July 6, 2020

Comments from Academics, Scientists and Clinicians on the Draft Risk Evaluation for Perchloroethylene (PERC)

Submitted online via *Regulations.gov* to docket EPA-HQ-OPPT-2019-0502

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 Perchloroethylene, 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] Perchloroethylene (PERC) is a solvent with both industrial and consumer uses, as a metal degreaser, lubricant, mold remover, and as a stain/spot cleaner.

According to the draft risk evaluation, EPA estimated a yearly aggregate production volume of 388 to 324 million pounds between 2012 and 2015 from manufacturing, processing, distribution in commerce, industrial, commercial and consumer uses, and disposal. [2] Similar to Trichloroethylene, nearly 65% of the production volume of PERC is as an intermediate in the manufacture of fluorinated compounds such as hydrofluorocarbons (HFCs) and hydrochlorofluorocarbons (HCFCs), and ~15% is as a dry cleaning solvent.[3] With regard to human health, PERC has been linked to neurotoxicity, liver and kidney toxicity, and is listed as a "probable" human carcinogen.[4] According to Environmental Working Group's Tapwater Database, which aggregates water contaminant data from public and environmental health agencies in all 50 states and the District of Columbia, PERC has also been detected in 47 states, with over 8,000 people drinking water which contains levels of PERC above EPA's Maximum Containment Limit of 5ppb (the USEPA Maximum Contaminant Level Goal is zero due to cancer risk). [5] The 5 ppb does not protect against risk of cancer and is higher than the California Public Health Goal of .06ppb which was based on cancer slope factors for liver tumors in males and female mice who were orally exposed to PERC.[6] Epidemiological studies of PERC and other common contaminants such as trichloroethylene, benzene,

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[1] US EPA. (2020). Toxic Substances Control Act (TSCA) Science Advisory Committee on Chemicals Review of Risk Evaluation for Perchloroethylene. Draft Risk Evaluation for Perchloroethylene Public. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0502-0022

[2] US EPA. (2020). Toxic Substances Control Act (TSCA) Science Advisory Committee on Chemicals Review of Risk Evaluation for Perchloroethylene. Draft Risk Evaluation for Perchloroethylene Public. Pg. 28. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0502-0022

[3] NTP. (2016). 14th Report on Carcinogens. Available: https://ntp.niehs.nih.gov/whatwestudy/assessments/cancer/roc/index.html?utm_source=direct&utm_medium=prod&utm_campaign=ntpgolinks&utm_term=roc13

[4] Guyton, K. Z., Hogan, K. A., Scott, C. S., Cooper, G. S., Bale, A. S., Kopylev, L., Barone, S., Makris, S. L., Glenn, B., Subramaniam, R. P., Gwinn, M. R., Dzubow, R. C., & Chiu, W. A. (2014). Human health effects of tetrachloroethylene: key findings and scientific issues. *Environmental health perspectives*, *122*(4), 325–334. https://doi.org/10.1289/ehp.1307359

[5] EWG. (2017). Tapwater Database: Tetrachloroethylene. Available: https://www.ewg.org/tapwater/contaminant.php?contamcode=2987#

[6] OEHHA. (2001). Public Health Goal for TETRACHLOROETHYLENE In Drinking Water. Available: https://oehha.ca.gov/media/downloads/water/chemicals/phg/pceaug2001.pdf

and 1,2-dichloroethylene have consistently reported an increased cancer incidence in exposed populations, such as in Camp Lejune, North Carolina, where military personnel and civilians were exposed via drinking water.[7,8]

We have previously commented on EPA's inadequate scientific methods that have been implemented in the completed draft risk evaluations, and many of these continue to be present in this evaluation.[9,10,11,12,13,14,15,16] We again identify multiple flaws in EPA's TSCA systematic review methodology, including; its failure to follow established methods for systematic review that are based on the best available science; its failure to use pre-established and pre-published protocols; its incomplete and non-transparent literature review practice; and its unvalidated, non-empirically based scoring system used in the evaluation of data quality, which excludes a study based on only one 'unacceptable' metric. The Science Advisory Committee on Chemicals (SACC) has repeatedly provided comments and recommendations needed to improve the risk evaluation process that echo the concerns we have raised in our previous comments, but the draft risk evaluation for Perchloroethylene fails to reflect the SACC's recommended changes.[17,18,19] Therefore, EPA should incorporate the SACC recommendations and other scientifically based changes to comprehensively assess risks as required by law before finalizing the Perchloroethylene evaluation.

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[7] Ruckart, P. Z., Bove, F. J., & Maslia, M. (2013). Evaluation of exposure to contaminated drinking water and specific birth defects and childhood cancers at Marine Corps Base Camp Lejeune, North Carolina: a case–control study. *Environmental Health*, *12*(1). doi: 10.1186/1476-069x-12-104

[8] Ruckart, P. Z., Bove, F. J., & Maslia, M. (2014). Evaluation of contaminated drinking water and preterm birth, small for gestational age, and birth weight at Marine Corps Base Camp Lejeune, North Carolina: a cross-sectional study. *Environmental Health*, *13*(1). doi: 10.1186/1476-069x-13-99

[9] US EPA. (2019). Toxic Substances Control Act (TSCA) Science Advisory Committee on Chemicals Review of Risk Evaluation for 1-Bromopropane. 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-2019-0235-0053

[10] 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

[11] US EPA. (2019). Toxic Substances Control Act (TSCA) Science Advisory Committee on Chemicals Review of Risk Evaluation for Methylene Chloride. Comment submitted by Swati Rayasam, Science Associate, Program on Reproductive Health and the Environment, University of California, San Francisco (UCSF PRHE) et al. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0437-0069

[12] US EPA. (2019). Draft Toxic Substances Control Act Risk Evaluations: Color 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

[13] US EPA. (2020). Draft Toxic Substances Control Act Risk Evaluations: N-Methyl-2-pyrrolidone (NMP). Comment submitted by Swati Rayasam, Science Associate, Program on Reproductive Health and the Environment, University of California, San Francisco et al. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0236-0048

[14] US EPA. (2020). Draft Toxic Substances Control Act Risk Evaluations: Carbon Tetrachloride. Comment submitted by Swati Rayasam, Science Associate, Program on Reproductive Health and the Environment, University of California, San Francisco et al. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0499-0041

[15] US EPA. (2020). Trichloroethylene (CASRN 79-01-6); Draft Toxic Substances Control Act (TSCA) Risk Evaluation. Available: https://www.epa.gov/sites/production/files/2020-02/documents/1_draft_risk_evaluation_for_trichloroethylene_tce_public.pdf

[16] US EPA. (2020). Draft Toxic Substances Control Act Risk Evaluations. Asbestos; Comment submitted by Nicholas Chartres et al., Associate Director, Science and Policy, Program on Reproductive Health and the Environment, Department of Obstetrics, Gynecology and Reproductive Sciences, University of California, San Francisco. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0501-0087

[17] US EPA. (2019). Toxic Substances Control Act (TSCA) Science Advisory Committee on Chemicals Review of Risk Evaluation for 1-Bromopropane. 1-BP TSCA SACC Meeting Minutes Final Report. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0235-0061

[18] US EPA. (2019). Toxic Substances Control Act (TSCA) Science Advisory Committee on Chemicals Review of Risk Evaluation for 1, 4 Dioxane and Cyclic Aliphatic Bromide Cluster (HBCD); SACC July 2019 Meeting Minutes and Final Report Docket. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0238-0063

[19] US EPA. (2019). Toxic Substances Control Act (TSCA) Science Advisory Committee on Chemicals Review of Risk Evaluation for Methylene Chloride; MeCl Meeting Minutes Final Report 03/02/2020. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0437-0080

Despite flaws in its evaluation which resulted in underestimating risks, EPA found that multiple uses of PERC present unreasonable risks of cancer, neurotoxicity, and kidney and liver toxicity to consumers and workers, and to people in the vicinity (bystanders and occupational non-users). However the Agency fails to identify particular risks faced by vulnerable populations and fails to adequately consider populations who hold multiple vulnerable identities, such as pregnant workers.[20,21] We assert that critical scientific flaws in EPA's risk evaluation approach has led to an underestimation of risk; and the actual risks are of greater magnitude than stated by EPA, and that additional conditions of use present unreasonable risks.

