March 27, 2020

Comments from Academics, Scientists and Clinicians on the Draft Risk Evaluation for Carbon Tetrachloride

Submitted online via *Regulations.gov* to docket EPA-HQ-OPPT-2019-0499

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 Carbon Tetrachloride, 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] Carbon tetrachloride is a high production volume solvent. Over one hundred forty two million pounds of carbon tetrachloride were produced or imported in the U.S. in 2015 according to the EPA's Chemical Data Reporting (CDR) database. Carbon Tetrachloride is a carcinogen and a Hazardous Air Pollutant (HAP) under the Clean Air Act. It presents a series of non-cancer health hazards such as potential reproductive effects, liver and kidney toxicity, and neurological damage.

In its draft risk evaluation, EPA continues to utilize its TSCA systematic review methodology, which multiple experts criticized for its non-empirically based scoring of studies that may result in downgrading epidemiological and animal studies and leads to excluding relevant studies without justification. Although EPA states that "Because systematic review is an iterative process, EPA/OPPT expects that some references may move from the on topic to the off-topic category and vice versa," this does not justify the exclusion of 2500 – 3000 "On Topic" references for Human Health Hazards in the Carbon Tetrachloride draft risk evaluation without explanation.[2]

EPA finds carbon tetrachloride presents risks of concern for some conditions of use, and particularly for occupational non-users (ONUs).[3] However, due to critical scientific flaws in EPA's risk assessment approaches that lead to underestimation of risk, the actual risks are of greater magnitude that stated by EPA and additional conditions of use present unreasonable risks. Additionally, EPA's "[a]ssessment of susceptible subpopulations does not include children or non-workers/non-ONUs."[4] However, the Public Health Statement regarding Carbon Tetrachloride finds that "[e]xposure to levels of carbon tetrachloride higher than these typical "background" levels is likely to occur only at specific industrial locations where carbon tetrachloride is still used or near chemical waste sites where emissions into air, water, or soil are not properly controlled."[5] In that same statement, ATSDR details that Carbon Tetrachloride has been

[1] US EPA. (2020). Toxic Substances Control Act (TSCA) Science Advisory Committee on Chemicals Review of Risk Evaluation for Carbon Tetrachloride, CCl4 Risk Evaluation Draft Public. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0499-0014

[2] US EPA. (2017). Carbon tetrachloride 1187 (CASRN 56-23-5) Bibliography: Supplemental File for the TSCA Scope Document.

[3] US EPA. (2020). Toxic Substances Control Act (TSCA) Science Advisory Committee on Chemicals Review of Risk Evaluation for Carbon Tetrachloride, CCl4 Risk Evaluation Draft Public. Pg. 178, Table 5-1. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0499-0014

[4] US EPA. (2020). Toxic Substances Control Act (TSCA) Science Advisory Committee on Chemicals Review of Risk Evaluation for Carbon Tetrachloride, CCl4 Risk Evaluation Draft Public. Pg .165. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0499-0014

[5] ATSDR. (2005). Public Health Statement: Carbon Tetrachloride (CAS # 56-23-5). Available: https://www.atsdr.cdc.gov/toxprofiles/tp30-c1-b.pdf

found at over a quarter of Superfund sites, which means that the potentially susceptible subpopulations living around those plants (non-workers, non-ONU) may have disproportionate levels of exposure when compared to the general populations. EPA's failure to consider the exposure of these populations to Carbon Tetrachloride is deeply concerning.

We have previously commented on EPA's inadequate scientific methods in previous risk evaluations that are also present in this one including: scientific flaws in EPA's systematic review methodology; scientifically unsupported assumptions about worker use of personal protective equipment (PPE); failure to include known exposure pathways such as air and water; failure to aggregate exposures from known pathways; and inadequate adjustment factors applied to account for susceptible/vulnerable populations. [6,7,8] EPA's Science Advisory Committee on Chemicals (SACC) also identified these and other scientific problems in EPA's previous draft risk evaluations which could lead to underestimating risk. The SACC provided clear directions for needed improvements, but the carbon tetrachloride draft risk evaluation fails to reflect the SACC's recommended changes.[9, 10, 11] EPA should incorporate the SACC recommendations and other scientifically based changes to comprehensively assess risks as required by law before finalizing the carbon tetrachloride evaluation.

Our comments address the following main points:

1. **EPA's TSCA systematic review methodology for identifying and evaluating the evidence continues to have serious scientific flaws and is not consistent with established methods; this flawed method lacks transparency and is not empirically based, making it likely to have resulted in a biased evidence base for Carbon Tetrachloride. EPA must address the comments from the Science Advisory Committee on Chemicals (SACC) in its Peer Review of Bromopropane (1-BP) and incorporate the recommended changes to its systematic review prior to finalizing the evaluation for Carbon Tetrachloride and for future TSCA risk evaluations.**
    a. **EPA fails to adhere to fundamental best practices of systematic review, which includes:**
        i. **Documenting how <u>every</u> reference identified in the literature search was used in the draft risk evaluation;**

[6] 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

[7] 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**

[8] 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

[9] 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

[10] 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

[11] 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

   ii. **Transparently applying a predefined eligibility criteria to the references in the literature search; and**
   iii. **Using a protocol that outlines the pre-established methods to be used throughout the systematic review process as required by EPA regulation under TSCA.**
   b. **EPA's method to rate the quality of the human epidemiological evidence can exclude a study based off only one 'unacceptable' criterion rather than considering all relevant science while accounting for "strengths and limitations" as required by EPA regulation under TSCA.**
   c. **EPA fails to use a pre-established protocol or methods for evidence integration as required by EPA regulation under TSCA.**
2. **To address the critical issues in the TSCA systematic review method identified by the SACC in its Peer Review of 1-Bromopropane (1-BP), EPA should immediately use well established systematic review methods for environmental health, such as those of the National Toxicology Program's Office of Health Assessment and Translation or the Navigation Guide developed by the University of California, San Francisco.**
3. **EPA continues to use methods that lack transparency to identify "key/ supporting/ influential information," and does not provide the details of the methods for the approach for using the "hierarchy of preferences" to exclude relevant studies.**
4. **The draft risk evaluation invokes Klimisch scores, which has been critiqued on its ability to evaluate study quality.**
5. **EPA must include chemical exposures from air, water, land and all other pathways in the exposure assessment for all populations, regardless of claims of coverage under other environmental statutes.**

We appreciate the opportunity to provide public input. Please do not hesitate to contact us with any questions regarding these or any of our previous comments on methylene chloride.

Sincerely,

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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 and is not consistent with established methods; this flawed method lacks transparency and is not empirically based, making it likely to have resulted in a biased evidence base for Carbon Tetrachloride. EPA must address the comments from the Science Advisory Committee on Chemicals (SACC) in its Peer Review of Bromopropane (1-BP) and incorporate the recommended changes to its systematic review prior to finalizing the evaluation for Carbon Tetrachloride and for future TSCA risk evaluations.**

EPA's systematic review method developed under TSCA (hereafter referred to as the "TSCA method")[12], as with the previous risk evaluations, fails to evaluate the evidence on Carbon Tetrachloride consistently or transparently. We have commented on the scientific flaws in the TSCA method extensively in previous submissions to EPA on the draft risk evaluations that have already been completed [13,14,15,16,17] and as summarized in a peer-reviewed commentary published in the *American Journal of Public Health*.[18] Further, several of these fundamental systematic review deficiencies in the TSCA method have also been identified by the Science Advisory Committee on Chemicals (SACC) in its peer review of the draft risk evaluation of Bromopropane (1-BP).[19] Further, we have also previously highlighted the comments and recommendations made to EPA by the SACC following its evaluation of the draft risk evaluation of Pigment Violet 29 (PV29)[20,21] and 1,4-dioxane and Cyclic Aliphatic Bromide Cluster

