HSIA
halogenated solvents industry alliance, inc.

September 27, 2022

Claudia Menasche
Office of Pollution Prevention and Toxics (7404T)
Environmental Protection Agency
1200 Pennsylvania Ave. NW
Washington, DC 20460–0001

Re: Docket No. EPA-HQ-OPPT-2016-0733

Dear Ms. Menasche:

These comments are submitted on Carbon Tetrachloride (CTC); Draft Revision to Toxic Substances Control Act (TSCA) Risk Determination issued at 87 Fed. Reg. 52766 (August 29, 2022). They are submitted on behalf of the Halogenated Solvents Industry Alliance, Inc. (HSIA), an association of producers and users of CTC. TSCA Section 6(4)(A) requires that "The Administrator shall conduct *risk evaluations pursuant to this paragraph to determine* whether a chemical substance presents an unreasonable risk…" (emphasis added).

These comments describe how the CTC risk evaluation[1] was not conducted *pursuant to*, or in a manner that satisfies, the TSCA risk evaluation requirements in Section 6(4). As a result, there is not an adequate basis for either the initial Risk Evaluation or this proposed revised risk determination.[2] In this regard, we urge EPA to make the corrections to the Risk Evaluation set forth in detail in the attached Request for Correction submitted on January 26, 2021.

Particularly for conditions of use (COUs) evaluated in the manufacture and processing as a reactant/intermediate, the exposure assessments were not realistic and do not reflect current industrial hygiene (IH) practices. The CTC Risk Evaluation also used a threshold approach for assessing carcinogenic risk, with the Point-of-Departure (POD) being 5 ppm based on increased liver adenomas in female mice from the Nagano *et al.* (2007) study. However, EPA's decision to

[1] EPA-740-R1-8014 (October 2020) (hereafter "Risk Evaluation").

[2] These comments should be read in concert with HSIA's March 27, 2020, comments on the draft CTC Risk Evaluation, EPA-HQ-OPPT-2019-0499-0039 and HSIA's Request for Correction: Risk Evaluation for Carbon Tetrachloride (submitted to docket #EPA-HQ-OPPT-2019-0499 on January 26, 2021). See Attachment 1.

consider the 5 ppm as a Lowest-Observed-Adverse-Effect-Level (LOAEL) and not a No-Observed-Adverse-Effect-Level (NOAEL) is not based on consideration of generally accepted approaches (even by EPA) for assessing animal carcinogenicity data or the weight of the scientific evidence. We request that EPA correct the Risk Evaluation to incorporate realistic and best available science into both the final Risk Evaluation and prior to finalizing this proposed revised risk determination.

I. Risk Determinations for CTC are Based on Flawed Risk Evaluations

A. EPA Did Not Use Best Available Science in the Exposure Assessments

1. Dermal Exposure Assessment

In the proposed revised draft risk determination for CTC, EPA finds unreasonable risks to workers from acute (dermal only) and chronic (dermal and inhalation) exposure in the manufacture of CTC and its use in the production of other chemicals (feedstock or intermediate use). Importantly, the models EPA used to estimate the amount of CTC that is retained by workers from dermal contact were not based on any supporting information and overestimated any potential exposure. These "worst-case scenarios" assumed unrealistic dermal exposure durations and failed to recognize basic industrial hygiene (IH) practices, including implementation of OSHA-compliant standard operating procedures (SOPs),[3] as well as engineering controls required by the National Emission Standards for Hazardous Air Pollutants (NESHAP) for Synthetic Organic Chemical Manufacturing Industry (SOCMI)[4] and Miscellaneous Organic Chemical Manufacturing (MON),[5] which require closed systems where exposure is tightly controlled. Thus, they are clearly inapplicable to facilities that manufacture CTC or use CTC as a process reactant or intermediate. Moreover, CTC is tightly regulated under the Montreal Protocol on Substances That Deplete the Ozone Layer and Title VI of the Clean Air Act (CAA), as described in greater detail in the attached Request for Correction. Because of its

[3] See SOPs for Personal Protection at CTC Manufacturing Sites, Appendix 2, detailing the OSHA standards in place at CTC Manufacturing sites. These standards also apply to HSIA member-company manufacturing and processing sites as detailed in HSIA Response to EPA's Questions on Standard Operating Procedures (SOPs) at Carbon Tetrachloride and Other Solvent Manufacturing Sites, Appendix 3.

