September 11, 2023

Comments from University of California, San Francisco Program on Reproductive Health and the Environment on the Carbon Tetrachloride Rulemaking under TSCA section 6(a)

Submitted online via Regulations.gov to docket EPA-HQ-OPPT-2020-0592-0008

These comments are submitted on behalf of the University of California, San Francisco Program on Reproductive Health and the Environment. We declare collectively that we have no direct or indirect financial or fiduciary interest in any chemical or product that is the subject of these comments. 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 proposed risk management rule ("Proposed Rule") for carbon tetrachloride,[1] issued under EPA's Toxic Substances Control Act ("TSCA"). Carbon tetrachloride is a pervasive high production volume solvent; over 142 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.[2,3] Carbon tetrachloride is a carcinogen, a Hazardous Air Pollutant (HAP) under the Clean Air Act, and does not naturally occur in the environment.[4] EPA has found that exposures to carbon tetrachloride in the air occur in every community in the U.S., including those with no nearby sources of emissions, at levels posing a cancer risk of greater than 1-in-1,00,000.[5] Carbon tetrachloride in ambient air poses greater cancer risks than every other HAP except formaldehyde.[6] Carbon tetrachloride also presents several non-cancer health hazards such as adverse reproductive effects, liver and kidney toxicity, and neurological harm.

EPA previously determined that carbon tetrachloride, as a whole chemical, poses unreasonable risk of injury to human health,[7] and is therefore required under TSCA section 6(a) to promulgate a regulation to ensure that "the chemical no longer presents [unreasonable] risk."[8] EPA has now proposed a rule that would allow all ongoing uses of carbon tetrachloride to continue, subject to a Workplace Chemical Protection Program ("WCPP"). EPA indicates that it expects the WCPP to "reduce exposures to CTC" to eliminate unreasonable risk;[9] however this is not enough as EPA has a legal obligation to ensure that the final rule does eliminate unreasonable risk.[10]

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[1] Carbon Tetrachloride (CTC); Regulation Under the Toxic Substances Control Act (TSCA), 88 Fed. Reg. 49,180 (proposed July 28, 2023) (to be codified at 40 C.F.R. 751).

[2] US EPA. (2020). Risk Evaluation for Carbon Tetrachloride (Methane, Tetrachloro-). p 31. Available: https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/final-risk-evaluation-carbon-tetrachloride#documents

[3] ATSDR. (2005). *Toxicological Profile for Carbon Tetrachloride*. p. 187. Available: https://www.atsdr.cdc.gov/toxprofiles/tp30.pdf.

[4] US EPA. (2022). Initial List of Hazardous Air Pollutants with Modifications. Available: https://www.epa.gov/haps/initial-list-hazardous-air-pollutants-modifications

[5] EPA, 2019 AirToxScreen National Cancer Risk by Pollutant, https://www.epa.gov/system/files/documents/2022-12/2019_National_CancerRisk_by_tract_poll.xlsx (last visited Aug. 18, 2023).

[6] EPA, 2019 AirToxScreen National Cancer Risk by Pollutant, https://www.epa.gov/system/files/documents/2022-12/2019_National_CancerRisk_by_tract_poll.xlsx (last visited Aug. 18, 2023).

[7] US EPA. (2020). Risk Evaluation for Carbon Tetrachloride (Methane, Tetrachloro-). Available: https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/final-risk-evaluation-carbon-tetrachloride#documents

[8] 15 U.S.C. §2605(a)

[9] Carbon Tetrachloride (CTC); Regulation Under the Toxic Substances Control Act (TSCA), 88 Fed. Reg. 49,180 p. 49,195 (proposed July 28, 2023) (to be codified at 40 C.F.R. 751).

[10] 15 U.S.C. § 2605(a).

EPA's decisions regarding carbon tetrachloride regulation under TSCA, including the determination of a workplace exposure limit and assessment of health benefits to workers and fenceline communities, should be informed by a quantitative analysis of non-cancer health effects, as recommended by the National Academies.[11] This is a more scientifically appropriate approach to risk estimation than EPA's current methods and constitutes the best available science.

As part of its rulemaking activities, EPA conducted an analysis of exposure and risks to residents of fenceline communities who live near facilities releasing carbon tetrachloride to the air. Based on this analysis, EPA concluded that it could not "rule out unreasonable risk to fenceline communities."[12] Peer review of the fenceline assessment methodology by EPA's Scientific Advisory Committee on Chemicals,[13] and our comments on the proposed TSCA risk management rules for methylene chloride[14] and perchloroethylene,[15] have identified critical deficiencies in EPA's approach that result in underestimation of risk, which have not been corrected in the carbon tetrachloride analysis. Even using a flawed model likely to underestimate risk, EPA's fenceline analysis of carbon tetrachloride found substantial risks of cancer to fenceline communities; however, EPA's proposed rule includes no actions to address these risks. EPA has not conducted sufficient analysis to demonstrate that the proposed rule will eliminate unreasonable risks to fenceline communities, as required by TSCA.

EPA could address these shortcomings of the Proposed Rule by issuing a near-term prohibition on all conditions of use, which is the only option that would eliminate unreasonable risk to workers and fenceline communities. Alternatively, EPA could specify a time-limited period of continued use for the allowed conditions of use to be followed by prohibition.

Our detailed comments address the following issues:

1. **EPA should apply existing methods to generate quantitative estimates of non-cancer effects from chronic carbon tetrachloride exposures.**

2. **EPA's economic analysis should not use a "lowering factor" to reduce cancer risk reduction estimates without rigorous scientific review.**

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

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

[12] Carbon Tetrachloride (CTC); Regulation Under the Toxic Substances Control Act (TSCA), 88 Fed. Reg. 49,180. p 49,209. (proposed July 28, 2023) (to be codified at 40 C.F.R. 751).

[13] US EPA. (2022). Final Report on Draft TSCA Screening Level Approach for Assessing Ambient Air and Water Exposures to Fenceline Communities Version 1.0.Available: https://www.epa.gov/system/files/documents/2022-01/draft-fenceline-report_sacc.pdf.