[12] US EPA. (2018). Application of Systematic Review in TSCA Risk Evaluations. Available: https://www.epa.gov/sites/production/files/2018-06/documents/final_application_of_sr_in_tsca_05-31-18.pdf

[13] 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

[14] 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

[15] US EPA. (2019). Draft Toxic Substances Control Act Risk Evaluations: 1,4-Dioxane and Cyclic Aliphatic Bromide Cluster (HBCD). 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-2019-0237-0059

[16] US EPA. (2019). Draft Toxic Substances Control Act Risk Evaluations: 1-Bromopropane. 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-2019-0235-0053

[17] US EPA. (2019). Draft Toxic Substances Control Act Risk Evaluations: Methylene Chloride. 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-2019-0437-0069

[18] 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

[19] US EPA. (2019). Peer Review of the Draft Risk Evaluation for 1 Bromopropane (1-BP). Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0235-0061

[20] US EPA. (2019). Draft Toxic Substances Control Act Risk Evaluations: 1-Bromopropane. 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-2019-0235-0053

[21] 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

(HBCD)[22,23] that echo the recommendations made again in the SACC's peer review of 1-BP. The SACC has made several comments and critical recommendations necessary to improve the TSCA method which EPA has not addressed in the Carbon Tetrachloride draft risk evaluation; therefore the scientific flaws in the TSCA method persist. Below, we highlight the comments and recommendations made by the SACC of most concern that remain unaddressed by EPA.

a. EPA fails to adhere to fundamental best practices of systematic review, which includes:

i. Documenting how every reference identified in the literature search was used in the draft risk evaluation;

ii. Transparently applying a predefined eligibility criteria to the references in the literature search; and

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

i. Documenting how every reference identified in the literature search was used in the draft risk evaluation

The 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."*[24]

The 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."*[25] *" The Evaluation flow charts suggest a full systematic review was performed, but the text describes a more limited review."*[26]

The SACC Committee for 1-BP highlights specifically how this lack of transparency limits the ability of the committee to follow EPA's decision-making process in identifying and using the included studies for the hazard identification step. A Committee member stated *"It is not clear how sources were identified and why specific sources were or were not used in the DRE"*[27] and then cites the results of the evaluation in

[22] US EPA. (2019). SACC July 2019 Meeting Minutes and Final Report Docket. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0238-0063

[23] US EPA. (2019). Proposed High-Priority Substance Designation Under the Toxic Substances Control Act. 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-2018-0430-0015

[24] US EPA. (2019). Peer Review of the Draft Risk Evaluation for 1 Bromopropane (1-BP). Pg. 22. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0235-0061

[25] US EPA. (2019). SACC July 2019 Meeting Minutes and Final Report Docket. Pg. 31. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0238-0063

[26] US EPA. (2019). SACC July 2019 Meeting Minutes and Final Report Docket. Pg. 32. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0238-0063

[27] US EPA. (2019). Peer Review of the Draft Risk Evaluation for 1 Bromopropane (1-BP). Pg. 23. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0235-0061

the powerpoint presentation slides located in the public docket.[28] Under "Description of Each PowerPoint Slides (by Slide Number) Systematic review PPP.pptx" it states for slide 9:

> "Figures 1-10. Literature Flow Diagram for Human Health Hazard Data Sources. The notes describe the differences between this figure and what the Committee member found in the bibliography and data quality evaluation supplemental files." [29]

Shown below here is the referenced slide, which is of *'Figure 1-10. Literature Flow Diagram for Human Health Hazard Data Sources'* used in the draft risk evaluation for 1-BP.

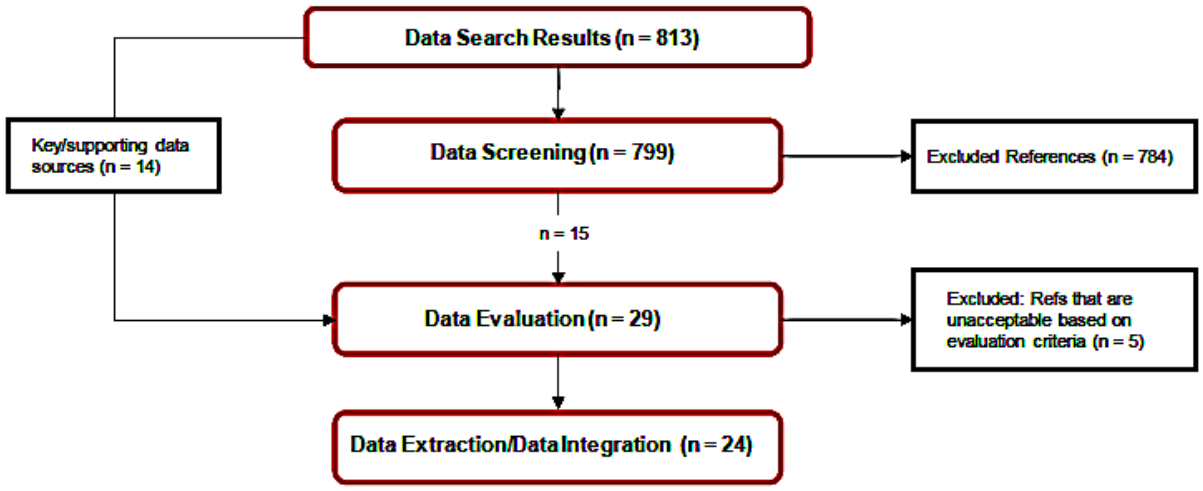


Figure 1-10. Literature Flow Diagram for Human Health Hazard Data Sources

The committee member highlights that:

> *"The numbers in Figure 1-10 do not match the numbers in the supplemental documents; the bibliography and the data quality evaluation."*

This inconsistency in the reporting of the included studies in the 1-BP draft risk evaluation and the accompanying supplementary files is also repeated in the Carbon Tetrachloride draft risk evaluation.[30] In Section '*1.5.1 Data and Information Collection of the Carbon Tetrachloride Draft Risk Evaluation'* of the Carbon Tetrachloride draft risk evaluation it states that:

> *"EPA then developed and applied inclusion and exclusion criteria during the title and abstract screening to identify information potentially relevant for the risk evaluation process… and results of*

[28] US EPA. (2019). Toxic Substances Control Act (TSCA) Science Advisory Committee on Chemicals Review of Risk Evaluation for 1-Bromopropane, Systematic review PPP. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0235-0058

[29] US EPA. (2019). Peer Review of the Draft Risk Evaluation for 1 Bromopropane (1-BP). Page 24-25. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0235-0061

[30] US EPA. (2020). Carbon Tetrachloride (Methane, Tetrachloro-); Draft Toxic Substances Control Act (TSCA) Risk Evaluation. Available: EPA Document# EPA-740-R1-8014

*screening were published in Carbon tetrachloride 1187 (CASRN 56-23-5) Bibliography: Supplemental File for the TSCA Scope Document…. **For studies determined to be on-topic (or relevant) after title and abstract screening, EPA conducted a full text screening** to further exclude references that were not relevant to the risk evaluation."* [31]

In *'Carbon tetrachloride Bibliography: Supplemental File for the TSCA Scope Document'* [32] there are 107 pages (p 744-851) of "On Topic" references following title and abstract screening for the *'Human health Hazard Literature Search Results'* with approximately 26-28 references per page, totaling approximately 2,782-2,996 references. However, in the Carbon Tetrachloride draft risk evaluation, *'Figure 1-8 Key Supporting Data Sources for Human Health Hazards'* (below) EPA states that:

> *"The literature search strategy used to gather human health hazard information for carbon tetrachloride yielded 6,489 studies. This included 18 key and supporting studies (identified from previous regulatory assessments) that skipped the initial screening process and proceeded directly to the data evaluation phase. Of the 6,489 studies identified for carbon tetrachloride 6,454 were excluded as off topic during the title and abstract screening phase."* [33]

Therefore, according to EPA after title and abstract screening there were only 35 **"On Topic"** studies included in the draft risk evaluation.