[4] 40 C.F.R. Part 63 Subparts F, G, H, I.

[5] 40 C.F.R. Part 63, Subpart FFFF.

ozone depletion potential, this regulatory program phased out the manufacture and import of CTC over 20 years ago, subject to limited exceptions such as use as a process agent or feedstock, where by definition it is used and entirely consumed, except for trace quantities.[6]

The manufacture of CTC and its use in the production of other chemicals (*i.e.*, refrigerants) are COUs that occur in closed system process units where potential dermal contact is limited to short-term tasks in the operation of unit activities. "Closed systems (including rigorous containment by technical means) generally relate to high integrity plant/machinery where the opportunity for exposure is negligible, both in terms of frequency and magnitude".[7] Following several meetings with OPPT staff, HSIA submitted to an EPA docket for CTC several documents that provide comprehensive details on the typical tasks involved in the manufacturing of CTC and the SOPs for these tasks including personal protective equipment (PPE).[8] The typical short-term (5-30 minutes) tasks that could potentially involve contact with liquid phase CTC are loading transport equipment, conducting minor maintenance and line openings, packaging wastes, and collecting process samples. Although not expected, should accidental contact with CTC occur during the performance of these tasks, concentrations and amounts are minimal. Incidental, intermittent, or splash contact may only occur if there is an accidental spill, overspray conditions, or unexpected failure of a control device.

Despite the SOPs in place to prevent any exposure and potential for exposure limited to the short-term tasks described above, EPA estimated dermal exposure to CTC for workers in manufacturing and processing using Kasting and Miller (2006) with the following assumptions: (1) one dermal contact with undiluted CTC which coats fully one or both hands per work shift; (2) workers do not wash their hands at any point during the 8-hour work shift if gloves are not worn;

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[6] Title VI of the Clean Air Act (implementing the Montreal Protocol) restricts the production and consumption of carbon tetrachloride. See also the implementing regulations at 40 C.F.R. Part 82, Subpart A.

[7] European Chemicals Agency (ECHA), Guidance on Information Requirements and Chemical Safety Assessment. Chapter R.14: Occupational Exposure Assessment, Version 3.0 (2016).

[8] See Appendices 2-5, including SOPs for Personal Protection at CTC Manufacturing Sites; HSIA Response to EPA's Questions on Standard Operating Procedures (SOPs) at Carbon Tetrachloride and Other Solvent Manufacturing Facilities (September 27, 2021). EPA Docket #EPA-HQ-OPPT-2020-0592-0003.

and (3) a worker wears the same pair of gloves for the entire 8-hour work shift without stopping to wash their hands and/or change their gloves.[9] EPA provides no documentation or justification for these assumptions other than the intent to establish a theoretical "worst-case scenario." As a result of these assumptions, EPA very substantially overestimated worker exposure to CTC from dermal contact in facilities that manufacture and use CTC as a reactant or intermediate.

According to EPA, risk evaluations under TSCA § 6(b) are not screening level risk assessments, but are intended to "use scientific information, technical procedures, measures, protocols, methodologies and models consistent with the best available science." Therefore, instead of assuming a theoretical worst-case scenario, EPA should use in its dermal exposure models data and assumptions that are relevant and appropriate to actual workplace practices for the COUs being evaluated, information which EPA has had now for over a year. Unfortunately, the Risk Evaluation fails to acknowledge basic IH practices.

As noted in the information provided to EPA on use of PPE at chlorinated solvent production facilities with closed systems, any potential dermal exposures are for short durations and, combined with the industry standards for good IH practices at these facilities which require removal and disposal of potentially contaminated gloves and hand washing after each task completion, do not justify an 8-hour period for absorption of CTC through skin.[10] Moreover, CTC will evaporate from the skin and gloves between exposure periods. A more realistic approach to estimating the dermal dose of CTC in workers in closed system facilities (manufacturing and process reactant/intermediate use) can be obtained using the IH Skin Perm model.[11] This tool is commonly used by practitioners of IH and exposure assessment to produce reliable estimates of dermal exposure. And, as noted in the Risk Evaluation, "this model takes into account losses to evaporation and estimates the mass that is absorbed." In addition, IH

[9] Risk Evaluation, Supplemental Information on Releases and Occupational Exposure Assessment.

[10] See, for example, Appendix 2, page 4, describing how gloves are inspected and donned before use for short-term tasks and removed after use; Appendix 3, page 4, responding to EPA's questions regarding glove evaluation, use and replacement for short term tasks; and Appendix 4, page 9, comparing the model assumptions to the actual condition of use potential for dermal exposure.