[14] US EPA. (2023). Methylene Chloride; Rulemaking under TSCA section 6(a). Comment submitted by Program on Reproductive Health and the Environment, University of California, San Francisco et al. Available: https://www.regulations.gov/comment/EPA-HQ-OPPT-2020-0465-0282

[15] US EPA. (2023). Perchloroethylene (PCE); Rulemaking under TSCA Section 6(a). Comment submitted by University of California, San Francisco Program on Reproductive Health and the Environment (UCSF PRHE) et al. Available: https://www.regulations.gov/comment/EPA-HQ-OPPT-2020-0720-0283

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DETAILED COMMENTS

1. EPA should apply existing methods to generate quantitative estimates of non-cancer health effects from chronic carbon tetrachloride exposures.

EPA's methods for non-cancer risk assessment do not provide a quantitative estimate of risk at all exposure levels, and therefore the magnitude of risk reduction or benefits provided by the proposed action cannot be calculated for non-cancer endpoints.

The analyses supporting EPA's Proposed Rule for carbon tetrachloride maintain the risk characterization methods used for non-cancer effects in the risk evaluation, which rely on calculation of a margin of exposure ("MOE"), defined as:

> Margin of Exposure = Non-cancer point of departure / Human exposure.[16]

The MOE approach is a scientifically inappropriate approach for characterizing risk and is inconsistent with TSCA's requirements to use the "best available science" and to ensure protection of "potentially exposed and susceptible subpopulations" ("PESS"). The MOE, which

[16] US EPA. (2020). Risk Evaluation for Carbon Tetrachloride (Methane, Tetrachloro-). p 190. Available: https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/final-risk-evaluation-carbon-tetrachloride#documents

relies on a point of departure ("POD") with no extrapolation to lower doses, is a simplistic approach that only compares the POD to the exposure level and judges whether this ratio "indicates potential risk to human health" or "suggests that the risks are negligible."[17] The MOE does not estimate the proportion of the exposed population projected to experience a specified health endpoint or the number of individuals affected, and it perpetuates the scientifically flawed notion that a "safe" or "no risk" level of chemical exposure exists and can be identified for a diverse exposed population.[18,19] In addition, the values used to determine whether there is a "sufficient" MOE are not scientifically supported; for example, the 10-fold factor used to represent human variability has been identified by the National Academies of Sciences, Engineering, and Medicine ("NAS") and scientific experts as an underestimate and insufficient to protect the population from chemical exposures.[20,21] The NAS[22] and the World Health Organization ("WHO")[23] outlined superior methods for risk estimation that have been demonstrated in peer-reviewed journal publications[24,25 26,27,28] and represent the "best available science" for estimating non-cancer risk.

We applied the WHO methodology, using data from EPA's risk evaluation, to estimate the risks of adverse non-cancer liver effects (fatty changes in the liver). Detailed calculations are provided in the Technical Appendix to these comments. Application of the WHO methodology indicates that the risks of adverse non-cancer liver effects at existing occupational exposure levels reported in the carbon tetrachloride risk evaluation are high, as multiple conditions of use have estimated high-end exposures well in excess of the level associated with 1% incidence of effects.

Our analysis finds that:

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[17] US EPA. (2020). Risk Evaluation for Carbon Tetrachloride (Methane, Tetrachloro-). p 190. Available: https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/final-risk-evaluation-carbon-tetrachloride#documents

[18] Woodruff, T. J., Rayasam, S. D. G., Axelrad, D. A., Koman, P. D., Chartres, N., Bennett, D. H., Birnbaum, L. S., Brown, P., Carignan, C. C., Cooper, C., Cranor, C. F., Diamond, M. L., Franjevic, S., Gartner, E. C., Hattis, D., Hauser, R., Heiger-Bernays, W., Joglekar, R., Lam, J., . . . Zeise, L. (2023). A science-based agenda for health-protective chemical assessments and decisions: overview and consensus statement. Environ Health, 21(Suppl 1), 132. https://doi.org/10.1186/s12940-022-00930-3

[19] McGartland, A., Revesz, R., Axelrad, D. A., Dockins, C., Sutton, P., Woodruff, T. J. (2017). Estimating the health benefits of environmental regulations. Science, 357(6350), 457-458. https://doi.org/10.1126/science.aam8204

[20] National Research Council. (2009).Table 4-1. In Science and decisions: Advancing risk assessment. https://doi.org/10.17226/12209

[21] Varshavsky, J. R., Rayasam, S. D. G., Sass, J. B., Axelrad, D. A., Cranor, C. F., Hattis, D., Hauser, R., Koman, P. D., Marquez, E. C., Morello-Frosch, R., Oksas, C., Patton, S., Robinson, J. F., Sathyanarayana, S., Shepard, P. M., Woodruff, T. J. (2023). Current practice and recommendations for advancing how human variability and susceptibility are considered in chemical risk assessment. Environmental health : a global access science source, 21(Suppl 1), 133. https://doi.org/10.1186/s12940-022-00940-1

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

[23] WHO. (2017). Guidance document on evaluating and expressing uncertainty in hazard characterization. Harmonization project document 11, 2nd edition. https://www.who.int/publications/i/item/9789241513548

[24] Nielsen, G. H., Heiger-Bernays, W. J., Levy, J. I., White, R. F., Axelrad, D. A., Lam, J., Chartres, N., Abrahamsson, D. P., Rayasam, S. D. G., Shaffer, R. M., Zeise, L., Woodruff, T. J., Ginsberg, G. L. (2023). Application of probabilistic methods to address variability and uncertainty in estimating risks for non-cancer health effects. Environ Health, 21(Suppl 1), 129. https://doi.org/10.1186/s12940-022-00918-z

[25] Blessinger, T., Davis, A., Chiu, W. A., Stanek, J., Woodall, G. M., Gift, J., Thayer, K. A., Bussard, D. (2020). Application of a unified probabilistic framework to the dose-response assessment of acrolein. Environ Int, 143, 105953. https://doi.org/10.1016/j.envint.2020.105953

[26] Ginsberg, G. L. (2012). Cadmium risk assessment in relation to background risk of chronic kidney disease. J Toxicol Environ Health A, 75(7), 374-390. https://doi.org/10.1080/15287394.2012.670895

[27] Nielsen, G. H., Heiger-Bernays, W. J., Levy, J. I., White, R. F., Axelrad, D. A., Lam, J., Chartres, N., Abrahamsson, D. P., Rayasam, S. D. G., Shaffer, R. M., Zeise, L., Woodruff, T. J., Ginsberg, G. L. (2023). Application of probabilistic methods to address variability and uncertainty in estimating risks for non-cancer health effects. Environ Health, 21(Suppl 1), 129. https://doi.org/10.1186/s12940-022-00918-z