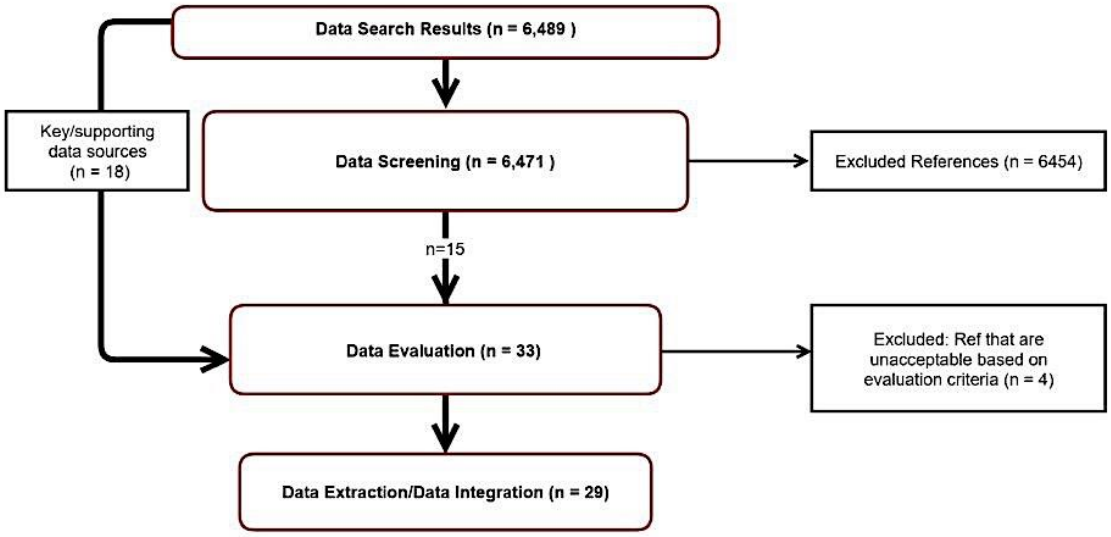


Figure 1-8. Key/Supporting Data Sources for Human Health Hazards

However, this inconsistent with the results of the *'Carbon tetrachloride (CASRN 56-23-5) Bibliography: Supplemental File for the TSCA Scope Document'* which demonstrates, there are >2500 "On Topic" references following the title and abstract screening. Therefore, EPA has not accounted for or screened

[31]US EPA. (2020). Carbon Tetrachloride (Methane, Tetrachloro-); Draft Toxic Substances Control Act (TSCA) Risk Evaluation. Pg. 38. Available: EPA Document# EPA-740-R1-8014

[32] US EPA. (2017). Carbon Tetrachloride(CASRN:56-23-5) Bibliography:
Supplemental File for the TSCA Scope Document. Available: https://www.epa.gov/sites/production/files/2017-06/documents/ccl4_comp_bib_0.pdf

[33]US EPA. (2020). Carbon Tetrachloride (Methane, Tetrachloro-); Draft Toxic Substances Control Act (TSCA) Risk Evaluation. Pg. 43. Available: EPA Document# EPA-740-R1-8014

these >2500 references in assessing the Human Health Hazard in the Carbon Tetrachloride draft risk evaluation.

Further, the numbers shown in the flow diagram Figure 1-8 do not accurately reflect the numbers at each step and do not account for all of the 6,489 references identified from the 'Data Search Results'. As shown, in the 'Data Screening Step', of the 6471 studies, 6454 studies were excluded. Therefore, 17 studies should have moved to the 'Data Evaluation Step', not 15 as shown here, with 18 'Key/supporting data sources' being added, for a total of 35 studies entering the 'Data Evaluation', not 33 as shown here.

Such inconsistencies are deeply concerning and threatens the validity of the Carbon Tetrachloride draft risk evaluation.

ii. Transparently applying a predefined eligibility criteria to the references in the literature search

The 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."* [34]

The SACC is referring to Section 1.5.1 *'Data and Information Collection'* in the 1-BP draft risk evaluation, which is the same section in the Carbon Tetrachloride draft risk evaluation and refers to how studies were included and excluded from the systematic reviews. [35] This lack of transparency on why studies were excluded from the 1-BP draft risk evaluation is repeated again with how EPA has excluded studies from the Carbon Tetrachloride draft risk evaluation without transparently accounting for them or giving justification for its exclusions.

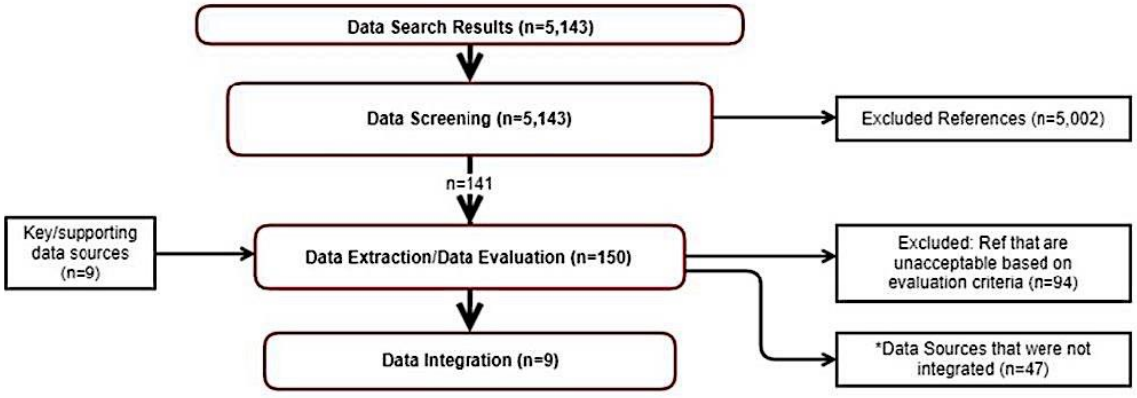
As discussed above in point i., over 107 pages of "On Topic" references considered relevant after title and abstract screening are unaccounted for when EPA assesses the Human Health Hazard in the Carbon Tetrachloride draft risk evaluation. Further, as shown below, in *'Figure 1-5 Key/Supporting Data Sources for Releases and Occupational Exposures'* of the carbon Tetrachloride draft risk evaluation there are 150 data sources included at the *'Data Extraction/Data Evaluation Step'* and 141 of these are excluded without any justification. EPA simply states:

> *"As shown in Figure 1-5, the literature search strategy for carbon tetrachloride's environmental releases and occupational exposures yielded 5,143 data sources... Of the 150 sources from which data were extracted and 278 evaluated, 94 sources only contained data that were rated as unacceptable based on flaws detected during the evaluation. Of the 56 sources forwarded for data integration, data from sources were integrated, and 47 sources contained data that were not integrated (e.g., lower 1281 quality data that were not needed due to the existence of higher quality data, data for release media that were removed from scope after data collection)".* [36]

[34] US EPA. (2019). Peer Review of the Draft Risk Evaluation for Bromopropane (1-BP). Pg. 25. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0235-0061

[35] US EPA. (2020). Carbon Tetrachloride (Methane, Tetrachloro-); Draft Toxic Substances Control Act (TSCA) Risk Evaluation. Pg. 38. Available: EPA Document# EPA-740-R1-8014

[36] US EPA. (2020). Carbon Tetrachloride (Methane, Tetrachloro-); Draft Toxic Substances Control Act (TSCA) Risk Evaluation. Pg. 38. Available: EPA Document# EPA-740-R1-8014



*The quality of data in these sources (n=47) were acceptable for risk assessment purposes, but they were ultimately excluded from further consideration based on EPA's integration approach for environmental release and occupational exposure data/information. 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). If warranted, EPA may use data/information of lower rated quality as supportive evidence in the environmental release and occupational exposure assessments.

