aggregate inhalation and dermal exposures:

> *"As part of this risk evaluation, EPA considered aggregate exposures by evaluating exposure and risk from both the inhalation and dermal routes for workers and consumers in scenarios where such exposures are expected. EPA expects workers to be exposed via both inhalation of 1-BP vapor and dermal contact with liquid containing 1-BP. Similarly, EPA expects certain consumer*

[67] Id. Page 63.

[68] US EPA (2019). Draft Toxic Substances Control Act (TSCA) Risk Evaluations and TSCA Science Advisory Committee on Chemicals (SACC) Meetings; Cyclic Aliphatic Bromide Cluster (HBCD) and 1,4-Dioxane; Notice of Availability and Public Meetings. Comment submitted by Swati Rayasam, Science Associate, Program on Reproductive Health and the Environment, Department of Obstetrics, Gynecology and Reproductive Sciences, University of California, San Francisco et al. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0237-0059 and https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0238-0056

[69] US EPA (2019) 1-Bromopropane (1–BP); Draft Toxic Substances Control Act (TSCA) Risk Evaluation. Page 260. Table 5-1. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0235-0022

[70] US EPA (2019) 1-Bromopropane (1–BP); Draft Toxic Substances Control Act (TSCA) Risk Evaluation. Page 24. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0235-0022

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

*users to be exposed via both the inhalation of 1-BP vapor and dermal contact with liquid containing 1-BP."*

While EPA acknowledges that it would consider aggregate exposures from both inhalation and dermal routes for both workers and consumers, and even lists scenarios where such exposure would be expected, in the draft risk evaluation there is no such aggregation. For example, EPA did not combine its cancer risk estimates for inhalation and dermal contact, even though these two types of exposure occur concurrently for workers. If risks were properly aggregated, they would show a marked increase for non-cancer and cancer risks relative to the Agency's benchmarks.

Additionally, EPA fails to take into account ambient 1-bromopropane exposure for the general population when it considers these particular aggregate worker exposures despite evidence of significant background exposure because the Agency excluded studies such as the NCS and NHANES from consideration, as detailed above.[72]

**4. EPA's misuse of critical risk assessment elements like NOAEL / LOAEL and Uncertainty Factors could lead to an underestimation of risk.**

In this and previous draft risk evaluations, EPA has incorrectly treated the no-observed-adverse-effect-level (NOAEL) as if it is a *no/zero* effect level. However, NOAELs are not zero response concentrations; they are a concentration at which there is not an observable response in the experiment. EPA already recognizes the features that make BMDs superior: BMDs account for the shape of the dose–response function; are independent of study design, such as the space between dosing; and are comparable across chemicals.[73] This failure to assess 1-bromopropane's risk to the general population is of particular concern as the studies included the draft risk evaluation demonstrated adverse reproductive, developmental, and neurological effects.

There are multiple methodological reasons that an effect may not be observed, including low statistical power and inadequate statistical analysis. An empirical comparison of NOAELs and BMRs finds that the average NOAEL approximates the dose that represents a 1–5% Benchmark Response (BMR).[74] However, some NOAELs are more similar to a 10% BMR.[75] Thus, it is more appropriate to assume that NOAELs are more similar to a 5-10% benchmark response.

For calculating cancer or non-cancer risks, we recommend using a point of departure (POD) of a benchmark dose (BMD) at 1%. The POD should be based on a BMD calculation, not the NOAEL/LOAEL, unless the data are insufficient to model. EPA should be calculating BMD and should also be calculating the risk-specific dose, and if they don't have sufficient data to calculate the risk levels then the Agency should state that clearly rather than relying on NOAELs which are subject to study design and interpretation.

[72] Id. Page 148-49.

[73] Wignall JA, Shapiro AJ, Wright FA, Woodruff TJ, Chiu WA, Guyton KZ, Rusyn I. 2014. Standardizing benchmark dose calculations to improve science-based decisions in human health assessments. Environmental health perspectives. 122(5).

[74] Allen BC, Kavlock RJ, Kimmel CA, Faustman EM. 1994. Dose–response assessment for developmental toxicity. II. Comparison of generic benchmark dose estimates with no observed adverse effect levels. Fundam Appl Toxicol. 23:487–495.

[75] Wignall JA, Shapiro AJ, Wright FA, Woodruff TJ, Chiu WA, Guyton KZ, et al.2014. Standardizing benchmark dose calculations to improve science-based decisions in human health assessments. Environ Health Perspect 122(5):499–505.