[28] Chiu WA, Axelrad DA, Dalaijamts C, Dockins C, Shao K, Shapiro AJ, Paoli G. Beyond the RfD: broad application of a probabilistic approach to improve chemical dose-response assessment for non-cancer effects. Environmental Health Perspectives, 2018 June;126(6):067009. doi:10.1289/EHP3368

- In EPA's risk characterization, the point of departure for non-cancer effects (fatty changes in the liver) is 31.1 mg/m^3, and the benchmark MOE is 30.[29] Therefore, EPA concludes that "risks are negligible" for exposures at or below 1.04 mg/m^3 (31.1 mg/m^3 / 30 = 1.04 mg/m^3). However, using the WHO methodology, at that exposure level the risk of fatty changes in the liver can be as high as 0.33%, or 1-in-300.
- According to EPA, current occupational exposure central tendency estimates range from 0.5 – 0.89 mg/m^3 (8-hr TWA), depending on the condition of use. [30] For the higher-exposure conditions of use, using the WHO methodology, risks of non-cancer liver effects at central tendency exposures are up to 0.25%, or 1-in-400.
- EPA estimates that high-end occupational exposures range from 1.0 - 4.0 mg/m^3 (8-hr TWA), depending on the condition of use.[31] High-end occupational risks of non-cancer liver effects using the WHO methodology are as high as 0.33% (1-in-300) to greater than 3.33% (1-in-30).
- At EPA's proposed workplace exposure limit (existing chemical exposure level, or "ECEL") of 0.2 mg/m^3 (8-hr TWA),[32] the risk of fatty changes in the liver using the WHO methodology are 1-in-10,000. The proposed ECEL is based on cancer risks. EPA derived an alternate ECEL value based on non-cancer risk of 1 mg/m^3. At this exposure level, risk of fatty changes in the liver using the WHO methodology are as high as 1-in-300 workers.

These results are just a brief illustration of the information that can be obtained from the application of the WHO methodology and should be a critical input to EPA's risk management decisions under TSCA. It is important to note that the data used for human variability in this analysis, a critical input for risk estimation, may understate the extent of human variability and thus underestimate risk (see Technical Appendix for discussion).

Multiple carbon tetrachloride conditions of use have estimated central-tendency exposures above the level associated with 1-in-1,000 risk (0.6 mg/m^3) and high-end exposures well in excess of the level associated with 1% incidence of fatty changes in the liver (1.8 mg/m^3). Exposure levels for the conditions of use with the greatest number of workers are shown in the following table.

[29] US EPA. (2020). Risk Evaluation for Carbon Tetrachloride (Methane, Tetrachloro-). Table 3-6. Available: https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/final-risk-evaluation-carbon-tetrachloride#documents

[30] US EPA. (2020). Risk Evaluation for Carbon Tetrachloride (Methane, Tetrachloro-). Table 2-21. Available: https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/final-risk-evaluation-carbon-tetrachloride#documents

[31] US EPA. (2020). Risk Evaluation for Carbon Tetrachloride (Methane, Tetrachloro-). Table 2-21. Available: https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/final-risk-evaluation-carbon-tetrachloride#documents

[32] Carbon Tetrachloride (CTC); Regulation Under the Toxic Substances Control Act (TSCA), 88 Fed. Reg. 49,180. p 49,194. (proposed July 28, 2023) (to be codified at 40 C.F.R. 751).

Occupational exposure summary for selected carbon tetrachloride conditions of use with high-end exposures greater than level (1.8 mg/m^3) associated with 1% risk of adverse non-cancer liver effects				
Condition of Use	**Number of Workers[a]**	**Exposure: Central Tendency (mg/m^3 8-hr TWA)[b]**	**Exposure: High-End (mg/m^3 8-hr TWA)[b]**	**EPA's Proposed Risk Management Action[c]**
Manufacturing	2,100	0.76	4.0	WCPP
Processing as a Reactant or Intermediate	3,400	0.76	4.0	WCPP
Industrial Processing Aid	3,900	0.89	2.92	WCPP
WCPP = Workplace Chemical Protection Program [a] U.S. EPA (2023). Economic Analysis of the Proposed Regulation of Carbon Tetrachloride Under TSCA Section 6(a), Table ES-3. [b] US EPA (2020). Risk Evaluation for Carbon Tetrachloride, Table 2-21. [c] Carbon Tetrachloride (CTC): Regulation Under the Toxic Substances Control Act (TSCA). Proposed Rule. 88 FR 49180, July 28, 2023.				

This analysis indicates there are a significant number of workers with very high risk of adverse non-cancer liver effects at baseline exposures; EPA can use the risk calculations presented in the Technical Appendix to these comments along with the reported exposure levels and number of workers to estimate the number of workers with adverse non-cancer liver effects and the reduction in affected workers due to the proposed risk management actions.

Given that baseline high-end exposures for some COUs are more than two times the levels associated with 1% risk, it is likely that there are workers for whom fatty changes in the liver have led to more advanced liver effects, such as non-alcoholic fatty liver disease – a monetizable endpoint relevant to EPA's risk management activities. The economic analysis for the proposed methylene chloride rule correctly observed that reduced incidence of non-alcoholic fatty liver disease is among the anticipated benefits of that rule,[33] and this is also true of the carbon tetrachloride proposed rule. If there are any workplaces where employees are exposed to both methylene chloride and carbon tetrachloride, their risk of non-cancer liver effects, including the possibility of non-alcoholic fatty liver disease, will be significantly elevated from the risks estimated for each chemical in isolation.

This analysis considers only one of the non-cancer health effects of carbon tetrachloride identified by EPA. EPA should apply the WHO methodology to all non-cancer hazards (central nervous system effects, kidney toxicity, reproductive and developmental toxicity, irritation and

[33] US EPA (2023). Economic Analysis of the Proposed Regulation of Methylene Chloride Under TSCA Section 6(a). Section 8.9.1 "Fatty liver disease". Available: https://www.regulations.gov/document/EPA-HQ-OPPT-2020-0465-0175

sensitization, and genetic toxicity) to ensure that all health risks and all health benefits are accounted for in the risk management decision.