Figure 1-5. Key/Supporting Data Sources for Releases and Occupational Exposures

In a systematic review, studies that make it to 'Full text screening' but are excluded thereafter should only be excluded with an explicit justification. The Institute of Medicine (IOM) report '*Finding What Works in Health Care: Standards for Systematic Review*' has 21 standards covering the entire systematic review process that, if adhered to, result in a scientifically valid, transparent, and reproducible systematic review. [37] The IOM report that:

> *"In light of the subjective nature of study selection and the large volume of possible citations, the importance of* ***maintaining a detailed account of study selection cannot be understated****…The SR final report should include a flow chart that shows the number of studies that remain after each stage of the selection process….* ***The flow chart documents the number of records identified through electronic databases searched****, whether additional records were identified through other sources,* ***and the reasons for excluding articles****. Maintaining a record of excluded as well as selected articles is important."* [38](Emphasis ours)

The critical importance of stating the rationale for excluding studies throughout the systematic review process is highlighted in *IOM Standard 3.4.2 "Document the disposition of each report identified including reasons for their exclusion if appropriate."*[39]

Further, how EPA has developed and applied the eligibility criteria for these references throughout the Carbon Tetrachloride draft risk evaluation is also deeply concerning. EPA states that:

> "*For studies determined to be on-topic (or relevant) after title and abstract screening, EPA conducted a full text screening to further exclude references that were not relevant to the risk evaluation. Screening decisions were made based on eligibility criteria documented in the form*

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

[38] Institute of Medicine. (2011). Finding What Works in Health Care: Standards for Systematic Reviews. 3. Standards for Finding and Assessing Individual Studies. Washington, DC: The National Academies Press

[39] Institute of Medicine. (2011). Finding What Works in Health Care: Standards for Systematic Reviews. 3. Standards for Finding and Assessing Individual Studies. Washington, DC: The National Academies Press

of the populations, exposures, comparators, and outcomes (PECO) framework or a modified framework. Data sources that met the criteria were carried forward to the data evaluation stage. The inclusion and exclusion criteria for full text screening for carbon tetrachloride are available in Appendix F of the Problem Formulation of the Risk Evaluation for Carbon Tetrachloride 1196 (U.S. EPA, 2018d)[40]

However, the literature and screening strategy as specifically applied to the Carbon Tetrachloride draft risk evaluation is described in '*Strategy for Conducting Literature Searches for Carbon Tetrachloride (CCL4): Supplemental Document to the TSCA Scope Document*', which was published in June of 2017.[41] The results of the screening of literature search were published in *'Carbon tetrachloride (CASRN 56-23-5) Bibliography: Supplemental File for the TSCA Scope Document*' (no date is given in this document although the webpage on which this document is made available says 'last updated on June 22, 2017').[42] However, as highlighted by EPA in the Carbon Tetrachloride draft risk evaluation, for studies determined to be 'on-topic' (or relevant) after title and abstract screening, EPA conducted a full text screening to further exclude references that were not relevant to the risk evaluation and '*Screening decisions were made based on eligibility criteria documented in the form of the populations, exposures, comparators, and outcomes (PECO) framework or a modified framework….. The inclusion and exclusion criteria for full text screening for carbon tetrachloride are available in Appendix F of the Problem Formulation of the Risk Evaluation for Carbon Tetrachloride (U.S. EPA, 2018d.).'* [43] However, the *'Problem Formulation of the Risk Evaluation for Carbon Tetrachloride'* that outlined this PECO framework was published in May 2018, after the searches and initial screening had been completed.[44] The timing of this is very concerning as the PECO framework was developed after the studies had already been identified in the literature search and screened at the title and abstract stage and therefore could have been developed to include/exclude studies that would support a pre-defined health hazard conclusion.

The PECO statement (framework) should shape the entire review process, including the search strategy to be used, the study eligibility criteria to be applied, how the data will be extracted from the included studies, the strategy for synthesizing the evidence and how the results will be reported.[45] The IOM states that:

*'**Using prespecified inclusion and exclusion criteria to choose studies is the best way to minimize the risk of researcher biases influencing the ultimate results of the SR.** The SR research protocol should make explicit which studies to include or exclude based on the patient population and patient outcomes of interest, the healthcare intervention and comparators, clinical settings (if relevant), and study designs (e.g., randomized vs. observational research) that are appropriate for the research question.'* [46]

[40]US EPA. (2020). Carbon Tetrachloride (Methane, Tetrachloro-); Draft Toxic Substances Control Act (TSCA) Risk Evaluation. Pg. 38-39 Available: EPA Document# EPA-740-R1-8014

[41] US EPA. (2017). Strategy for Conducting Literature Searches for Carbon Tetrachloride (CCL4): Supplemental Document to the TSCA Scope Document'. Available: https://www.epa.gov/sites/production/files/2017-06/documents/ccl4_lit_search_strategy_053017_markup_0.pdf

[42] US EPA. (2017). Carbon Tetrachloride(CASRN:56-23-5) Bibliography:
Supplemental File for the TSCA Scope Document. Available: https://www.epa.gov/sites/production/files/2017-06/documents/ccl4_comp_bib_0.pdf

[43]US EPA. (2020). Carbon Tetrachloride (Methane, Tetrachloro-); Draft Toxic Substances Control Act (TSCA) Risk Evaluation. Available: EPA Document# EPA-740-R1-8014

[44] US EPA. (2018). Problem Formulation of the Risk Evaluation for Carbon Tetrachloride. Available: https://www.epa.gov/sites/production/files/2018-06/documents/ccl4_problem_formulation_05-31-18.pdf

[45] NTP. (2015). Handbook for conducting a literature-based health assessment using OHAT approach for systematic review and evidence integration. U.S. Dept. of Health and Human Services, National Toxicology Program.

[46] Institute of Medicine. (2011). Finding What Works in Health Care: Standards for Systematic Reviews. 3. Standards for Finding and Assessing Individual Studies. Washington, DC: The National Academies Press

While the IOM use PICO (population, intervention, comparator, outcomes) and not PECO statements as their standards relate to systematic reviews applied in the clinical sciences, these principles are the same, as they are designed *'minimize the risk of researcher biases influencing the ultimate results of the SR'.* The critical importance of this is again further reinforced in *IOM standard 3.3.1 "Include or exclude studies based on the protocol's pre-specified criteria."* [47]

Therefore, EPA's failure to predefine the study eligibility criteria applied to the 'on topic' references in the Carbon Tetrachloride draft risk evaluation, introduces significant researcher bias that most likely impacted the results of the draft risk evaluation.

iii. Using 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 these issues relating to its lack of transparency in accounting for all references identified in the literature search and applying a pre-defined eligibility criteria to references in the literature search, EPA must immediately implement protocols for all future draft risk evaluations. 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.[48] Most importantly, it allows greater transparency in the decision-making process throughout the systematic review and it is a fundamental element required to ensure the integrity of evidence-based evaluations and it is a critical methodological step absent in Carbon Tetrachloride draft risk evaluation. 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.[49] 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.

a. EPA's method to rate the quality of the human epidemiological evidence can exclude a study based off only one 'unacceptable' criterion rather than considering all relevant science while accounting for "strengths and limitations" as required by EPA regulation under TSCA.