Our comments address the following main points:

1. **EPA's TSCA systematic review method is incomplete and does not follow established methods for systematic review that are based on the best available science.**
2. **EPA fails to document how every reference identified in the literature search was used in the draft risk evaluation.**
3. **EPA fails to use a protocol that outlines the pre-established methods to be used throughout the systematic review process as required by EPA regulation under TSCA.**
4. **EPA's TSCA systematic review method utilizes a quantitative scoring method that is incompatible with the best available science in fundamental ways and excludes multiple relevant studies from consideration in the risk evaluation.**
5. **EPA fails to adequately protect the general population or potentially exposed or susceptible subpopulations and underestimates the true risk from Perchloroethylene.**
    a. **EPA's reliance on existing statutes to manage exposure pathways for the general population and potentially exposed or susceptible subpopulations will underestimate risk and is scientifically unsupported.**
    b. **EPA leaves out potentially exposed or susceptible subpopulations when discussing both worker/occupational non-users and consumers, particularly in dry cleaners.**
    c. **EPA is underestimating exposures by failing to consider combined dermal and inhalation routes of exposure, pathways of exposure, and conditions of use.**
    d. **EPA's use of the 10x UF underestimates risk to vulnerable populations. The Agency must adopt a more protective UF, such as the one used by the State of California and we recommend 100 at a minimum based on neurotoxicity effects.**

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

Sincerely,

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

[20] US EPA. (2020). Trichloroethylene (CASRN 79-01-6); Draft Toxic Substances Control Act (TSCA) Risk Evaluation. Page 374. Available: EPA Document #740R18008

[21] NTP. (2016). 14th Report on Carcinogens. Available: https://ntp.niehs.nih.gov/whatwestudy/assessments/cancer/roc/index.html?utm_source=direct&utm_medium=prod&utm_campaign=ntpgolinks&utm_term=roc13

Nicholas Chartres, PhD
Associate Director, Science & Policy
Program on Reproductive Health and the Environment
Department of Obstetrics, Gynecology and Reproductive Sciences
University of California, San Francisco

Tracey Woodruff, PhD, MPH
Director and Professor
Program on Reproductive Health and the Environment
Department of Obstetrics, Gynecology and Reproductive Sciences
University of California, San Francisco

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

Courtney Cooper, BS
Research Coordinator
Program on Reproductive Health and the Environment
Department of Obstetrics, Gynecology and Reproductive Sciences
University of California, San Francisco

Carl F. Cranor, PhD, MSL
Distinguished Professor of Philosophy, Faculty Member, Environmental Toxicology, Department of Philosophy
University of California, Riverside

Nadia Gaber, PhD
Postdoctoral Scholar
Program on Reproductive Health and the Environment
Department of Obstetrics, Gynecology and Reproductive Sciences
University of California, San Francisco

Robert M. Gould, MD
Associate Adjunct Professor, Department of Obstetrics, Gynecology and Reproductive Sciences,
University of California, San Francisco
Past-President, Physicians for Social Responsibility

Jyotsna S. Jagai, MS, MPH, PhD
Research Assistant Professor
University of Illinois Chicago

Jean-Marie Kauth, PhD, MPH
Professor
Benedictine University

Gail Lee, REHS, MSEM
Sustainability Director
University of California, San Francisco

Rainer Lohmann, PhD
Professor of Oceanography, Graduate School of Oceanography
University of Rhode Island

Heather Patisaul, PhD
Associate Dean for Research
North Carolina State University

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

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

DETAILED COMMENTS

1. EPA's TSCA systematic review method is incomplete and does not follow established methods for systematic review that are based on the best available science.

Under TSCA, EPA is required to make decisions about chemical risks based on the "best available science" and the "weight of the scientific evidence".[22] EPA defines "weight of the scientific evidence" in regulation as:

> "…a systematic review method, applied in a manner suited to the nature of the evidence or decision, that uses a pre-established protocol to comprehensively, objectively, transparently, and consistently identify and evaluate each stream of evidence, including strengths, limitations, and relevance of each study and to integrate evidence as necessary and appropriate based upon strengths, limitations, and relevance.'' [23]

However, EPA states in the Draft Risk Evaluation for Perchloroethylene that it will modify the systematic review process considering time constraints:

> *"Although EPA will make an effort to adopt as many best practices as practicable from the systematic review community, EPA expects modifications to the process to ensure that the*

[22] 15 USC §2625 (h)-(i)
[23] 40 CFR 702.33

identification, screening, evaluation and integration of data and information can support timely regulatory decision making under the aggressive timelines of the statute." [24]

There are multiple well-developed evidence-based, peer-reviewed and validated methods for conducting systematic reviews in environmental health that EPA could readily apply, including the National Toxicology Program's Office of Health Assessment and Translation (OHAT) method[25] and UCFS's Navigation Guide Systematic Review Method, which has been demonstrated in six case studies.[26,27,28,29,30, 31,32,33] The National Academies of Sciences, Engineering and Medicine (NASEM) has cited both of these systematic review methods as exemplary of the type of methods EPA should use in hazard and risk assessment.[34,35, 36,37] Further, the NASEM utilized both methods in its 2017 assessment of the potential health impacts of endocrine active environmental chemicals.[38] Specifically, in its 2017 review the NASEM found:

> "The two approaches [OHAT and Navigation Guide] are very similar… and they are based on the same established methodology for the conduct of systematic review and evidence assessment (e.g., Cochrane Collaboration, AHRQ Evidence-based Practice Center Program, and GRADE). Both the OHAT and Navigation Guide methods include the key steps recommended by a previous National Academies committee (NRC 2014) for problem formulation, **protocol development**, specifying a study question, developing PECO statement, identifying and selecting the evidence, evaluating the evidence, and

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[24] US EPA. (2020) Draft Risk Evaluation for Perchloroethylene Public. Pg. 53. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0502-0022

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

[26] Johnson PI, Sutton P, Atchley DS, Koustas E, Lam J, Sen S, Robinson KA, Axelrad DA, Woodruff TJ. The Navigation Guide - evidence-based medicine meets environmental health: systematic review of human evidence for PFOA effects on fetal growth. Environ Health Perspect. 2014;122(10):1028-39. Epub 2014/06/27. doi: 10.1289/ehp.1307893. PubMed PMID: 24968388; PMCID: 4181929.

[27] Koustas E, Lam J, Sutton P, Johnson PI, Atchley DS, Sen S, Robinson KA, Axelrad DA, Woodruff TJ. The Navigation Guide - evidence-based medicine meets environmental health: systematic review of nonhuman evidence for PFOA effects on fetal growth. Environ Health Perspect. 2014;122(10):1015-27. Epub 2014/06/27. doi: 10.1289/ehp.1307177. PubMed PMID: 24968374; PMCID: 4181920.

[28] Lam J, Koustas E, Sutton P, Johnson PI, Atchley DS, Sen S, Robinson KA, Axelrad DA, Woodruff TJ. The Navigation Guide - evidence-based medicine meets environmental health: integration of animal and human evidence for PFOA effects on fetal growth. Environ Health Perspect. 2014;122(10):1040-51. Epub 2014/06/27. doi: 10.1289/ehp.1307923. PubMed PMID: 24968389; PMCID: 4181930

[29] Vesterinen H, Johnson P, Atchley D, Sutton P, Lam J, Zlatnik M, Sen S, Woodruff T. The relationship between fetal growth and maternal glomerular filtration rate: a systematic review. J Maternal Fetal Neonatal Med. 2014:1-6. Epub Ahead of Print; PMCID: 25382561.

[30] Johnson PI, Koustas E, Vesterinen HM, Sutton P, Atchley DS, Kim AN, Campbell M, Donald JM, Sen S, Bero L, Zeise L, Woodruff TJ. Application of the Navigation Guide systematic review methodology to the evidence for developmental and reproductive toxicity of triclosan. Environ Int. 2016;92-93:716-28. doi: 10.1016/j.envint.2016.03.009. PubMed PMID: 27156197.

[31] Lam J, Sutton P, Halladay A, Davidson LI, Lawler C, Newschaffer CJ, Kalkbrenner A, Joseph J. Zilber School of Public Health, Windham GC, Daniels N, Sen S, Woodruff TJ. Applying the Navigation Guide Systematic Review Methodology Case Study #4: Association between Developmental Exposures to Ambient Air Pollution and Autism. PLoS One. 2016;21(11(9)). doi: 10.1371/journal.pone.0161851.

[32] Lam J, Lanphear B, Bellinger D, Axelrad D, McPartland J, Sutton P, Davidson LI, Daniels N, Sen S, Woodruff TJ. Developmental PBDE exposure and IQ/ADHD in childhood: A systematic review and meta-analysis. Environmenal Health Perspectives. 2017;125(8). doi: doi: 10.1289/EHP1632.