EPA should apply the WHO methodology to non-cancer hazards in the TSCA program to inform its unreasonable risk determinations, the analysis of benefits of regulatory alternatives, and (when workplace chemical protections are proposed for uses that are not prohibited) to determine the level of an ECEL.

2. EPA's economic analysis should not use a "lowering factor" to reduce cancer risk reduction estimates without rigorous scientific review.

EPA's economic analysis uses two methods for calculating the estimated cancer risk reduction from the Proposed Rule. One method applies a scientifically unsupported "lowering factor" to reduce the projected cancer benefits of the Proposed Rule with a particular impact on older populations. [34] EPA's explanation of the lowering factor is extremely brief and unclear, but it appears that this method applies novel and scientifically unsupported assumptions that the cancer risk reduction per year of reduced or eliminated exposure declines as age increases. This is not only incorrect, as advanced age is a risk factor for many cancers,[35] but it results in underestimation of the cancer benefits. For adrenal cancers from carbon tetrachloride, the lowering factor reduces cancer risk reduction estimates by almost half. This novel method does not appear to be scientifically-based, as the only citation provided for this approach is EPA's 2013 economic analysis of standards for formaldehyde in composite wood products,[36] which, like the Proposed Rule, was issued by the Office of Chemical Safety and Pollution Prevention. EPA does not cite any scientific publications, and there is no indication that this proposed "lowering factor" approach has been peer reviewed or otherwise subject to scrutiny by scientific experts. This goes directly against EPA's mandate under TSCA to evaluate risk in a manner consistent with the "best available science." The flawed application of a "lowering factor" disproportionately reduces estimated benefits to older populations. EPA should not apply this approach to its benefits analysis, or any other assessment, until it has been reviewed and supported by a rigorous scientific review. Additionally, EPA should apply the excess lifetime risk regardless of age when determining the benefits from the Proposed Rule, as has been standard practice.

[34] US EPA (2023). Economic Analysis of the Proposed Regulation of Carbon Tetrachloride Under TSCA Section 6(a). p 4-13. Available: https://www.regulations.gov/document/EPA-HQ-OPPT-2020-0592-0121

[35] National Cancer Institute. (2021). Age and Cancer Risk. Available: https://www.cancer.gov/about-cancer/causes-prevention/risk/age

[36] US EPA (2013). Economic Analysis of the Formaldehyde Standards for Composite Wood Products Act Implementing Regulations Proposed Rule. Office of Chemical Safety and Pollution Prevention. Available: https://www.regulations.gov/document/EPA-HQ-OPPT-2016-0461-0037

Technical Appendix: Analysis of carbon tetrachloride non-cancer risk using WHO/IPCS methodology

In the TSCA risk evaluation of carbon tetrachloride, EPA selected fatty changes in the liver from a chronic study of rats for estimation of risks from chronic inhalation exposures.

For risk characterization of non-cancer health effects, the TSCA risk evaluation calculates a "margin of exposure" (MOE) for each exposure scenario, which is the ratio of the point of departure (POD) to the exposure level. For carbon tetrachloride, the TSCA risk evaluation concluded that an MOE of 30 or more "suggests that the risks are negligible" and a lower MOE "indicates potential risk to human health."[37] EPA's approach to risk characterization does not actually estimate risks of adverse effects in the population with chronic exposure to carbon tetrachloride, but instead simply applies a "bright line" judgment of whether or not the MOE is adequate. A more informative approach for both risk characterization and risk management would be to apply the probabilistic dose-response assessment methods of the International Programme on Chemical Safety (IPCS),[38] part of the World Health Organization (WHO), to estimate the risk of adverse effects at various levels of exposure. The IPCS methodology has previously been described and applied in several peer-reviewed journal articles.[39,40,41,42,43]

We applied the IPCS approach for "quantal-deterministic" endpoints and the "approximate probabilistic" calculation (see IPCS report Fig 3.5, panel C)[44] to estimate risks of fatty changes in the liver from chronic inhalation exposure to carbon tetrachloride. The analysis involved the following steps:

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

[37] US EPA. (2020). Risk Evaluation for Carbon Tetrachloride (Methane, Tetrachloro-). p 190. Available: https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/final-risk-evaluation-carbon-tetrachloride#documents

[38] World Health Organization. Guidance document on evaluating and expressing uncertainty in hazard characterization. IPCS harmonization project document; no. 11. 2014.

[39] Chiu WA, Slob W. A Unified Probabilistic Framework for Dose–Response Assessment of Human Health Effects. Environmental Health Perspectives, 2015 December;123(12): 1241–1254. doi:10.1289/ehp.1409385

[40] Nielsen GH, Heiger-Bernays WJ, Levy JI, White RF, Axelrad DA, Lam J, Chartres N, Abrahamsson D.P, Rayasam SDG, Shaffer RM, Zeise, L, Woodruff TJ, Ginsberg GL. (2023). Application of probabilistic methods to address variability and uncertainty in estimating risks for non-cancer health effects. Environ Health, 21(Suppl 1), 129. https://doi.org/10.1186/s12940-022-00918-z

[41] Chiu WA, Axelrad DA, Dalaijamts C, Dockins C, Shao K, Shapiro AJ, Paoli G. Beyond the RfD: broad application of a probabilistic approach to improve chemical dose-response assessment for non-cancer effects. Environmental Health Perspectives, 2018 June;126(6):067009. doi:10.1289/EHP3368

[42] Blessinger T, Davis A, Chiu WA, Stanek J, Woodall GM, Gift J, Thayer KA, Bussard D. Application of a unified probabilistic framework to the dose-response assessment of acrolein. Environment International, 2020 October;143:105953. doi: 10.1016/j.envint.2020.105953

[43] Chiu WA, Paoli GM. Recent Advances in Probabilistic Dose–Response Assessment to Inform Risk-Based Decision Making. Risk Analysis, 2021 April;41(4):596-609. doi: 10.1111/risa.13595

[44] World Health Organization. Guidance document on evaluating and expressing uncertainty in hazard characterization. IPCS harmonization project document; no. 11. 2014.