The 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."* [50]

The SACC Peer Review of 1, 4 Dioxane recommended:

[47] Institute of Medicine. (2011). Finding What Works in Health Care: Standards for Systematic Reviews. 3. Standards for Finding and Assessing Individual Studies. Washington, DC: The National Academies Press

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

[49] 40 CFR 702 Pg. 33733

[50] US EPA. (2019). Peer Review of the Draft Risk Evaluation for Bromopropane (1-BP). Pg. 21. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0235-0061

> *"Follow best practices in the field and simplify the data quality criteria." "Do not be overly stringent and exclude studies based on a single criterion."*[51]

In the Carbon Tetrachloride draft risk evaluation, EPA has again used a data quality evaluation process that excludes studies based on a single 'unacceptable' criterion, based on an arbitrary list of metrics including several scoring metrics not related to bias, but rather to reporting. EPA states that:

> "**Studies with any single metric scored as 4 will be automatically assigned an overall quality score of *Unacceptable* and further evaluation of the remaining metrics is not necessary**. An *Unacceptable* score means that serious flaws are noted in the domain metric that consequently make the data unusable (or invalid)."[52]

As shown below in the figure from the *'Systematic Review Supplemental File: Updates to the Data Quality Criteria for Epidemiological for the Draft Risk Evaluation for Carbon Tetrachloride'*[53] in Metric 13 'Statistical power' a study can only be scored as 'Medium' or 'Unacceptable'. In fact, with EPA's updated criteria, epidemiological studies can no longer score high on seven metrics, but no such change has been made for the animal or *in vitro* studies. Further, there is no empirical justification for these 'scores' on the different metrics.

As we have previously commented,[54] EPA does not provide a method for how "adequacy" of the statistical power of a study on which to base its score will be determined and it also fails to provide any rationale for excluding studies with less than 80% statistical power. Further, in Metric 13 'Statistical power' EPA has confused bias with imprecision, as individual primary studies that are "underpowered" are still valuable to science-based decision-making. Small studies may be imprecise for example but that does not mean they should be confused with a study that is biased.[55] In fact, a small study can be imprecise but still less biased than a larger study.[56] Importantly, when combined in a meta-analysis that increases the statistical power of the body of evidence, small studies that are underpowered can demonstrate an effect between an exposure and health outcomes.

[51] US EPA. (2019). SACC July 2019 Meeting Minutes and Final Report Docket. Pg. 38. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0238-0063.

[52] 83 FR 26998 Pg. 227

[53] US EPA. (2020). Systematic Review Supplemental File: Updates to the Data Quality Criteria for Epidemiological Studies. Available: https://www.epa.gov/sites/production/files/2020 01/documents/8_ccl4_updates_to_the_data_quality_criteria_for_epidemiological_studies_updated_january_2020.pdf

[54] US EPA. (2018). The Application of 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

[55] 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.

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

Metric 13. Statistical power (sensitivity)	
High (score = 1)	Do not select for this metric
Medium (score = 2)	• ***For cohort and cross-sectional studies:*** The number of participants are adequate to detect an effect in the exposed population and/or subgroups of the total population. **OR** • The paper reported statistical power high enough (≥ 80%) to detect an effect in the exposure population and/or subgroups of the total population. • ***For case-control studies:*** The number of cases and controls are adequate to detect an effect in the exposed population and/or subgroups of the total population. **OR** • The paper reported statistical power was high (≥ 80%) to detect an effect in the exposure population and/or subgroups of the total population.
Low (score =3)	• Do not select for this metric.
Unacceptable (score = 4)	• ***For cohort and cross-sectional studies:*** The number of participants are inadequate to detect an effect in the exposed population and/or subgroups of the total population. • ***For case-control studies:*** The number of cases and controls are inadequate to detect an effect in the exposed population and/or subgroups of the total population.
Not rated/applicable	• *Do not select for this metric*

We have previously illustrated how EPA's method of excluding a study based on a single criterion, not related to bias but study reporting, could result in critical high quality research that is necessary to inform science-based decision-making being excluded by EPA. [57] This was demonstrated in a 2017 systematic review by Lam et al. *"Developmental PBDE Exposure and IQ/ADHD in Childhood: A Systematic Review and Meta-analysis."*[58] In this review none of the four high-quality[59] studies included in the meta-analysis reported a power calculation, and therefore would have been considered 'unacceptable' by EPA, yet together, these studies found "a 10-fold increase (in other words, times 10) in PBDE exposure associated with a decrement of 3.70 IQ points (95% confidence interval:0.83,6.56)."

Further, the exclusion of studies based on one 'unacceptable' criterion is not consistent with the EPA's 2017 framework rules which requires EPA to consider all relevant science while accounting for

[57] US EPA. (2018). The Application of 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

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

[59] "High quality" defined as "definitely" or "probably" low or very low risk of bias (Figure 2a in the *Lam et al* paper) based on specific and detailed definitions of risk of bias established before the review was conducted.

"strengths and limitations." [60] EPA should instead attempt to request the missing information required to make the determination from the study authors.[61] If EPA is not able to retrieve this missing information from the study authors, a potential bias (if the metric being assessed relates to bias and not reporting) may then be considered in the study. However, the study should not be excluded from the body of evidence due to this one criterion.

b. EPA fails to use a pre-established protocol or methods for evidence integration as required by EPA regulation under TSCA.

The SACC Peer Review of 1-BP commented:

> *"Improve the clarity of data integration. Multiple times papers that had been identified for data extraction and integration were not used with no explanation as to why"* [62]

The SACC Peer Review of PV29 commented:

> *"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. This was not transparent from reading the documents provided."*[63]

EPA's TSCA regulation requires that it use a systematic review method to "integrate evidence,"[64] but as has been demonstrated by these previous SACC committees and in the Carbon Tetrachloride draft risk evaluation, EPA again fails to adequately address this step. The Carbon Tetrachloride draft risk evaluation fails to clearly define how the quality of the body of evidence has been evaluated for each evidence stream and it has failed to pre-specify the method for integrating two or more streams of evidence in formulating the final conclusions. As shown below *in 'Figure 3-1 Hazard Identification and Dose Response Process'* of the Carbon Tetrachloride draft risk evaluation, EPA conflates data quality evaluation and evidence integration in the *'Human Health Hazard Assessment'* and does not clearly outline how these two critically important steps were completed. [65]

[60] 40 CFR 702 Pg. 33733

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

[62] US EPA. (2019). Peer Review of the Draft Risk Evaluation for Bromopropane (1-BP). Pg. 25. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0235-0061

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

[64] 40 CFR 702.33

[65] US EPA. (2020). Carbon Tetrachloride (Methane, Tetrachloro-); Draft Toxic Substances Control Act (TSCA) Risk Evaluation. Pg. 98. Available: EPA Document# EPA-740-R1-8014