[33] Lam J, Koustas E, Sutton P, Cabana M., Whitaker E., Padula A, Vesterinen H, Daniels N, Woodruff TJ. Applying the Navigation Guide: Case Study #6. Association Between Formaldehyde Exposures and Asthma. In preparation. 2019.

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

[35] National Academies of Sciences Engineering, and Medicine. (2018). Progress Toward Transforming the Integrated Risk Information System (IRIS) Program: A 2018 Evaluation. Washington, DC: The National Academies Press; 2018.

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

[37] National Academies of Sciences, Engineering, and Medicine. 2019. Review of DOD's Approach to Deriving an Occupational Exposure Level for Trichloroethylene. Washington, DC: The National Academies Press. https://doi.org/10.17226/25610.

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

integrating the evidence." [39]

Lack of time is not a credible rationale for EPA's failure to conduct an evidence-based systematic review for the Draft Risk Evaluation for Perchloroethylene, including using pre-established and pre-published protocols. EPA should implement a systematic review method that is compatible with empirically based existing methods and aligns with the Institute of Medicine's definition of a systematic review, including but not limited to, using explicit and pre-specified scientific methods for every step of the review. [40] If EPA uses one of the aforementioned methods (OHAT or Navigation Guide), the Agency would not have to "make an effort to adopt as many best practices as practicable."

2. EPA fails to document how <u>every</u> reference identified in the literature search was used in the draft risk evaluation.

In section 1.5.2 Data Evaluation, EPA states that:

> "During the data evaluation stage, the EPA assesses the quality of the methods and reporting of results of the individual studies identified during problem formulation using the evaluation strategies described in *Application of Systematic Review in TSCA Risk Evaluations* (U.S. EPA 2018b). The **EPA evaluated the quality of the on-topic PCE study reports** identified in *Perchloroethylene (CASRN 127-18-4) Bibliography: Supplemental File for the TSCA Scope Document;* (U.S. EPA 2017e), **and gave all studies** an overall high, medium, low or unacceptable confidence rating during data evaluation."[41]

In the 'Perchloroethylene Bibliography: Supplemental File for the TSCA Scope Document' for Human Health Hazard Literature Search Results, there are 28 pages of 'on topic' references, with approximately 25 citations per page, totaling approximately **700** 'on topic' references. [42] However, in 'Review Supplemental File: Data Quality Evaluation of Human Health Hazard Studies – Epidemiologic Studies'[43] there are only **93** Epidemiological studies that go through data quality evaluation, leaving >**600** 'on-topic' references unaccounted for by EPA.

EPA goes on to state that:

> "Note: The literature search results for human health hazard of PCE yielded 3794 studies. This included 40 key and supporting studies identified from previous EPA assessments. Of the 3754 new studies screened for relevance, 3715 were excluded as off topic." [44]

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[39] National Academies of Sciences Engineering, and Medicine. (2017). Application of Systematic Review Methods in an Overall Strategy for Evaluating Low-Dose Toxicity from Endocrine Active Chemicals. Page. 119.Washington, D.C.: The National Academies Press; 2011

[40] Institute of Medicine. (2011). Finding What Works in Health Care: Standards for Systematic Reviews. Page 1. Washington, DC: The National Academies Press

[41] US EPA. (2020) Draft Risk Evaluation for Perchloroethylene Public. Pg. 59. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0502-0022

[42] US EPA. (2020) Perchloroethylene (CASRN: 127-18-4) Bibliography: Supplemental File for the TSCA Scope Document. Available: https://www.epa.gov/sites/production/files/2017-06/documents/perc_comp_bib.pdf

[43] US EPA. (2020) Draft Risk Evaluation for Perchloroethylene (Ethene, 1,1,2,2-Tetrachloro) CASRN: 127-18-4 Systematic Review Supplemental File: Data Quality Evaluation of Human Health Hazard Studies – Epidemiologic Studies Available: https://www.epa.gov/sites/production/files/2020-04/documents/13_pce_data_quality_evaluation_of_human_health_hazard_studies_-_epidemiological_studies.pdf https://www.epa.gov/sites/production/files/2020-04/documents/14_pce_data_extraction_for_human_health_hazard_studies.pdf

[44] US EPA. (2020) Draft Risk Evaluation for Perchloroethylene Public. Pg. 57. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0502-0022

Source in the Perchloroethylene Draft Risk Evaluation	Number that are 'on topic'/go through data evaluation
Systematic Review Supplemental File: Data Quality Evaluation	93
Figure 1-9 Literature Flow Diagram for Human Health Hazard	79
Bibliography	>700

Table showing the differences in numbers of on topic/data evaluation studies in different sections of the Perchloroethylene Draft Risk Evaluation. It is unclear what is the final number of studies or what is included/excluded.

Such inconsistencies in the reporting of the 'on' and 'off topic' studies across the draft risk evaluation and supplementary materials is concerning and threatens the validity of the Draft Risk Evaluation for Perchloroethylene.

Further, as shown below in 'Figure 1-9 Literature Flow Diagram for Human Health Hazards', EPA states that there are **79** studies that go through Data Evaluation. However, as highlighted previously, there are **93** Epidemiological studies alone that go through data quality evaluation as cited in the 'Systematic Review Supplemental File: Data Quality Evaluation of Human Health Hazard Studies– Epidemiologic Studies.' [45] Therefore, there are **14** epidemiological studies that have been unaccounted for in the data evaluation step without any explanation by EPA.

[45] US EPA. (2020) Draft Risk Evaluation for Perchloroethylene (Ethene, 1,1,2,2-Tetrachloro) CASRN: 127-18-4 Systematic Review Supplemental File: Data Quality Evaluation of Human Health Hazard Studies – Epidemiologic Studies Available: https://www.epa.gov/sites/production/files/2020-04/documents/13_pce_data_quality_evaluation_of_human_health_hazard_studies_-_epidemiological_studies.pdf

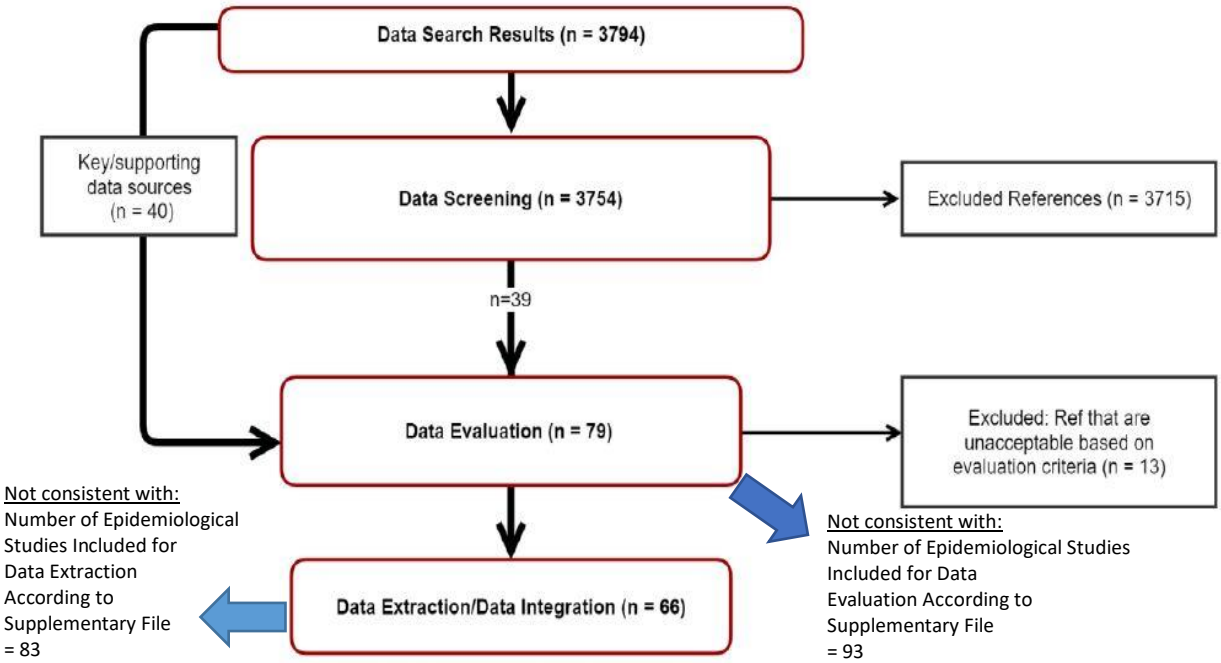

Figure 1-9. Literature Flow Diagram for Human Health Hazard Data Sources

Additionally, as shown in Figure 1-9 (above), EPA sates that only **66** studies have gone through the 'Data Extraction' step, yet according to 'Systematic Review Supplemental File: Data Quality Evaluation of Human Health Hazard Studies– Epidemiologic Studies' EPA only excludes **10** studies based on an 'unacceptable' rating, leaving **83** epidemiological studies to be included for data extraction. [46] Therefore, there are **17** epidemiological studies that have been removed from the Perchloroethylene draft risk evaluation, again, without any explanation from EPA.