STEP 1: Derivation of IPCS POD and corresponding uncertainty adjustments

The IPCS methodology requires the use of an ED_{50} (median effective dose) value as the point of departure (POD) for quantal-deterministic endpoints. Since an ED_{50} is not available from the EPA risk evaluation, we began with EPA's benchmark concentration, lower confidence limit (BMCL) values and applied adjustments provided by the IPCS methodology. At the same time, we incorporated quantitative uncertainties as recommended by IPCS for each of these adjustments.

The benchmark dose used in the TSCA risk evaluation was originally developed in EPA's Integrated Risk Information System (IRIS) assessment of carbon tetrachloride. EPA used a benchmark response (BMR) of 10% to derive the BMCL and applied a toxicokinetic adjustment to represent a human equivalent concentration (HEC). For the TSCA risk evaluation, the chronic non-cancer $BMCL_{10}$ (HEC) value for continuous exposure was adjusted to an 8-hour time weighted average (TWA) to represent occupational exposure, and is 31.1 mg/m^3.[45]

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

- $BMC_{10} = BMCL_{10} \times (BMC_{10} / BMCL_{10})$

This adjustment requires computation of the $BMC_{10} / BMCL_{10}$ ratio. The necessary values for this ratio were obtained from IRIS assessment of carbon tetrachloride.[46] Since BMC_{10} values are available only before application of final adjustments to derive the HEC, both the BMC and BMCL values prior to these adjustments were used in calculating the ratios. Due to uncertainties in the toxicokinetic adjustments, the IRIS assessment presents two pairs of BMC and BMCLs (in units of μmol/hr/kg liver) that were used to derive the HEC. Each pair provides the same ratio:

- $BMC_{10} / BMCL_{10} = 3.26 / 2.59 = 1.26$
- $BMC_{10} / BMCL_{10} = 4.60 / 3.65 = 1.26$

With this ratio, the BMC_{10} in HEC units can be calculated:

- BMC_{10} (HEC) $= BMCL_{10}$ (HEC) x $(BMC_{10} / BMCL_{10}) = 31.1\ mg/m^3 \times 1.26 = 39.1\ mg/m^3$

Uncertainty in the BMC_{10} in the IPCS methodology, represented by the ratio of 95th percentile to 50th percentile (P95/P50), is provided by the same ratio of $BMC_{10} / BMCL_{10}$, or 1.26.

The second POD adjustment is to convert from the BMC_{10} to an ED_{50}. The ED_{50} and its uncertainty are determined by applying the following conversion from Chiu et al. 2018: "if

[45] US EPA. (2020). Risk Evaluation for Carbon Tetrachloride (Methane, Tetrachloro-). Table 3-6. Available: https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/final-risk-evaluation-carbon-tetrachloride#documents

[46] U.S. EPA. (2010). Toxicological Review of Carbon Tetrachloride, Table 5-6. Available: https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=225974

ED50 not reported: BMD at the reported BMR is multiplied by an additional factor of 3.0; additional uncertainty through adding 1.5^2 to $(P95/P50)^2$."[47]

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

Determination of point of departure (POD) and its uncertainty[a] for probabilistic dose-response analysis of chronic carbon tetrachloride inhalation:[b] fatty changes in the liver		
Aspect	**P50**	**P95/P50**
BMC_{10} (HEC)	39.1 mg/m^3	1.26
BMC_{10}-to-ED_{50} adjustment	3	1.5
IPCS POD = ED_{50} (HEC)	**117.4 mg/m^3**	**1.59[c]**

[a] Uncertainty is expressed as the ratio of the 95th percentile (P95) to the 50th percentile (P50)
[b] 8-hour time-weighted average
[c] (Composite P95/P50) = $10^{[(\log 1.26)^2 + (\log 1.5)^2]^{0.5}} = 1.59$

Step 2: Application of interspecies (animal-to-human) adjustments

For interspecies (animal-to-human) adjustments, the IPCS methodology first considers a factor for body-size scaling, and then a factor for remaining toxicokinetic (TK) and toxicodynamic (TD) differences. Since the determination of the EPA $BMCL_{10}$ value incorporated dosimetric adjustments, no further adjustment for body size is necessary (P50 = 1). The uncertainty in the bodyweight scaling is not quantified in this analysis (P95/P50 = 1).

For the TK/TD differences remaining after bodyweight scaling, the IPCS report recommends a central estimate (P50) of 1 (i.e., no additional interspecies differences) and representing uncertainty with a P95/P50 factor of 3.[48] We incorporated these IPCS recommendations. The interspecies adjustments are entered In the IPCS approximate probabilistic calculation template as follows:

[47] Chiu WA, Axelrad DA, Dalaijamts C, Dockins C, Shao K, Shapiro AJ, Paoli G. Beyond the RfD: broad application of a probabilistic approach to improve chemical dose-response assessment for non-cancer effects. Environmental Health Perspectives, 2018 June;126(6):067009. Figure 4. doi:10.1289/EHP3368
[48] World Health Organization. Guidance document on evaluating and expressing uncertainty in hazard characterization. IPCS harmonization project document; no. 11. Table 4-3. 2014.

Interspecies adjustments for probabilistic dose-response analysis of chronic carbon tetrachloride inhalation: fatty changes in the liver		
Aspect	**P50**	**P95/P50**
$AF_{Interspecies\text{-}BS}$	1	1
$AF_{Interspecies\text{-}TK/TD}$	1	3

Step 3: Application of intraspecies (human variability) adjustments

In the IPCS methodology, the value of the human variability adjustment factor ($AF_{intraspecies}$) varies depending on the incidence of the adverse effect in the exposed population – with a larger adjustment factor necessary to extrapolate to lower levels of incidence. The IPCS report provides $AF_{intraspecies}$ for several incidence (I) values. As with the POD, the IPCS methodology uses the P50 as a central estimate and the P95/P50 as a measure of uncertainty for each value of I. $AF_{intraspecies}$ values provided by IPCS for several values of I, along with an additional value of I of interest for this analysis, are provided in the following table:

Lognormal approximation of uncertainty distributions for intraspecies variability for varying levels of population incidence (I)		
Incidence (I)	**$AF_{intraspecies}$**	
	P50	**P95/P50**
5%[a]	4.98	2.82
3.33%[b]	5.99	3.17
1%[a]	9.69	4.32
0.5%[a]	12.36	5.06
0.33% (1-in-300)[b]	14.17	5.53
0.25% (1-in-400) [b]	15.48	5.85
0.1% (1-in-1,000)[a]	20.42	6.99
0.01% (1-in-10,000)[a]	37.71	10.39