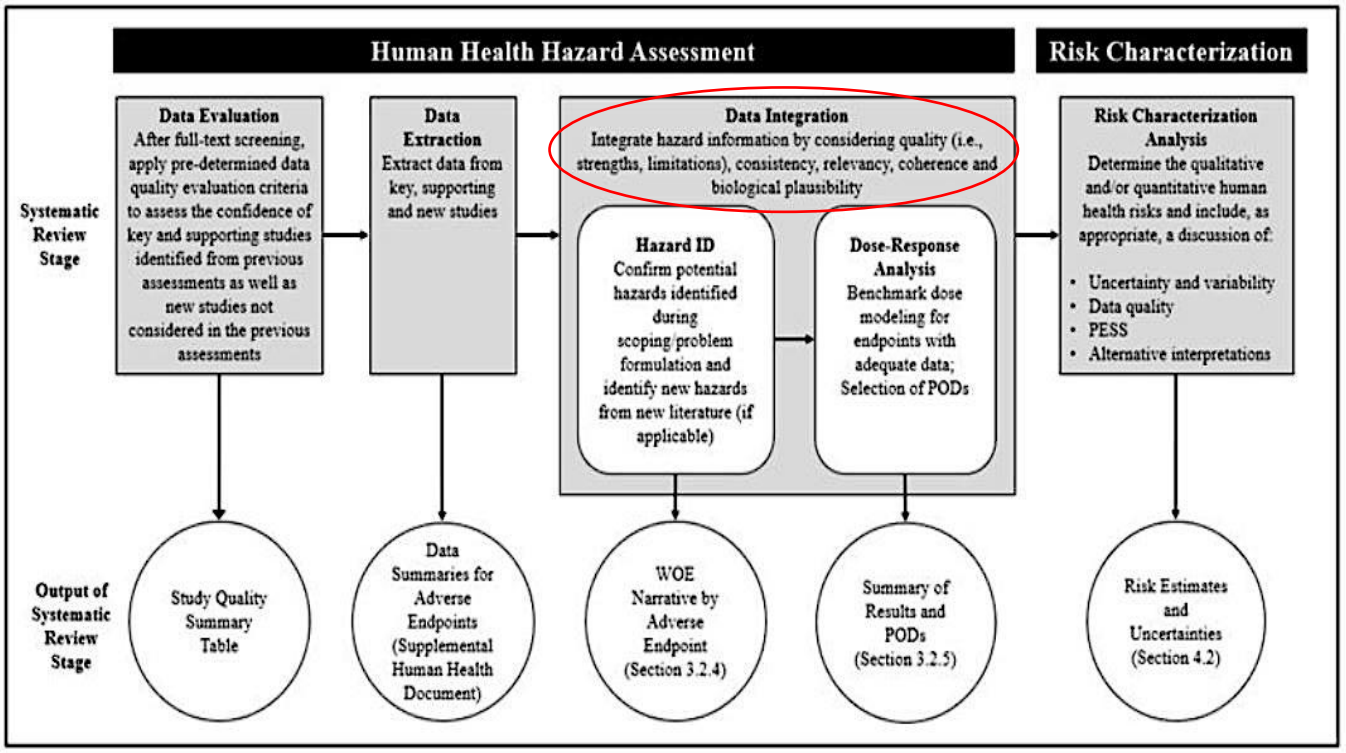


Figure 3-1. Hazard Identification and Dose-Response Process

In section *'3.2.4 Weight of Scientific Evidence*' EPA goes onto describe how they conflate both an evaluation of the quality of the body of evidence and the evidence integration steps during the 'weight of the scientific evidence' process:

> *"The following sections describe the weight of the scientific evidence for both non-cancer and cancer hazard endpoints. Factors considered in weighing the scientific evidence included* ***consistency and coherence among human and animal studies, quality of the studies (such as whether studies exhibited design flaws that made them unacceptable) and biological plausibility****. Relevance of data was considered primarily during the screening process but may also have been considered when weighing the evidence."* [66]

We have commented previously[67,68] that we recommend an approach to evidence integration that has been recommended and successfully applied by the International Agency for Research on Cancer (IARC),[69] the National Toxicology Program's office of Health Assessment and Translation (OHAT),[70]

[66]US EPA. (2020). Carbon Tetrachloride (Methane, Tetrachloro-); Draft Toxic Substances Control Act (TSCA) Risk Evaluation. Pg. 120. Available: EPA Document# EPA-740-R1-8014

[67] 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

[68] US EPA. (2018). The Application of 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

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

[70] 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

Navigation Guide[71] and the National Academies of Science.[72,73,74] This data integration process is highlighted below, using the example of the OHAT method.[75] This process consists of: an overall rating in the confidence of the body of evidence for each specified outcome using explicit, predefined criteria (Figure 1); translating the overall rating into a conclusion on the level of evidence for a health effect (Figure 2); and then finally formulating 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 (Figure 3).

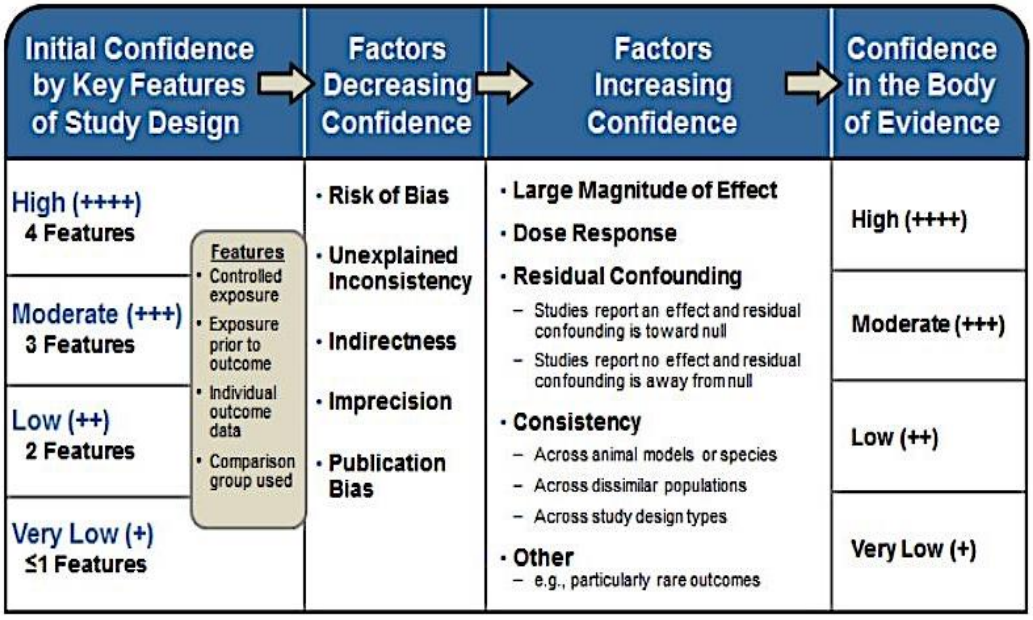


Figure 1: OHAT's method for rating the confidence in the body of evidence. This step is missing from the Carbon Tetrachloride Draft Risk Evaluation. [76]

[71] Woodruff TJ, Sutton P. (2014). 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

[72] 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

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

[74] 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.

[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] 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. Pg. 48.

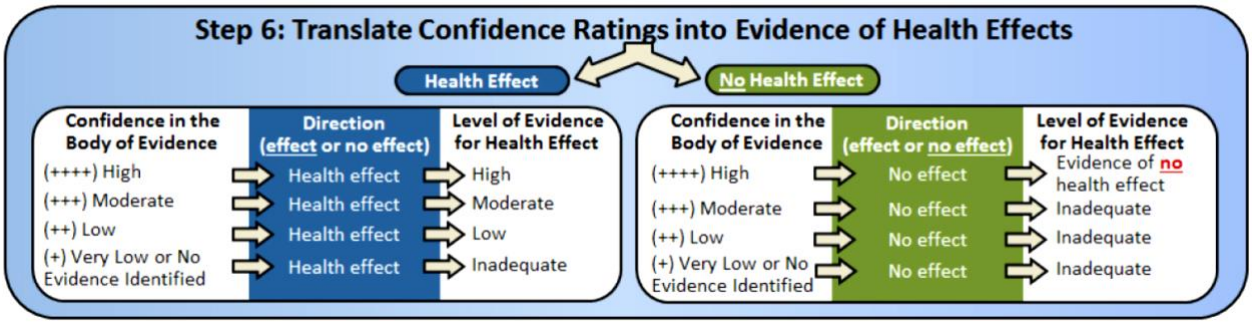


Figure 2: OHAT's method to translate confidence in the body of evidence to come to a conclusion on the level of evidence for a health effect. [77] This step is missing from the Carbon Tetrachloride Draft Risk Evaluation. [78]