The EPA's SACC has also made comments and recommendations on the literature identification step with recommendations for how this step in the systematic review process should be conducted to comprehensively assess risks as required by law.

The EPA SACC in its Peer Review of 1-BP commented: "The Committee expected all of the quality sources identified in the SR would be used in the DRE and if not, that the general public would be able to follow the rationale as to why they were not used. The Committee generally concluded that it was difficult at best to determine exactly what was done during the SR…..**Committee members expressed that they experienced challenges in trying to follow the actions taken in the SR**, and how the results of the SR were used in the draft risk assessment." [47]*(emphasis ours)*

[46] US EPA. (2020) Draft Risk Evaluation for Perchloroethylene (Ethene, 1,1,2,2-Tetrachloro) CASRN: 127-18-4 Systematic Review Supplemental File: Data Quality Evaluation of Human Health Hazard Studies – Epidemiologic Studies Available: https://www.epa.gov/sites/production/files/2020-04/documents/13_pce_data_quality_evaluation_of_human_health_hazard_studies_-_epidemiological_studies.pdf

[47] US EPA. (2019). Peer Review for the United States Environmental Protection Agency (EPA) Draft Risk Evaluation for 1-Bromopropane (1-BP). Page. 22. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0235-0061

The EPA SACC in its Peer Review of 1-BP recommended: "Since large percentages of studies are excluded (Section 1.5.1, page 42), the number of items being rejected for each criterion should be summarized to enable readers to determine why studies were excluded." [48]

The EPA SACC in its Peer Review of 1, 4 Dioxane commented: "Committee members did not find the systematic review to be a transparent and objective method for gathering the relevant scientific information, scoring its quality, and integrating the information evaluate."[49]

The EPA SACC in its Peer Review of 1, 4 Dioxane commented: "The Evaluation flow charts suggest a full systematic review was performed, but the text describes a more limited review."[50]

NAS Recommendation for this Step: "It is crucial that the selection of eligible studies is based on prespecified criteria in a manner that limits potential for bias (IOM Standard 3.3)…**Screening studies requires careful judgments and meticulous documentation about eligibility**" [51]

3. EPA fails to use a protocol that outlines the pre-established methods to be used throughout the systematic review process as required by EPA regulation under TSCA.

In order for EPA to adequately address issues relating to its lack of transparency in accounting for all references identified in the literature search, the Agency must immediately implement protocols for all future draft risk evaluations. This is a critical methodological step absent in the Draft Risk Evaluation for Perchloroethylene, and the use of pre-established protocols minimizes such biases in the evidence base by explicitly pre-defining how: the questions will be formulated, the searches will be conducted, the eligibility criteria will be applied, and the quality of the included studies will be assessed.[52] Most importantly, it allows greater transparency in the decision-making process throughout the systematic review and is a fundamental element to ensure the integrity of evidence-based evaluations. Further, not using predefined protocols directly contradicts the EPA's 2017 framework rules mandating that the agency use "a pre-established protocol" to conduct risk assessments.[53] We again urge EPA to immediately implement the use of pre-established protocols to enhance transparency in the decision-making process and consistency in their draft risk evaluations. Protocols developed for applying the OHAT method and the Navigation Guide Systematic Review Method have been published and can serve as a template to further expedite EPA's systematic reviews under TSCA. [54,55, 56]

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[48] US EPA. (2019). Peer Review for the United States Environmental Protection Agency (EPA) Draft Risk Evaluation for 1-Bromopropane (1-BP). Page. 25. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0235-0061

[49] US EPA. (2019). Peer Review for EPA Draft Risk Evaluations for 1,4-Dioxane and Cyclic Aliphatic Bromide Cluster (HBCD). Page.31. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0237-0064

[50] US EPA. (2019). Peer Review for EPA Draft Risk Evaluations for 1,4-Dioxane and Cyclic Aliphatic Bromide Cluster (HBCD). Page. 32 Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0237-0064

[51] National Academies of Sciences, Engineering, and Medicine. 2019. Review of DOD's Approach to Deriving an Occupational Exposure Level for Trichloroethylene. Page. 32. Washington, DC: The National Academies Press. https://doi.org/10.17226/25610.

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

[53] 40 CFR 702 Pg. 33733

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

[55] All Navigation Guide systematic review protocols can be found at: https://prhe.ucsf.edu/navigation-guide

[56] National Toxicology Program. Completed Evaluations. Available: https://ntp.niehs.nih.gov/whatwestudy/assessments/noncancer/completed/index.html

4. EPA's TSCA systematic review method utilizes a quantitative scoring method that is incompatible with the best available science in fundamental ways and excludes multiple relevant studies from consideration in the risk evaluation

As shown in 'Draft Risk Evaluation for Perchloroethylene Systematic Review Supplemental File: Updates to the Data Quality Criteria for Epidemiological Studies',[57] EPA's TSCA systematic review method utilizes a quantitative scoring method that is incompatible with the best available science in fundamental ways:

- **Firstly**, quantitative scores to assess the quality of an individual study are arbitrary and not evidence-based; the NASEM recommend against such scoring methods.[58] The implicit assumption in quantitative scoring methods is that we know empirically how much each risk of bias domain contributes to study quality, and that these domains are independent of each other; this is not a scientifically supportable underlying assumption. An examination of the application of quality scores in meta-analysis found that quality-score weighting produced biased effect estimates, with the authors explaining that quality is not a singular dimension that is additive, but that it is possibly non-additive and non-linear. [59,60]

- **Secondly**, EPA's scoring method wrongly conflates how well a study is reported with how well the underlying research was conducted. Study reporting addresses how well research findings are written up, i.e., whether there is a complete and transparent description of what was planned, what was done, what was found, and what the results mean. How completely and clearly a study is reported is not a scientifically valid measure of the quality of the underlying research.[61,62,63,64] The "Strengthening of Reporting of Observational Studies in Epidemiology" or "STROBE" Initiative is an example of a checklist of items that should be included in articles reporting such research. EPA's TSCA method uses reporting measures in its scoring of the quality of human studies, including incorporating reporting guidelines into the reasons for scoring studies "low quality" (Metrics 1 and 15) or "unacceptable for use" (Metrics 3, 4, 6, 7) as shown in the table below. The authors of the STROBE guidelines specifically note the guidelines are not a measure of the quality of the underlying research, stating:

[57] US EPA. (2020) Draft Risk Evaluation for Perchloroethylene (Ethene, 1,1,2,2-Tetrachloro) CASRN: 127-18-4 Systematic Review Supplemental File: Updates to the Data Quality Criteria for Epidemiological Studies Available: https://www.epa.gov/sites/production/files/2020-04/documents/13_pce_data_quality_evaluation_of_human_health_hazard_studies_-_epidemiological_studies.pdf

[58] National Research Council. Review of EPA's Integrated Risk Information System (IRIS) Process. Page 69. Washington, DC: National Academies Press; 2014

[59] Herbison P, Hay-Smith J, Gillespie W. Adjustment of meta-analyses on the basis of quality scores should be abandoned. J Clin Epidemiol. 2006;59(12):1249-56. Epub 2006 Sep 11; PMCID: 17098567.

[60] Greenland S, O'Rourke K. On the bias produced by quality scores in meta-analysis, and a hierarchical view of proposed solutions. Biostatistics. 2001;2(4):463-71.

[61] Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0 [Updated March 2011]: The Cochrane Collaboration. Available from http://www.cochrane-handbook.org.; 2011.