[a] IPCS Table 4.5
[b] Calculated for this analysis using the same methods that were used to derive IPCS Table 4.5

Step 4: Calculation of HD_M^I

The output of the IPCS methodology is generically described as an HD_M^I value – the human dose (HD) associated with a particular magnitude of effect (M) at a particular population incidence (I). For this analysis, the "M" represents fatty changes in the liver, and several values of I are used to determine the risk for a range of exposures relevant for carbon tetrachloride. The IPCS approach is a probabilistic method, so the HD_M^I is a distribution; selected values from that distribution are presented in the tables below as follows:

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

The following tables present the results for several values of I (e.g., I = 5%, 1%, etc.) using the POD, $AF_{interspecies}$ and $AF_{intraspecies}$ values shown above. Some values for I were selected to inform the risk characterization section below based on findings of the EPA risk evaluation (e.g., occupational exposure levels) and the level of EPA's proposed workplace exposure limit.

Calculation of HD_M^I for chronic carbon tetrachloride inhalation[a] fatty changes in the liver (Incidence = 5%)		
Aspect	**P50**	**P95/P50**
BMC_{10} (HEC)	39.1 mg/m^3	1.26
BMC_{10}-to-ED_{50} adjustment	3	1.5
IPCS POD = ED_{50} (HEC)	**117.4 mg/m^3**	**1.59**
$AF_{Interspecies-BS}$	1	1
$AF_{Interspecies-TK/TD}$	1	3
$AF_{Intraspecies\ (I=5\%)}$	4.98	2.82
HD_M^I	23.6 mg/m^3 [(b)]	4.86[c]
	P05	**P95**
HD_M^I [(d)]	**4.9 mg/m^3**	115 mg/m^3

[a] 8-hour time-weighted average
[b] HD_M^I (P50) = IPCS POD / ($AF_{Interspecies-BS}$ x $AF_{Interspecies-TK/TD}$ x $AF_{Intraspecies}$)
[c] (Composite P95/P50) = $10^{[(\log 1.59)^2 + (\log 1)^2 + (\log 3)^2 + (\log 2.82)^2]^{0.5}} = 4.86$
[d] HD_M^I (P05) = HD_M^I (P50) / (Composite P95/P50)
HD_M^I (P95) = HD_M^I (P50) x (Composite P95/P50)

Calculation of HD_M^I for chronic carbon tetrachloride inhalation[a] fatty changes in the liver (Incidence = 3.33%)		
Aspect	**P50**	**P95/P50**
BMC_{10} (HEC)	39.1 mg/m^3	1.26
BMC_{10}-to-ED_{50} adjustment	3	1.5
IPCS POD = ED_{50} (HEC)	**117.4 mg/m^3**	**1.59**
$AF_{Interspecies\text{-}BS}$	1	1
$AF_{Interspecies\text{-}TK/TD}$	1	3
$AF_{Intraspecies\ (I=3.33\%)}$	5.99	3.17
HD_M^I	19.6 mg/m^3 [(b)]	5.26[c]
	P05	**P95**
HD_M^I [(d)]	**3.7 mg/m^3**	103 mg/m^3

[a] 8-hour time-weighted average
[b] HD_M^I (P50) = IPCS POD / ($AF_{Interspecies\text{-}BS}$ x $AF_{Interspecies\text{-}TK/TD}$ x $AF_{Intraspecies}$)
[c] (Composite P95/P50) = $10^{[(\log 1.59)^2 + (\log 1)^2 + (\log 3)^2 + (\log 3.17)^2]^{0.5}} = 5.26$
[d] HD_M^I (P05) = HD_M^I (P50) / (Composite P95/P50)
HD_M^I (P95) = HD_M^I (P50) x (Composite P95/P50)

Calculation of HD_M^I for chronic carbon tetrachloride inhalation[a] fatty changes in the liver (Incidence = 1%)		
Aspect	**P50**	**P95/P50**
BMC_{10} (HEC)	39.1 mg/m^3	1.26
BMC_{10}-to-ED_{50} adjustment	3	1.5
IPCS POD = ED_{50} (HEC)	**117.4 mg/m^3**	**1.59**
$AF_{Interspecies\text{-}BS}$	1	1
$AF_{Interspecies\text{-}TK/TD}$	1	3
$AF_{Intraspecies\ (I=1\%)}$	9.69	4.32
HD_M^I	12.1 mg/m^3 [(b)]	6.61[c]
	P05	**P95**
HD_M^I [(d)]	**1.8 mg/m^3**	80 mg/m^3

[a] 8-hour time-weighted average
[b] HD_M^I (P50) = IPCS POD / ($AF_{Interspecies\text{-}BS}$ x $AF_{Interspecies\text{-}TK/TD}$ x $AF_{Intraspecies}$)
[c] (Composite P95/P50) = $10^{[(\log 1.59)^2 + (\log 1)^2 + (\log 3)^2 + (\log 4.32)^2]^{0.5}} = 6.61$
[d] HD_M^I (P05) = HD_M^I (P50) / (Composite P95/P50)
HD_M^I (P95) = HD_M^I (P50) x (Composite P95/P50)

Calculation of HD_M^I for chronic carbon tetrachloride inhalation[a] fatty changes in the liver (Incidence = 0.5%)		
Aspect	**P50**	**P95/P50**
BMC_{10} (HEC)	39.1 mg/m^3	1.26
BMC_{10}-to-ED_{50} adjustment	3	1.5
IPCS POD = ED_{50} (HEC)	**117.4 mg/m^3**	**1.59**
$AF_{Interspecies\text{-}BS}$	1	1
$AF_{Interspecies\text{-}TK/TD}$	1	3
$AF_{Intraspecies\ (I=0.5\%)}$	12.36	5.06
HD_M^I	9.5 mg/m^3 [(b)]	7.49[c]
	P05	**P95**
HD_M^I [(d)]	**1.3 mg/m^3**	71 mg/m^3