Additionally, we have concerns with how EPA is using factors to adjust for scientific uncertainties in the risk (referred to by EPA as uncertainty factors). The first issue is that the term uncertainty factor does not reflect the variability and adjustment elements that the factor represents. This issue is discussed by the NAS report *Science and Decisions* on page 132:

> *"Another problem posed by the current noncancer framework is that the term uncertainty factors is applied to the adjustments made to calculate the RfD to address species differences, human variability, data gaps, study duration, and other issues.* ***The term engenders misunderstanding: groups unfamiliar with the underlying logic and science of RfD derivation can take it to mean that the factors are simply added on for safety or because of a lack of knowledge or confidence in the process.*** *That may lead some to think that the true behavior of the phenomenon being described may be best reflected in the unadjusted value and that these factors create an RfD that is highly conservative. But the factors are used to adjust for differences in individual human sensitivities, for humans' generally greater sensitivity than test animals' on a milligrams-per-kilogram basis, for the fact that chemicals typically induce harm at lower doses with longer exposures, and so on. At times, the factors have been termed safety factors, which is especially problematic given that they cover variability and uncertainty and are not meant as a guarantee of safety."*[76] *(emphasis ours)*

"Uncertainty factors" are generally used to make adjustments to the dose-response. Therefore, rather than uncertainty factors, these should really be thought of as *adjustment* factors, as per their function within a dose-response assessment.

Second, EPA has been setting its Margin of Exposure (MOE) for 1-bromopropane at 100 and calculating it as shown below. While we have previously detailed why MOE is not an appropriate approach for risk characterization, [77] nonetheless we will comment on issues with EPA's application of MOE in the 1-bromopropane draft risk evaluation.

$(UF_S=1) \times (UF_A=10) \times (UF_H=10) \times (UF_L=1)^3 = 100$
Total UF=Benchmark MOE=100

$UF_S$ - Subchronic to chronic "uncertainty factor"
$UF_A$ - Interspecies "uncertainty factor"
$UF_H$ - Intraspecies "uncertainty factor"
$UF_L$ - LOAEL to NOAEL "uncertainty factor"

Based on the above calculation, EPA is only adjusting for animal and human variability (Inter- and Intraspecies), and by setting the $UF_L$ and $UF_s$ at 1, the Agency indicates that there is no need to adjust from either less chronic NOAELs to chronic NOAELs or from LOAELs to NOAELs. Reiterating the above issue, EPA is treating NOAEL as if it represents *no effect*, rather than *no observed effect,* even though

[76] National Research Council. (2009). *Science and Decisions: Advancing Risk Assessment*. Page 132. Retrieved from https://www.nap.edu/catalog/12209/science-and-decisions-advancing-risk-assessment

[77] US EPA (2019). Draft Toxic Substances Control Act (TSCA) Risk Evaluations and TSCA Science Advisory Committee on Chemicals (SACC) Meetings; Cyclic Aliphatic Bromide Cluster (HBCD) and 1,4-Dioxane; Notice of Availability and Public Meetings. Comment submitted by Swati Rayasam, Science Associate, Program on Reproductive Health and the Environment, Department of Obstetrics, Gynecology and Reproductive Sciences, University of California, San Francisco et al. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0237-0059 and https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0238-0056

Wignall et al. demonstrated that NOAEL can represent upwards of 10% of the BMR. Despite our misgivings with EPA's use of MOE, if the Agency continues to use it going forward, we recommend it use an MOE of at least 1000 based on our above statements about the NOAEL.

Third, while *Science and Decisions* acknowledged single-value "uncertainty factors" may sometimes be preferable either out of necessity or reflecting science-policy choices, a 2007 Science Advisory Board recommended that EPA "incrementally replace the current system of single-point uncertainty factors with a set of distributions, using probabilistic methods." [78] And in *Science and Decisions,* NAS stated "Use of default distributions for adjustments in extrapolations, rather than default point-estimate uncertainty factors, provides an improved representation of variability and uncertainty and offers an opportunity for further refinements and incentives to gather and analyze existing information and to generate new data targeted to specific extrapolation needs." [79] In testing the feasibility and implications of replacing traditional reference doses with probabilistic estimates (as recommended by NAS), Chiu et al. found that in comparison to traditional methods, these estimates provided a more consistent, scientifically rigorous, and transparent basis for risk management decisions.[80] These methods can also be applied to a multitude of decision-making contexts such as benefit-cost analysis, and life-cycle impact analysis. Moving forward, EPA should employ such probabilistic methods in the final 1-bromopropane risk evaluation in place of these single-point "uncertainty factors" and MOE.

[78] National Research Council. (2009). *Science and Decisions: Advancing Risk Assessment*. Page 294. Retrieved from https://www.nap.edu/catalog/12209/science-and-decisions-advancing-risk-assessment

[79] Id. Page 174.

[80] 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. Environ Health Perspect. doi:10.1289/EHP3368.