[62] Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, Norris S, Falck-Ytter Y, Glasziou P, DeBeer H, Jaeschke R, Rind D, Meerpohl J, Dahm P, Schünemann HJ. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. Journal of Clinical Epidemiology. 2011;64(4):383-94. doi: 10.1016/j.jclinepi.2010.04.026

[63] Devereaux PJ, Choi PT, El-Dika S, Bhandari M, Montori VM, Schünemann HJ, Garg AX, Busse JW, Heels-Ansdell D, Ghali WA, Manns BJ, GH. G. An observational study found that authors of randomized controlled trials frequently use concealment of randomization and blinding, despite the failure to report these methods. J Clin Epidemiol. 2004;57(12):1232-6; PMCID: 15617948

[64] Soares HP, Daniels S, Kumar A, Clarke M, Scott C, Swann S, B; D, Group. RTO. Bad reporting does not mean bad methods for randomised trials: observational study of randomised controlled trials performed by the Radiation Therapy Oncology Group. BMJ. 2004;328((7430)):22-4.; PMCID: PMC313900.

"The STROBE Statement is a checklist of items that should be addressed in articles reporting on the 3 main study designs of analytical epidemiology: cohort, case control, and cross-sectional studies. **The intention is solely to provide guidance on how to report observational research well; these recommendations are not prescriptions for designing or conducting studies. Also, while clarity of reporting is a prerequisite to evaluation, the checklist is not an instrument to evaluate the quality of observational research.**" [65] *(Emphasis ours)*

- **Thirdly**, EPA's scoring method excludes research based on one single reporting or methodological limitation. EPA has created an arbitrary list of metrics that make studies "unacceptable for use in the hazard assessment," for each type of evidence stream, i.e., epidemiologic, animal, *in vitro.* For human epidemiologic studies EPA lists six domains of study quality with 22 metrics, with varying numbers of metrics per domain. As shown below, 14 of the 22 metrics can be scored as a 4 (unacceptable) due to a "serious flaw. There is no empirical basis for EPA's selected list of "serious flaws".

Table showing EPA's list of 14 metrics that make studies "unacceptable for use in the hazard assessment," shown in "Updates to the Data Quality Criteria for Epidemiological Studies" in the Draft Risk Evaluation for Perchloroethylene

Domain	Metric
Domain 1. Study Participation	Metric 1. Participant selection (selection, performance biases)
	Metric 2. Attrition (missing data/attrition/exclusion, reporting biases)
	Metric 3. Comparison Group (selection, performance biases)
Domain 2. Exposure Characterization	Metric 4. Measurement of Exposure (Detection/measurement/information, performance biases)
	Metric 5. Exposure levels (Detection/measurement/information biases)
	Metric 6. Temporality (Detection/measurement/information biases)
Domain 3. Outcome Assessment	Metric 7. Outcome measurement or characterization (detection/measurement/information, performance, reporting biases)
Domain 4. Potential Confounding/Variable Control	Metric 9. Covariate Adjustment (confounding)
	Metric 10. Covariate Characterization (measurement/information, confounding biases)
Domain 5. Analysis	Metric 12. Study Design and Methods
	Metric 13. Statistical power (sensitivity)

[65] Vandenbroucke JP, von Elm E, Altman DG, Gøtzsche PC, Mulrow CD, Pocock SJ, Poole C, Schlesselman JJ, Egger M, Initiative. S. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. Int J Surg. 2014;12(12):1500-24. doi: 10.1016/j.ijsu.2014.07.014.

Domain 6. Other (if applicable) Considerations for Biomarker Selection and Measurement	Metric 16. Use of Biomarker of Exposure (detection/measurement/information biases)
	Metric 17. Effect biomarker (detection/measurement/information biases)
	Metric 20. Sample contamination (detection/measurement/information biases)

> EPA should not have a single evaluation exclude a study from consideration. The approach is again inconsistent with two previously validated methods used to evaluate the risk of bias in human epidemiological studies recommended by the NASEM, the Navigation Guide[66] and OHAT method. [67] While there will be variation in the internal validity (and thus quality) across studies, it is more appropriate to exclude studies based on pre-defined inclusion/exclusion criteria when there is a large database (such as only evaluating cohort studies), rather than an arbitrary rating of the evidence, based off one domain that is not empirically supported. Further, EPA's list of "serious flaws" are not all related to real flaws in the underlying research, including reporting guidelines, which are wrongly equated with "serious flaws" in study quality as described in detail above, and Analysis, "Statistical Power" (metric 13), which can be rated unacceptable (shown in the table above). However, statistical power alone is not a valid measure of study quality and should not be used to exclude studies from consideration.[68]

However, in 'Draft Risk Evaluation for Perchloroethylene Systematic Review Supplemental File: Data Quality Evaluation of Human Health Hazard Studies – Epidemiologic Studies' EPA has excluded 10 studies, with 5 due to an unacceptable rating due to how well a study has been reported (metric 4) and 3 due to an unacceptable rating due to statistical power (metric 13). EPA has therefore excluded valuable evidence from the Perchloroethylene Draft Risk Evaluation based on considerations that are not related to real flaws in the underlying research.

Studies excluded in Data Quality Evaluation of Human Health Hazard Studies:

> Table 18: **Auperin et al. 1994** (HERO ID 630334): Evaluation of Cancer Outcomes metric 4 & 5
> Table 27: **Schlehofer et al. 1995** (HERO ID 630954): Evaluation of Cancer Outcomes metric 4 & 5
> Table 32: **Chang et al. 2003** (HERO ID 699203): Evaluation of Cancer Outcomes metric 4
> Table 35: **Sung et al. 2007 (**HERO ID 699225): Evaluation of Cancer Outcomes metric 4
> Table 62: **McLean et al. 2014** (HERO ID 2799576): Evaluation of Cancer Outcomes metric 12 & 13
> Table 71: **Bove et al. 2014** (HERO ID 2800329): Evaluation of Neurological/Behavior Outcomes metric 13*
> Table 72: **Bove et al. 2014** (HERO ID 2800329): Evaluation of Cancer Outcomes metric 13*
> Table 74: **Aschengrau et al. 2015** (HERO ID 2966280): Evaluation of Cancer Outcomes metric 2

[66] 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.

[67] 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.

[68] A power calculation is an estimate of the size of the study population needed to detect an effect of a given size.

*** Note: The draft risk evaluation lists two separate Bove 2014 retrospective cohort studies, one on civilian employees and one on military personnel; both studies have neurological/behavior outcomes and cancer outcomes. The study on military personnel was rated as High and extracted for the Draft Risk Evaluation, while the study on civilian employees was rated as Unacceptable due to Metric 13 as "The number of participants and cases were not adequate to evaluate dose-response in the exposed population…The study authors state this may be in part due to the relatively young nature of the cohort. The majority of participants were under 65 and only 14% had died."**

Table 88: **Desrosiers et al. 2015** (HERO ID 3490931): Evaluation of Growth (early life) and Development Outcomes metric 4 & 5
Table 91: **Dow 1976** (HERO ID 4214209): Evaluation of Irritation Outcomes metric 5

Multiple authoritative review bodies, including the EPA SACC, the NASEM, and IOM have concluded that overly quantitative criteria that exclude relevant studies are inappropriate in systematic review methods; using a scoring method is inappropriate and can exclude relevant evidence. Below are highlights from relevant reports from the EPA SACC, NASEM and IOM.

The EPA SACC Peer Review of 1-BP commented: "Several Committee members discussed in depth that it was not appropriate to determine an "unacceptable" rating during data quality evaluation based solely on one criterion."[69]

The EPA SACC Peer Review of 1, 4 Dioxane recommended: "Do not be overly stringent and exclude studies based on a single criterion."[70]

The EPA SACC Peer Review of 1, 4 Dioxane recommended: "Follow best practices in the field and simplify the data quality criteria." [71]

NAS Recommendation for this Step: "Most significantly, the quantitative scores are contrary to standard systematic review practices, as numerical scores falsely imply a relationship between scores and effect or association, along with several other critical limitations"[72]

NAS Recommendation for this Step: "The committee recommends that DOD abandon the use of this study applicability tool in favor of established tools to assess risk of bias of animal and human studies. For example, one option could be the approach developed by the National Toxicology Program's Office of Health Assessment and Translation."[73]

The IOM Recommendation for this step: "Quality scoring systems have not been validated. Studies assessed as excellent quality using one scoring method may be subsequently assessed as lower quality using another scoring method. Moreover, with an emphasis on risk of bias, the SR more appropriately assesses the quality of study design and conduct rather than the quality of reporting. The committee chose the term "risk of bias" to describe the focus of the assessment of individual studies and the term "quality" to describe the focus of the assessment of a body of evidence." [74]

EPA should therefore not use a quantitative scoring method to assess quality in individual studies, it should not conflate study reporting with study quality, and it should not exclude otherwise quality research based on a single reporting or methodological limitation. Rather EPA should employ a