[a] 8-hour time-weighted average
[b] HD_M^I (P50) = IPCS POD / ($AF_{Interspecies\text{-}BS}$ x $AF_{Interspecies\text{-}TK/TD}$ x $AF_{Intraspecies}$)
[c] (Composite P95/P50) = $10^{[(\log 1.59)^2 + (\log 1)^2 + (\log 3)^2 + (\log 5.06)^2]^{0.5}} = 7.49$
[d] HD_M^I (P05) = HD_M^I (P50) / (Composite P95/P50)
HD_M^I (P95) = HD_M^I (P50) x (Composite P95/P50)

Calculation of HD_M^I for chronic carbon tetrachloride inhalation[a] fatty changes in the liver (Incidence = 0.33%)		
Aspect	**P50**	**P95/P50**
BMC_{10} (HEC)	39.1 mg/m^3	1.26
BMC_{10}-to-ED_{50} adjustment	3	1.5
IPCS POD = ED_{50} (HEC)	**117.4 mg/m^3**	**1.59**
$AF_{Interspecies\text{-}BS}$	1	1
$AF_{Interspecies\text{-}TK/TD}$	1	3
$AF_{Intraspecies\ (I=0.33\%)}$	14.17	5.53
HD_M^I	8.3 mg/m^3 [(b)]	8.05[c]
	P05	**P95**
HD_M^I [(d)]	**1.0 mg/m^3**	67 mg/m^3

[a] 8-hour time-weighted average
[b] HD_M^I (P50) = IPCS POD / ($AF_{Interspecies\text{-}BS}$ x $AF_{Interspecies\text{-}TK/TD}$ x $AF_{Intraspecies}$)
[c] (Composite P95/P50) = $10^{[(\log 1.59)^2 + (\log 1)^2 + (\log 3)^2 + (\log 5.53)^2]^{0.5}} = 8.05$
[d] HD_M^I (P05) = HD_M^I (P50) / (Composite P95/P50)
HD_M^I (P95) = HD_M^I (P50) x (Composite P95/P50)

Calculation of HD_M^I for chronic carbon tetrachloride inhalation[a] fatty changes in the liver (Incidence = 0.25%)		
Aspect	**P50**	**P95/P50**
BMC_{10} (HEC)	39.1 mg/m^3	1.26
BMC_{10}-to-ED_{50} adjustment	3	1.5
IPCS POD = ED_{50} (HEC)	**117.4 mg/m^3**	**1.59**
$AF_{Interspecies\text{-}BS}$	1	1
$AF_{Interspecies\text{-}TK/TD}$	1	3
$AF_{Intraspecies\ (I=0.25\%)}$	15.48	5.85
HD_M^I	7.6 mg/m^3 [(b)]	8.43[c]
	P05	**P95**
HD_M^I [(d)]	**0.9 mg/m^3**	64 mg/m^3

[a] 8-hour time-weighted average
[b] HD_M^I (P50) = IPCS POD / ($AF_{Interspecies\text{-}BS}$ x $AF_{Interspecies\text{-}TK/TD}$ x $AF_{Intraspecies}$)
[c] (Composite P95/P50) = $10^{[(\log 1.59)^2 + (\log 1)^2 + (\log 3)^2 + (\log 5.85)^2]^{0.5}} = 8.43$
[d] HD_M^I (P05) = HD_M^I (P50) / (Composite P95/P50)
HD_M^I (P95) = HD_M^I (P50) x (Composite P95/P50)

Calculation of HD_M^I for chronic carbon tetrachloride inhalation[a] fatty changes in the liver (Incidence = 0. 1%)		
Aspect	**P50**	**P95/P50**
BMC_{10} (HEC)	39.1 mg/m^3	1.26
BMC_{10}-to-ED_{50} adjustment	3	1.5
IPCS POD = ED_{50} (HEC)	**117.4 mg/m^3**	**1.59**
$AF_{Interspecies\text{-}BS}$	1	1
$AF_{Interspecies\text{-}TK/TD}$	1	3
$AF_{Intraspecies\ (I=0.1\%)}$	20.42	6.99
HD_M^I	5.8 mg/m^3 [(b)]	9.79[c]
	P05	**P95**
$HD_M^{I\ (d)}$	**0.6 mg/m^3**	56 mg/m^3

[a] 8-hour time-weighted average
[b] HD_M^I (P50) = IPCS POD / ($AF_{Interspecies\text{-}BS}$ x $AF_{Interspecies\text{-}TK/TD}$ x $AF_{Intraspecies}$)
[c] (Composite P95/P50) = $10^{[(\log 1.59)^2 + (\log 1)^2 + (\log 3)^2 + (\log 6.99)^2]^{0.5}} = 9.79$
[d] HD_M^I (P05) = HD_M^I (P50) / (Composite P95/P50)
HD_M^I (P95) = HD_M^I (P50) x (Composite P95/P50)

Calculation of HD_M^I for chronic carbon tetrachloride inhalation[a] fatty changes in the liver (Incidence = 0. 01%)		
Aspect	**P50**	**P95/P50**
BMC_{10} (HEC)	39.1 mg/m^3	1.26
BMC_{10}-to-ED_{50} adjustment	3	1.5
IPCS POD = ED_{50} (HEC)	**117.4 mg/m^3**	**1.59**
$AF_{Interspecies\text{-}BS}$	1	1
$AF_{Interspecies\text{-}TK/TD}$	1	3
$AF_{Intraspecies\ (I=0.01\%)}$	37.71	10.39
HD_M^I	3.1 mg/m^3 [(b)]	13.84[c]
	P05	**P95**
$HD_M^{I\ (d)}$	**0.2 mg/m^3**	43 mg/m^3

[a] 8-hour time-weighted average
[b] HD_M^I (P50) = IPCS POD / ($AF_{Interspecies\text{-}BS}$ x $AF_{Interspecies\text{-}TK/TD}$ x $AF_{Intraspecies}$)
[c] (Composite P95/P50) = $10^{[(\log 1.59)^2 + (\log 1)^2 + (\log 3)^2 + (\log 10.39)^2]^{0.5}} = 13.84$
[d] HD_M^I (P05) = HD_M^I (P50) / (Composite P95/P50)
HD_M^I (P95) = HD_M^I (P50) x (Composite P95/P50)

The National Academies and WHO/IPCS have both recommended using the lower confidence limit (LCL) on a probabilistic dose-response distribution for use in decision-making, in place of a traditional reference dose (RfD) or reference concentration (RfC). The National Academies said in *Science and Decisions* that:

> multiple risk-specific doses could be provided in the various risk characterizations that EPA produces to aid environmental decision-making.
>
> A Risk-Specific Reference Dose: For quantal effects, the RfD can be defined to be the dose that corresponds to a particular risk specified to be de minimis (for example, 1 in 100,000) at a defined confidence level (for example, 95%) for the toxicity end point of concern.[49]

The IPCS said:

> the LCL of the HD_M^I can be used as a probabilistic RfD to replace the deterministic RfD. In this case, the probabilistic RfD is the dose that protects the population from a specified magnitude and incidence of effect with a pre-specified per cent coverage (confidence).[50]

[49] National Research Council. (2009). Science and decisions: Advancing risk assessment. p. 140. Available: https://doi.org/10.17226/12209
[50] WHO. (2017). Guidance document on evaluating and expressing uncertainty in hazard characterization. Harmonization project document 11, 2nd edition. p. 12. Available: https://www.who.int/publications/i/item/9789241513548

Consistent with the guidance from the National Academies and the IPCS, we summarize the above results in the following table of the lower confidence limit (5th percentile or P05) risk-specific doses (HD_M^I) for multiple levels of risk (incidence or I).

Risk-specific dose estimates for fatty changes in the liver from exposure to carbon tetrachloride	
Incidence (I)	**HD_M^I lower -confidence limit (P05) (8-hour time-weighted average)**
5%	4.9 mg/m^3
3.33%	3.7 mg/m^3
1%	1.8 mg/m^3
0.5%	1.3 mg/m^3
0.33% (1-in-300)	1.0 mg/m^3
0.25% (1-in-400)	0.9 mg/m^3
0.1% (1-in-1,000)	0.6 mg/m^3
0.01% (1-in-10,000)	0.2 mg/m^3

Risk characterization of carbon tetrachloride non-cancer risks using the probabilistic dose-response analysis

We compared key exposure values from the EPA TSCA carbon tetrachloride risk evaluation and proposed rule to the risk specific doses provided above and found that:

- In EPA's risk characterization, the point of departure for non-cancer risks (fatty changes in the liver) is 31.1 mg/m^3, and the benchmark MOE is 30.[51] Therefore, EPA concludes that "risks are negligible" for exposures at or below 31.1/30 = 1.04 mg/m^3. At that exposure level, risk of fatty changes in the liver may be as high as 0.33%, or 1-in-300.
- According to EPA, current occupational exposure central tendency estimates range from 0.5 – 0.89 mg/m^3 (8-hr TWA), depending on the condition of use.[52] For the higher-exposure conditions of use, risks of non-cancer liver effects at central tendency exposures are up to 0.25%, or 1-in-400.
- EPA estimates that high-end occupational exposures range from 1.0 - 4.0 mg/m^3 (8-hr TWA), depending on the condition of use.[53] High-end occupational risks of non-cancer liver effects therefore are as high as 0.33% (1-in-300) to greater than 3.33% (1-in-30).

[51] US EPA. (2020). Risk Evaluation for Carbon Tetrachloride (Methane, Tetrachloro-). Table 3-6. Available: https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/final-risk-evaluation-carbon-tetrachloride#documents
[52] US EPA. (2020). Risk Evaluation for Carbon Tetrachloride (Methane, Tetrachloro-). Table 2-21. Available: https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/final-risk-evaluation-carbon-tetrachloride#documents
[53] US EPA. (2020). Risk Evaluation for Carbon Tetrachloride (Methane, Tetrachloro-). Table 2-21. Available: https://www.epa.gov/assessing-and-managing-chemicals-under-tsca/final-risk-evaluation-carbon-tetrachloride#documents

- At EPA's proposed workplace exposure limit (existing chemical exposure level, or ECEL) of 0.2 mg/m^3 (8-hr TWA)[54] risk of fatty changes in the liver are 1-in-10,000. The proposed ECEL is based on cancer risks. EPA derived an alternate ECEL value based on non-cancer risk of 1 mg/m^3.[55] At this exposure level, risk of fatty changes in the liver are as high as 1-in-300 workers.

The estimates of HD_M^I developed in this analysis were based entirely on input values available from the WHO/IPCS methodology document and from EPA's IRIS and TSCA assessments of carbon tetrachloride. An important caveat to these calculations is that the values used to represent human variability are likely to be understated. The IPCS default human variability distribution is based on 37 data sets for human toxicokinetic variability and 34 data sets for human toxicodynamic variability. Most of these data sets were obtained from controlled human exposure studies of pharmaceuticals conducted in small samples of healthy adults, representing considerably less variability than found in the general population.[56,57,58] If human variability is underestimated, then the actual dose associated with each incidence level (e.g. I =1%, I = 0.1%) will be lower than the values obtained from this analysis – or in other words, risk at each dose will be underestimated.

[54] Carbon Tetrachloride (CTC); Regulation Under the Toxic Substances Control Act (TSCA), 88 Fed. Reg. 49,180. p 49,194 (proposed July 28, 2023) (to be codified at 40 C.F.R. 751).

[55] U.S. EPA. (2021). Existing Chemical Exposure Limit (ECEL) for Occupational Use of Carbon Tetrachloride. Memorandum from Karen Eisenreich to Erik Winchester. Available: https://www.regulations.gov/document/EPA-HQ-OPPT-2020-0592-0018

[56] WHO. (2017). *Guidance document on evaluating and expressing uncertainty in hazard characterization. Harmonization project document 11, 2nd edition.* https://www.who.int/publications/i/item/9789241513548

[57] Hattis, D., Lynch, M.K. (2007). Empirically observed distributions of pharmacokinetic and pharmacodynamic variability in humans—Implications for the derivation of single-point component uncertainty factors providing equivalent protection as existing reference doses. In Lipscomb, J.C. & Ohanian, E.V. (Eds.), *Toxicokinetics in risk assessment* (pp. 69-93). Taylor & Francis Group. https://doi.org/10.1201/b14275

[58] Axelrad, D. A., Setzer, R. W., Bateson, T. F., DeVito, M., Dzubow, R. C., Fitzpatrick, J. W., Frame, A. M., Hogan, K. A., Houck, K., Stewart, M. (2019). Methods for evaluating variability in human health dose-response characterization. Hum Ecol Risk Assess, 25, 1-24. https://doi.org/10.1080/10807039.2019.1615828