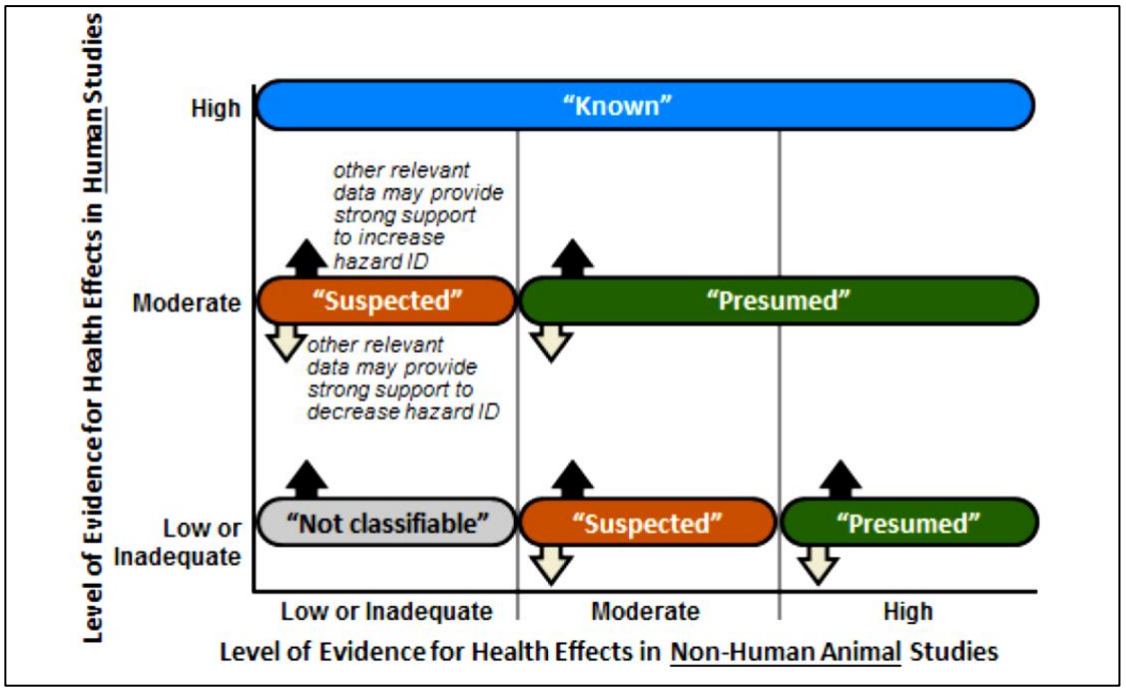


Figure 3: OHAT's process to translate the level of evidence for a health effect into a hazard identification conclusion. This step is missing from the Carbon Tetrachloride Draft Risk Evaluation. [79]

In the Carbon Tetrachloride draft risk evaluation EPA does not rate the confidence in the body of evidence or follow a predefined evidence integration process that transparently demonstrates how it arrived at is its final conclusion. Therefore, it is unclear how EPA translated the available evidence into its final conclusion. Therefore, EPA must immediately implement an evidence integration method that is consistent with best practice in systematic review and transparently present how the conclusions were reached.

[77] 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. Pg. 64

[78] 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. Pg. 64.

[79] 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. Pg. 67.

j. To address the critical issues in the TSCA systematic review method identified by the SACC in its Peer Review of 1-Bromopropane (1-BP), EPA should immediately use well established systematic review methods for environmental health, such as those of the National Toxicology Program's Office of Health Assessment and Translation or the Navigation Guide developed by the University of California, San Francisco.

EPA is required by TSCA statute to use the 'best available science' and the 'weight of the scientific evidence' to make decisions about the risk due to chemicals. EPA defined the 'weight of the scientific evidence' in its 2017 risk evaluation framework rule: [80]

> "a systematic review method…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**…"

There are several important parts of this definition that ensure EPA has the best evidentiary basis for its decisions. However, as we have highlighted in the previous section of these comments, EPA has failed to comply with its own definition of the 'weight of the scientific evidence' rule. To bridge between systematic reviews in environmental health and the clinical sciences, authoritative bodies, U.S. agencies, and academic scientists have developed and implemented validated, peer-reviewed systematic review methods including the Navigation Guide and the U.S. National Toxicology Program's OHAT. [81,82] The World Health Organization is currently implementing the Navigation Guide systematic review methodology to assess the global burden of work-related injury and disease.[83] Further, both of these methods have been identified as exemplary methods for systematic reviews by the NAS. [84,85,86]

EPA states in the Draft Risk Evaluation for Carbon Tetrachloride that they 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 identification, screening, evaluation and integration of data and information can support timely regulatory decision making under the aggressive timelines of the statute."* [87]

However, if EPA had adhered or used one of these aforementioned methods, the Agency would not have needed to *"make an effort to adopt as many best practices as practicable from the systematic*

[80] 40 CFR 702 Pg. 33733

[81] 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

[82] Woodruff TJ, Sutton P. (2014). The Navigation Guide systematic review methodology: a rigorous and transparent method for translating environmental health science into better health outcomes. Environmental health perspectives. 2014;122(10):100714.

[83] Mandrioli, D., Schlünssen, V., Ádám, B., Cohen, R. A., Colosio, C., Chen, W., … Scheepers, P. T. J. (2018). 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, Pg. 174–185. https://doi.org/10.1016/j.envint.2018.06.005

[84] 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

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

[86] 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.

[87] US EPA. (2020). Carbon Tetrachloride (Methane, Tetrachloro-); Draft Toxic Substances Control Act (TSCA) Risk Evaluation. Pg. 38. Available: EPA Document# EPA-740-R1-8014

review community" or respond to the deficiencies that have once again been highlighted in the Carbon Tetrachloride draft risk evaluation. We urge EPA to immediately use one of these validated, peer reviewed best practice methods for any future draft risk evaluations.

k. EPA continues to use methods that lack transparency to identify "key/ supporting/ influential information," and does not provide the details of the methods for the approach for using the "hierarchy of preferences" to exclude relevant studies.

EPA continues to use its novel hierarchy of preferences, introduced in these draft risk evaluations. The hierarchy of preferences is not part of the TSCA systematic review method document, nor in the scoping or problem formulation documents, and it has not been subject to peer review or public comment.

There has been and continues to be a lack of clarity on how EPA chose and evaluated the key sources, which at their time of incorporation outweigh the results from EPA's screening process. We have previously given comments on multiple risk evaluations about how EPA has **failed to have a consistent protocol** despite the risk evaluation rule laying out a **clear** guidance. [88,89,90]

There is a lack of clarity on how EPA came to its decisions about which studies it chose to exclude and which to include in its supplemental information. This pattern obscures the evidence base for this draft risk evaluation and potentially leading to biased results.

l. The draft risk evaluation invokes Klimisch scores, which has been critiqued on its ability to evaluate study quality.

EPA's draft risk evaluation references Klimisch scores (or ECHA reliability scores) when considering dermal and inhalation risks.[91] In general, the NAS in several reports has recommended against scoring because it is inherently subjective and prone to bias. [92,93]

The Agency invokes these scores particularly when discussing studies described in EPA's IRIS assessment for Carbon Tetrachloride, but they are not present in the IRIS assessment and only seem appear behind studies that score poorly.[94] Instruments such as the Klimisch Score intend to evaluate methodological criteria and data quality for animal studies, but utilize adherence to test guidance and study reporting; this is similar to Good Laboratory Practice which is typically only utilized in industry or government

[88] 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

[89] 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

[90] 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

[91] ECHA. (2011). Guidance on information requirements and chemical safety assessment. Available: https://echa.europa.eu/documents/10162/13643/information_requirements_r4_en.pdf

[92] 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.

[93] Jüni P, Witschi A, Bloch R, Egger M. (1999). The Hazards of Scoring the Quality of Clinical Trials for Meta-analysis. *JAMA.* 282(11). pp1054–1060. doi:10.1001/jama.282.11.1054

[94] US EPA. (2010). Toxocological Review of Carbon Tetrachloride. (CAS No. 56-23-5). Available: https://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?substance_nmbr=20

studies.[95] A systematic review by Bero et al. evaluating 30 instruments for assessing risk of bias in animal studies found that Klimisch et al. was not empirically tested and was also the only instrument used to interpret environmental toxicology data which failed to describe how it or its criteria were derived.[96] Additionally, when the researchers assessed Klimisch scores for risk of bias against 13 criteria, the instrument only met 2 (15%), containing details around the test animal used and dose-response, but failed to include things such as clear inclusion/exclusion criteria, blinding, or considerations of comorbidity. Zoeller and Vandenberg also echoed similar critiques, outlining that Klimisch scores confound GLP tenets such as reporting and recordkeeping with study quality and execution. It is deeply concerning that EPA is invoking potentially biased and non-empirically validated instrument when outlining dermal and inhalation risks from carbon tetrachloride, as it may present issues with regard to internal validity and external generalizability.

m. **EPA must include chemical exposures from air, water, land and all other pathways in the exposure assessment for all populations, regardless of claims of coverage under other environmental statutes.**

We commented on the 1-bromopropane draft risk evaluation, when EPA chose not to evaluate exposure via air. 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.[97] This is of particular concern for potentially exposed and susceptible subpopulations, as we outlined in our recent peer-reviewed commentary in *PLoS Biology*.[98] Carbon tetrachloride in particular has been implicated as a risk-driving chemical for its use in the industrial manufacture of chlorinated compounds.[99,100] Under TSCA, EPA must conduct a comprehensive assessment of exposures, and by failing to consider this pathway, EPA will miss potentially exposed or susceptible sub-populations within the general population.