[69] US EPA. (2019). Peer Review for the United States Environmental Protection Agency (EPA) Draft Risk Evaluation for 1-Bromopropane (1-BP). Page. 21. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0235-0061
[70] US EPA. (2019). Peer Review for EPA Draft Risk Evaluations for 1,4-Dioxane and Cyclic Aliphatic Bromide Cluster (HBCD). Page. 38. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0237-0064
[71] US EPA. (2019). Peer Review for EPA Draft Risk Evaluations for 1,4-Dioxane and Cyclic Aliphatic Bromide Cluster (HBCD). Page. 38. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0237-0064
[72] National Research Council. (2014). Review of EPA's Integrated Risk Information System (IRIS) Process. Page 69. Washington, DC: The National Academies Press; 2014.
[73] National Academies of Sciences, Engineering, and Medicine. 2019. Review of DOD's Approach to Deriving an Occupational Exposure Level for Trichloroethylene. Page. 4. Washington, DC: The National Academies Press. https://doi.org/10.17226/25610.
[74] Institute of Medicine. (2011). Finding What Works in Health Care: Standards for Systematic Reviews. Page 132. Washington, DC: The National Academies Press

scientifically valid method to assess risk of bias of individual studies such as the OHAT method[75] and the Navigation Guide Systematic Review Method.[76,77,78]

5. EPA fails to adequately protect the general population or potentially exposed or susceptible subpopulations and underestimates the true risk from Perchloroethylene.

a. EPA's reliance on existing statutes to manage exposure pathways for the general population and potentially exposed or susceptible subpopulations will underestimate risk and is scientifically unsupported.

PERC is an ubiquitous environmental contaminant to which the general population is commonly exposed through multiple pathways including air, drinking water and contaminated sites.[79] However, EPA has stated all possible pathways of exposure to the general population, including air, drinking water and contaminated sites were not considered in the PERC draft risk evaluation.[80] EPA's rationale is that these other pathways of exposure will be assessed and managed by statutes such as the Clean Air Act, Safe Drinking Water Act and Resource Conservation and Recovery Act.[81] However, exposures via these pathways are current and ongoing, and are not well-managed by EPA. Thus, current exposures need to be accounted for, otherwise the risks will be underestimated. EPA is required under both TSCA and by EPA regulation to account for all pathways of exposure. By not estimating total exposure from all potential pathways, EPA is significantly underestimating the risks of harm of PERC in the general population.

For example, a piece in the UCLA Law Review highlights how the Clean Air Act fails to consider air pollution "hotspots", which contain pollution levels that are folds higher than the standards, are downwind or nearby polluting industries, and most of which are primarily low-income communities of color.[82] Thus the current air standards are inadequate to protect potentially exposed or susceptible subpopulations from toxic chemicals like PERC on their own.

With regard to the Safe Drinking Water Act, while detected levels of PERC vary widely, 47 states serving 24 million people detectable levels of PERC in their drinking water according to Environmental Working

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

[76] 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. doi:10.1289/ehp.1307175.

[77] Koustas E, Lam J, Sutton P, Johnson PI, Atchley DS, Sen S, Robinson KA, Axelrad DA, Woodruff TJ. The Navigation Guide - evidence-based medicine meets environmental health: systematic review of nonhuman evidence for PFOA effects on fetal growth. Environ Health Perspect. 2014;122(10):1015-27. Epub 2014/06/27. doi: 10.1289/ehp.1307177. PubMed PMID: 24968374; PMCID: 4181920.

[78] Lam J, Koustas E, Sutton P, Johnson PI, Atchley DS, Sen S, Robinson KA, Axelrad DA, Woodruff TJ. The Navigation Guide - evidence-based medicine meets environmental health: integration of animal and human evidence for PFOA effects on fetal growth. Environ Health Perspect. 2014;122(10):1040-51. Epub 2014/06/27. doi: 10.1289/ehp.1307923. PubMed PMID: 24968389; PMCID: 4181930.

[79] IARC. (2014). *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*. Trichloroethylene, Tetrachloroethylene and Some Other Chlorinated Agents. Vol 106. Available: https://publications.iarc.fr/Book-And-Report-Series/Iarc-Monographs-On-The-Identification-Of-Carcinogenic-Hazards-To-Humans/Trichloroethylene-Tetrachloroethylene-And-Some-Other-Chlorinated-Agents-2014

[80] US EPA. (2020). Toxic Substances Control Act (TSCA) Science Advisory Committee on Chemicals Review of Risk Evaluation for Perchloroethylene. Draft Risk Evaluation for Perchloroethylene Public. Pg. 28. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0502-0022

[81] US EPA. (2020). Toxic Substances Control Act (TSCA) Science Advisory Committee on Chemicals Review of Risk Evaluation for Perchloroethylene. Draft Risk Evaluation for Perchloroethylene Public. Pg. 460. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0502-0022

[82] Carlson, Ann E. (2018). The Clean Air Act's Blind Spot: Microclimates and Hotspot Pollution. 65 UCLA Law Review 1036; UCLA School of Law, Public Law Research Paper No. 18-29. Available: https://ssrn.com/abstract=3228715

Group's Tapwater Database, which aggregates water contaminant data from public and environmental health agencies in all 50 states and the District of Columbia. EWG also reported that drinking water systems that serve about 8,000 exceeds the EPA Maximum Contaminant Level (MCL) for PERC of 5ppb (the USEPA Maximum Contaminant Level **Goal** is zero due to cancer risk). [83] The 5 ppb limit does not protect against risk of cancer and is higher than the California Public Health Goal of .06ppb which was based on cancer slope factors for liver tumors in males and female mice who were orally exposed to PERC, and set to limit the lifetime cancer risk of drinking water to consumers to no more than 1×10^{-4}.[84]

Finally, with regard to the Resource Conservation Recovery Act and the Comprehensive Environmental Response, Compensation, and Liability Act, scientists have identified PERC (as well as TCE) as one of the most common contaminants at hazardous waste sites.[85] EPA says one in four Americans lives within 3 miles of a contaminated site that could pose "serious risks to human health and the environment."[86] Therefore, communities near these hazardous waste sites, often low-income communities of color, may face the impacts of not just disposal of these chemical contaminants, but the impact of any potential leakage; this should be accounted for in the risk evaluation.[87,88] Additionally, there can still be exposures near 'former' or 'remediated' sites as studies have documented underreporting or falsified exposure data from sites [89,90]; slow response to health concerns from communities near sites indicates that exposures could still be ongoing. [91] Thus, current regulations governing disposal are also inadequate.

Thus, EPA must revise the draft risk evaluation, so it addresses all sources and pathways of exposure. TSCA, with its specific charge to consider potentially exposed or susceptible subpopulations, has a critical role to play in the protection of these communities and the general public facing PERC exposure. As we have previously detailed, established scientific principles for exposure assessment require that all known pathways of exposures be included in the assessment, or exposure will not be accurately quantified, and risk will be underestimated. [92] Therefore, based on EPAs failure to consider all exposure pathways, the PERC draft risk evaluation presents a limited analysis of PERC's risks to both the general population and potentially exposed or susceptible subpopulations.

b. EPA leaves out potentially exposed or susceptible subpopulations when discussing both worker/occupational non-users and consumers, particularly in dry cleaners.

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[83] EWG. (2017). Tapwater Database: Tetrachloroethylene. Available: https://www.ewg.org/tapwater/contaminant.php?contamcode=2987#

[84] Office of Environmental Health Hazard Assessment California Environmental Protection Agency, *Public Health Goal for Tetrachloroethylene in Drinking Water,* August 2001, at https://oehha.ca.gov/media/downloads/water/chemicals/phg/pceaug2001.pdf.

[85] Yoshikawa, M., M. Zhang, and K. Toyota. (2017). "Integrated Anaerobic-aerobic Biodegradation of Multiple Contaminants Including Chlorinated Ethylenes, Benzene, Toluene, and Dichloromethane." Water, Air, & Soil Pollution 228 (1): 25. doi:10.1007/ s11270-016-3216-1.

[86] US GAO. Key Issues: Hazardous Waste. Retrieved July 07, 2020. Available: https://www.gao.gov/key_issues/hazardous_waste/issue_summary

[87] Sapien, J., Mullins, J., Mullins, R., Integrity, T., Sapien, R., Narayanswamy, A., & Bogardus, K. (2007, May 18). Human exposure 'uncontrolled' at 114 Superfund sites. Retrieved July 06, 2020, from https://publicintegrity.org/environment/human-exposure-uncontrolled-at-114-superfund-sites/

[88] Commission for Racial Justice. (1987). Toxic wastes and race in the United States: A national report on the racial and socio-economic characteristics of communities with hazardous waste sites. New York, N.Y.: Public Data Access : Inquiries to the Commission.

[89] Gibbs Law Group. 2019. "Hunters Point Class Action Lawsuit (2019): Tetra Tech Lawsuits." Gibbs Law Group LLP. Accessed 10 October 2019. Available: https://www.classlawgroup.com/hunters-point-contamination-lawsuit/

[90] Shrader-Frechette, K., & Meade, T. (2019). Using routine, independent, scientific-data audits as an early-warning for potentially fraudulent toxic-site cleanup: PCE, TCE, and other VOCs at the former Naval-Ordnance Test Station, Pasadena, California. *Accountability in Research, 27*(1), 1-31. doi:10.1080/08989621.2019.1695200

[91] Hamilton, J. W. 2016. "Contamination at US Military Bases: Profiles and Responses." *Stanford Environmental Law Journal* 35: 223.

[92] 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

In the draft risk evaluation, when EPA lists potentially exposed or susceptible subpopulations, its listings leave out a number of susceptible groups. This is especially clear when considering the example of dry cleaners. Data from DATA USA, a collaborative of Deloitte, Datawheel, and MIT aggregating government data, find that workers making an average yearly wage of ~$21,000; 107,000 workers identify as female versus 49,200 who identify as male.[93]

However, under Worker and occupational non-users, the Agency lists:
"users (males and female workers of reproductive age) exposed to PCE as well as non-users or workers exposed to PCE indirectly by being in the same work area of the building. Also, adolescents and female workers of reproductive age (>16 to less than 50 years old)," [94]

When considering dry cleaners, the above statistic shows that the majority of workers are women, therefore Agency should consider pregnant workers and their developing fetuses under its Worker/ONU section. Additionally, data show that owners and workers in small businesses such as dry cleaners, often bring their children to work through an inability to afford childcare among other reasons. [95,96] Therefore, children's exposures (under age 16) should also be considered in this section, a point which we highlighted extensively in our 1-bromopropane comments. [97]

For consumers and bystanders the Agency lists:
"…consumers and bystanders associated with use of PCE containing consumer products as a potentially exposed and susceptible subpopulation due to greater exposure."[98]

EPA indicates later in the draft risk evaluation that only **some** individuals within the general population may use PERC consumer products as a rationale for them to be identified as a potentially exposed and susceptible subpopulation due to greater exposure. However, in the list of consumer uses in EPA's *Preliminary Information on Manufacturing, Processing, Distribution, Use, and Disposal*, the Agency states *"There are several uses of perchloroethylene in consumer products, including adhesives (arts and crafts, as well as light repairs), sealants for gun ammunition, and stainless steel polish.* ***The use of perchloroethylene in consumer adhesives is especially prevalent.****"*[99]

It is unclear whether EPA is indicating that many consumers in the general population are using adhesives (all of which contain PERC), or if they are saying that a small subset the population uses adhesives which contain PERC. The draft risk evaluation also goes on to identify that:

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[93] Data USA. (2020). Laundry & Drycleaning workers. Available: https://datausa.io/profile/soc/laundry-drycleaning-workers#about

[94] US EPA. (2020). Toxic Substances Control Act (TSCA) Science Advisory Committee on Chemicals Review of Risk Evaluation for Perchloroethylene. Draft Risk Evaluation for Perchloroethylene Public. Pg. 246. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0502-0022

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

[96] 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.

[97] US EPA. (2019). Toxic Substances Control Act (TSCA) Science Advisory Committee on Chemicals Review of Risk Evaluation for 1-Bromopropane. 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-2019-0235-0053

[98] US EPA. (2020). Toxic Substances Control Act (TSCA) Science Advisory Committee on Chemicals Review of Risk Evaluation for Perchloroethylene. Draft Risk Evaluation for Perchloroethylene Public. Pg. 246. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0502-0022

[99] US EPA. (2017). Tetrachloroethylene (perchloroethylene); TSCA Review and Risk Evaluation. Preliminary Information on Manufacturing, Processing, Distribution, Use, and Disposal: Tetrachloroethylene (Perchloroethylene). Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0732-0003

*"…**consumers are considered to include children and adults over age 11**, but bystanders in the home exposed via inhalation are considered to include any age group, from infant to adult, including pregnant women and/or women of reproductive age."[100](emphasis ours)*

While it makes sense that bystanders could be any age (infant to adult) and the draft risk evaluation takes into account developmental and reproductive concerns, the age cutoff for exposed child consumers being ages 11 and above is given here without any justification. Unless EPA has justification for the age cutoff, it cannot assume that children under 11 and pregnant women will not be users.

Finally, EPA fails to consider people who live in mixed-use housing above dry cleaners. Data show that people living above drycleaners can have higher exposures than the general population and to not consider these exposures could significantly underestimate risk. ATSDR in their report on PERC conclude *"[i]ndoor air of apartments where dry cleaners lived was about 0.04 ppm compared to 0.003 ppm in the apartments of the controls (Aggazzotti et al. 1994a), indicating that dry cleaners serve as a source of exposure for their families. Breath concentrations of tetrachloroethylene in dry cleaners, family members, and controls were 0.65, 0.05, and 0.001 ppm, respectively (Aggazzotti et al. 1994b)."* [101]

EPA's identification of potentially exposed and susceptible subpopulations in the PERC draft risk evaluation does not specifically account for the groups that can have higher exposure to PERC, and groups can have higher susceptibility due to concurrent health conditions. For example, workers at dry cleaners who are operating as essential businesses during the COVID pandemic, may be at increased respiratory risks for COVID, due to their chronic PERC exposures.[102]

c. EPA is underestimating exposures by failing to consider combined dermal and inhalation routes of exposure, pathways of exposure, and conditions of use.

EPA fails to consider combined exposures for dermal and inhalation, and multiple exposure routes, despite identifying them as important. The Agency acknowledges that not considering the routes of exposure together may lead EPA to underestimate risk for the general population and potentially exposed and susceptible subpopulations.

On page 32 of the PERC draft risk evaluation EPA indicates that:
*"Exposures to PCE were evaluated by inhalation and dermal routes separately. **Inhalation and dermal exposures are assumed to occur simultaneously for workers and consumers**. EPA chose not to utilize additivity of exposure pathways at this time within a condition of use because of the uncertainties present in the current exposure estimation procedures and this may lead to an underestimate of exposure."* [103] *(Emphasis ours)*

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[100] US EPA. (2020). Toxic Substances Control Act (TSCA) Science Advisory Committee on Chemicals Review of Risk Evaluation for Perchloroethylene. Draft Risk Evaluation for Perchloroethylene Public. Pg. 246. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0502-0022

[101] US EPA. (2020). Toxic Substances Control Act (TSCA) Science Advisory Committee on Chemicals Review of Risk Evaluation for Perchloroethylene. Draft Risk Evaluation for Perchloroethylene Public. Pg. 291. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0502-0022

[102] Coronavirus (COVID-19): Guidelines, Links and the Latest News. (2020, March 19). Retrieved June 13, 2020, from https://americandrycleaner.com/coronavirus-covid-19-guidelines-links-and-latest-news-0

[103] US EPA. (2020). Toxic Substances Control Act (TSCA) Science Advisory Committee on Chemicals Review of Risk Evaluation for Perchloroethylene. Draft Risk Evaluation for Perchloroethylene Public. Pg 32. EPA does not explain what it means by "the uncertainties present in the current exposure estimation procedures" or why these uncertainties would preclude combining dermal and inhalation exposures.