On page 94 of the Draft Risk Evaluation, EPA states that it is:

"not evaluating any exposure pathways to human receptors (i.e., general population) from environmental releases and waste streams associated with industrial/commercial activities for carbon tetrachloride which result in releases to the following pathways: ambient air pathway (carbon tetrachloride is listed as a Hazardous Air Pollutant (HAP) in the Clean Air Act (CAA))…" [101]

[95] Myers, J. P., Saal, F. S. V., Akingbemi, B. T., Arizono, K., Belcher, S., Colborn, T., … Zoeller, R. T. (2009). Why Public Health Agencies Cannot Depend on Good Laboratory Practices as a Criterion for Selecting Data: The Case of Bisphenol A. *Environmental Health Perspectives*, *117*(3), 309–315. doi: 10.1289/ehp.0800173.

[96] Krauth, D., Woodruff, T. J., & Bero, L. (2013). Instruments for Assessing Risk of Bias and Other Methodological Criteria of Published Animal Studies: A Systematic Review. *Environmental Health Perspectives*, *121*(9), 985–992. doi: 10.1289/ehp.1206389.

[97] 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

[98] 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

[99] California Air Resources Board. (2020). Carbon Tetrachloride at Memorial Academy. Retrieved from https://ww3.arb.ca.gov/ch/aq_result/barriologan/barriologan_ccl4.htm

[100] James, W., Jia, C., & Kedia, S. (2012). Uneven magnitude of disparities in cancer risks from air toxics. *International journal of environmental research and public health*, *9*(12), 4365–4385. https://doi.org/10.3390/ijerph9124365

[101] US EPA. (2020). Toxic Substances Control Act (TSCA) Science Advisory Committee on Chemicals Review of Risk Evaluation for Carbon Tetrachloride, CCl4 Risk Evaluation Draft Public. Pg. 94. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0499-0014

Because of this unsubstantiated claim, EPA failed to include a single source for Environmental Exposures to Carbon Tetrachloride, as "none were determined to be relevant to the draft risk evaluation through the data screening process." [102] This incorrect determination that emissions are not in scope removes from consideration a significant number of high-quality studies, as outlined in EPA's supplement on Environmental releases and is deeply concerning. Environmental pathways play a major role in contributing to aggregate exposures and EPA's exclusion of them means that the Agency is not able to accurately assess risks, including to potentially exposed or susceptible sub-populations.

We have commented previously, about EPA's move to exclude "exposure pathways under other environmental statutes, administered by EPA, which adequately assess and effectively manage exposures and for which long-standing regulatory and analytical processes already exist, i.e., the Clean Air Act (CAA), the Safe Drinking Water Act (SDWA), the Clean Water Act (CWA) and the Resource Conservation and Recovery Act (RCRA)." [103] And we find several scientific problems with this approach.

EPA states that inhalation exposures are "effectively managed" under other statutes, implying that these exposures do not present an unreasonable risk—but EPA did not provide any evidence to support this claim. Further, in its 2014 National Air Toxics Assessment EPA acknowledged that "[m]ost risk from NATA background concentrations is from carbon tetrachloride,"[104] due to the fact that despite its few emissions sources, carbon tetrachloride has a half-life of 30 years.[105] In fact, a review of EPA's air toxics data reveals that every census tract in the U.S. has excess cancer risk of about 3.5 in a million due to carbon tetrachloride in the air— this is 3 times greater than what EPA typically considers an unreasonable cancer risk.[106]

We can't know if exposure risks to the general population will be effectively managed under the Clean Air Act. The first step is setting the Maximum Achievable Control Technology (MACT) standard, which for hazardous air pollutants under the Clean Air Act does not require a risk evaluation. Under this regulatory scheme, the mandate is for the standard to achieve the reduction in emissions possible, considering technology, costs, and energy requirements.[107] After the promulgation of the MACT standard, under the legal requirements for the Clean Air Act, it would take EPA 8 years to evaluate *residual* risk (which is the next step after the MACT standard) to the population and, if necessary, create a stricter standard. [108] During the 8 years, people will continue to be exposed to harmful chemical levels.

Unlike the Clean Air Act, under TSCA, EPA must conduct a risk evaluation to determine if an unreasonable risk exists, without consideration of costs or other non-risk factors, including to potentially exposed or susceptible sub-populations. If an unreasonable risk exists, TSCA mandates that EPA make a rule to remove the unreasonable risk, [109] and prevent the continued exposure of populations to this carcinogen and hazardous air pollutant.

[102] US EPA. (2020). Toxic Substances Control Act (TSCA) Science Advisory Committee on Chemicals Review of Risk Evaluation for Carbon Tetrachloride, CCl4 Risk Evaluation Draft Public. Pg. 42. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0499-0014

[103] US EPA. (2020). Toxic Substances Control Act (TSCA) Science Advisory Committee on Chemicals Review of Risk Evaluation for Carbon Tetrachloride, Problem Formulation of the Risk Evaluation for Carbon Tetrachloride (Methane, Tetrachloro-) CASRN: 56-23-5. Available: https://www.regulations.gov/document?D=EPA-HQ-OPPT-2016-0733-0068

[104] US EPA. (2018). Technical Support Document EPA's 2014 National Air Toxics Assessment. Office of Air Quality Planning and Standards, Research Triangle Park. Available: https://www.epa.gov/sites/production/files/2018-09/documents/2014_nata_technical_support_document.pdf

[105] ATSDR. (2017). CASE STUDIES IN ENVIRONMENTAL MEDICINE (CSEM), CARBON TETRACHLORIDE TOXICITY. Available: https://www.atsdr.cdc.gov/csem/carbon_tetrachloride/docs/Carb_Tet-H.pdf

[106] US EPA. (2011). National Air Toxics Assessment: 2011 NATA Assessment Results, Pollutant Specific Results: Carbon Tetrachloride. Available: https://www.epa.gov/national-air-toxics-assessment/2011-nata-assessment-results#pollutant

[107] 42 USC §7412 (d)(2)-(3)

[108] 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

[109] 15 USC §2605

Congress was aware of these other environmental statutes as the time of the passage of the 2016 amendments to TSCA and did not provide an exemption where other statutes addressed chemicals. On the contrary, the TSCA law directs EPA to conduct a risk evaluation that includes all exposures to determine if an unreasonable risk exists, and if it does, enact rules to remove the unreasonable risk. Additionally, the 9th circuit ruled that **EPA's rule unambiguously does not grant it discretion to exclude potential exposures to chemicals from its risk evaluations,** (emphasis ours) thus the agency can't exclude, as they have tried to here, the many ways the general population is exposed to chemicals in the air, water, or soil, regardless of whether standards or rules exist under other environmental statutes.[110]

[110] SAFER CHEMICALS, HEALTHY FAMILIES v. U.S. ENVIRONMENTAL PROTECTION AGENCY. UNITED STATES COURT OF APPEALS FOR THE NINTH CIRCUIT. 2019. n.d. Web. 18 Mar. 2020. Available: http://cdn.ca9.uscourts.gov/datastore/opinions/2019/11/14/17-72260.pdf