As we have previously stated, it is scientifically inappropriate for EPA to not combine exposures from inhalation and dermal routes, and to consider them separately.[104] It is additionally problematic that EPA acknowledges that it assumes both workers **and** consumers are exposed simultaneously but still fails to account for combined exposures. EPA's lack of consideration of combined exposure has been a pervasive problem through the draft risk evaluations for the first 10 chemicals and is likely to continue through the next 20 chemicals, based on the recently released draft scopes.[105]

The 1-BP SACC highlighted in their report that:

> "The Committee found that the draft risk evaluation failed to consider cumulative or aggregate exposures. It was pointed out that a worker who is occupationally exposed may also be exposed through other conditions of use in the home. Yet, these exposures are decoupled in the draft risk evaluation. The Committee was concerned that 1-BP off-gassing from insulation in home and schools is inadequately assessed, thereby underestimating exposures."[106]
>
> The 1-BP SACC also recommended that EPA estimate "cumulative exposures, which involves both dermal and inhalation contact" because dermal exposure would "most likely correspond with simultaneous inhalation exposure" and "vapor and dermal exposures are not separable."[107] [108]

Therefore, despite acknowledging that dermal and inhalation exposures occur simultaneously, the PERC draft risk evaluation fails to combine these two routes and thus fails to derive composite risk estimates. By looking at each exposure pathway separately and not additively, the draft risk evaluation may underestimate the risk of a large segment of the population who face exposures to PERC through multiple pathways.[109] The draft risk evaluation also outlines inhalation and dermal exposures **individually** present an unreasonable risk, therefore, it is logical that EPA's failure to consider these pathways together would significantly underestimate of risk.

To accurately account for real-life exposures, it is critical that EPA combine exposures across pathways. EPA has described the concept of assessing aggregate exposures as "the risk cup," where every use of a chemical contributes to filling the cup.[110] The Agency can only determine if risks exceed levels of

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[104] 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

[105] US EPA. (2020). Phosphoric acid, triphenyl ester (TPP); TSCA Review. Comment submitted by Swati Rayasam, Science Associate, Science and Policy, 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-2018-0458-0032

[106] SACC Report on 1-BP Evaluation at 16.

[107] EPA. (2020). TSCA Science Advisory Committee on Chemicals Meeting Minutes and Final Report No. 2019-03, Peer Review for the United States Environmental Protection Agency (EPA) Draft Risk Evaluation for 1-Bromopropane (1-BP) (SACC Report on 1-BP), December 12, 2019. Pgs. 47 and 73. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0235-0061

[109] US EPA. (2020). Phosphoric acid, triphenyl ester (TPP); TSCA Review. Comment submitted by Swati Rayasam, Science Associate, Science and Policy, 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-2018-0458-0032

[109] US EPA. (2020). Phosphoric acid, triphenyl ester (TPP); TSCA Review. Comment submitted by Swati Rayasam, Science Associate, Science and Policy, 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-2018-0458-0032

[110] US EPA (January 31, 1997) PRN 97-1: Agency Actions under the Requirements of the Food Quality Protection Act. Available: https://www.epa.gov/pesticide-registration/prn-97-1-agency-actions-under-requirements-food-quality-protection-act#risk

concern, which is whether the risk cup is full or overflowing, by adding together all contributing exposures and taking into consideration extrinsic and intrinsic factors which contribute to vulnerability as outlined below in point d. However, if known chemical uses and exposures are ignored, the cup levels will be an underestimate of the true risk posed, suggesting that risks are below levels of concern when in reality the cup might be full or overflowing, indicating an unreasonable risk that warrants action. This is compounded by the fact that the population is not only exposed to a single chemical through multiple pathways, but that they are exposed to mixtures of *multiple* chemicals (disclosed or undisclosed due to CBI) through *multiple* pathways. These chemicals may present human health hazards both individually and compounding health hazards synergistically. If risks were properly aggregated, they would show a marked increase for non-cancer and cancer risks relative to the Agency's benchmarks. We have highlighted this issue in previous comments on EPA's draft risk evaluations. [111]

We strongly recommend that EPA take the recommendation of its own peer review panel and consider combined exposures within and across these populations in its final risk evaluations, or risk will be underestimated due to inaccurate assessment of real-world exposures and have previously submitted detailed comments to this extent. [112]

d. EPA's use of the 10x UF underestimates risk to vulnerable populations. The Agency must adopt a more protective UF, such as the one used by the State of California and we recommend 100 at a minimum based on neurotoxicity effects.

In the draft risk evaluation, EPA identifies that the uncertainty factor of 10x UF was "…unable to directly account for all possible PESS considerations and subpopulations in the risk estimates. **It is unknown whether the 10x UF to account for human variability will cover the full breadth of human responses, and subpopulations with particular disease states or genetic predispositions may fall outside of the range covered by this UF**… EPA cannot rule out that consumers at very high frequencies of use may be at risk for chronic hazards, especially if those consumers also exhibit biological susceptibilities. **EPA can also not rule out that certain subpopulations, whether due to very elevated exposure or biological susceptibility, may be at risk**…"*[113]*

In the 2017 framework rule EPA is required to "determine whether a chemical substance presents an unreasonable risk of injury to health or the environment, without consideration of costs or other non-risk factors, including an unreasonable risk to a potentially exposed or susceptible subpopulation."[114] Therefore, as EPA must make specific determinations of unreasonable risk for potentially exposed and susceptible subpopulations, the Agency should increase the 10X UF when it lacks confidence that the 10X UF will assure the absence of risk to these subpopulations and there is data to show that the 10X is insufficient to account for human variability.

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[111] 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

[112] US EPA. (2016). Asbestos; TSCA Review and Risk Evaluation. Comment submitted by Veena Singla, PhD, Associate Director, Science and Policy, Program on Reproductive Health and the Environment, University of California, San Francisco et al. https://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0736-0479

[113] US EPA. (2020). Toxic Substances Control Act (TSCA) Science Advisory Committee on Chemicals Review of Risk Evaluation for Perchloroethylene. Draft Risk Evaluation for Perchloroethylene Public. Pg. 403. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0502-0022

[114] 40 CFR Part 702 pg. 33726

We recently provided comments to EPA on the draft scopes for the next 20 chemicals to be considered under TSCA. In these comments we stated that EPA's typical safety factor of 10 is insufficient to account for variability due to life stage, genetics, underlying disease status, and external stressors that may be due to poverty or other difficult life conditions. [115] For example, for cancer, the NASEM noted that cancer risk assessment methods do not account for variability in human response to carcinogens recommended a factor of 25- to 50- be used to account for the variability between the median individual and those with more extreme responses.[116]

In addition, California EPA's (Cal EPA) guidance for incorporating differential susceptibilities to carcinogens and non-carcinogens incorporates more recent science on increased susceptibility during the prenatal period and age-related susceptibility for non-mutagenic carcinogenic agents.[117] Cal EPA's literature review on differential susceptibility to carcinogens and non-carcinogens was based on age and life stage derived age adjustment values for carcinogens which include the prenatal period[118] and Cal EPA recommends an increase in the default intraspecies uncertainty factors for non-carcinogens to 30 and 100 for specific endpoints such as asthma or neurotoxicity. [119] This is particularly relevant to PERC as one of the most sensitive endpoints for PERC is neurotoxicity. The benefit of the Cal EPA default factor is that it can then be modified upwards or downwards depending on chemical specific information. Therefore, we recommend again that, at a minimum, EPA should adopt Cal EPA's age adjustment values and intraspecies uncertainty factors for incorporating age/early life susceptibility. Cal EPA also developed child-specific risk values for chemicals (e.g., atrazine, lead, nickel, manganese, heptachlor) that specifically address routes of exposure and differences in susceptibility unique to children compared to adults.[120] EPA should review these evaluations and incorporate these values as appropriate.

[115] US EPA. (2020). Phosphoric acid, triphenyl ester (TPP); TSCA Review. Comment submitted by Swati Rayasam, Science Associate, Science and Policy, 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-2018-0458-0032

[116] National Research Council. Science and Decisions: Advancing Risk Assessment. Washington, D.C.: National Academies Press; 2009. Pg. 168

[117] OEHHA. In Utero and Early Life Susceptibility to Carcinogens: [Internet]. 2009. Available from: https://oehha.ca.gov/media/downloads/crnr/appendixjearly.pdf

[118] California EPA 2009. Cal EPA 2009. California Environmental Protection Agency, Office of Environmental Health Hazard Assessment. Technical Support Document for Cancer Potency Factors: Methodologies for derivation, listing of available values, and adjustments to allow for early life stage exposures. http://oehha.ca.gov/media/downloads/crnr/tsdcancerpotency.pdf

[119] Cal EPA 2008. California Environmental Protection Agency, Office of Environmental Health Hazard Assessment. Technical Support Document For the Derivation of Noncancer Reference Exposure Levels http://oehha.ca.gov/media/downloads/crnr/noncancertsdfinal.pdf

[120] California Environmental Protection Agency. Office of Environmental Health Hazard Assessment (OEHHA). Child-Specific Reference Doses (chRDs) Finalized to Date. Available from: http://oehha.ca.gov/risk-assessment/chrd/table-all-chrds