[11] IH SkinPerm is a peer-reviewed exposure assessment tool published by the American Industrial Hygiene Association (AIHA) Exposure Assessment Strategies Committee.

SkinPerm can be used to evaluate the impacts of differing patterns of exposure on fractional and total dose of absorption, *i.e.*, it allows for the incorporation of realistic exposure patterns.

Recognition of standard work practices and reliance on reasonable and realistic exposure data are critical to meet the statutory requirements of TSCA, as well as the "objectivity" criterion of the Information Quality Act. EPA's reliance on hypothetical assumptions for modeling of the amount of CTC that is absorbed by workers from dermal contact cannot be justified. Assumptions used for estimating worker exposures should be as relevant as possible for the COUs being evaluated. EPA's use of unrealistic dermal exposure assumptions has led to erroneous conclusions regarding the health risks to workers using CTC in closed systems. Because the Risk Evaluation is intended to determine whether CTC presents an unreasonable risk of injury to workers under TSCA § 6(b), which requires rulemaking to mitigate risks found to be unreasonable, it is imperative that it be revised to reflect the "best available science" in advance of any risk management rulemaking.

2. Flawed Assumptions Regarding Use of PPE in Risk Determinations

In its justification for revising the risk determinations for all COUs of CTC in the Risk Evaluation, EPA states that this change "reflects EPA's recognition that unreasonable risk may exist for subpopulations of workers that may be highly exposed because they are not covered by OSHA standards, or their employers are out of compliance with OSHA standards, or because many of OSHA's chemical-specific permissible exposure limits largely adopted in the 1970's are described by OSHA as being 'outdated and inadequate for ensuring protection of worker health,' or because the OSHA Permissible Exposure Limit may be inadequate for ensuring protection of worker health."

EPA has generalized this concern to all COUs for CTC, yet it is not pertinent at all to the manufacture of CTC, or its use as a fluorochemicals feedstock, based on the information provided by HSIA to EPA over a year ago on industry best practices for industrial hygiene.[12] There are two CTC manufacturers in the United States. Both manufacturers have submitted to EPA

[12] HSIA described that OSHA standards apply to all member sites that manufacture CTC (Appendix 2), which also applies to all manufactures of other chlorinated organics. (see Appendix 3).

documentation on the level of required PPE for general nonspecific tasks in a manufacturing plant for any operations of maintenance personnel, visitors or contractors who enter designated process areas. (Appendices 2-5.) These documents also provide a summary of the extensive training that is in place for employees (new and seasoned) to ensure SOP requirements are followed. There are no exceptions – the SOPS and training apply to all workers.

In the case of the COU for the manufacture of CTC, EPA must evaluate in the Risk Evaluation the circumstances under which CTC is intended, known, or reasonably foreseen to be manufactured. Since both U.S. manufacturers of CTC require PPE use for anyone entering the processing areas at a plant, and that information has been "clearly articulated" to EPA, then EPA "believes it is appropriate to also evaluate the levels of risk present in the scenarios considering" applicable OSHA requirements and industry or sector best practices into its risk evaluations as serve as the basis for the risk determinations and the risk management rules.[13]

B. EPA Did Not Use Best Available Science in the Cancer Hazard Assessment

In the final CTC Risk Evaluation EPA used the increase in the incidence of liver adenomas in the female BDF_1 mice exposed to 5 ppm CTC to estimate human cancer risks, as well as to derive an Existing Chemical Exposure Limit (ECEL). However, a more complete analysis of the data does not support the conclusion that the increase in liver adenomas in the 5 ppm-exposed female mice compared to controls is a treatment-related effect. In the 5 ppm-exposed female mice, Nagano *et al.* (2007) reported a statistically significant increase ($p \leq 0.05$) in liver adenomas when compared to controls using the Fisher's exact test. This is misleading because the p value is 0.05112 from the statistical analysis of the data using the Fisher's exact test is technically non-significant at a $p = 0.05$ and is substantively greater than a $p = 0.01$ recommended to reliably estimate statistical significance of tumors exhibiting control responses of 1% or greater as is the case for liver adenomas/carcinomas in mice.

Moreover, EPA's approach of relying on liver adenomas only for its decision on the POD and not adenomas and carcinomas combined is contrary to its own methodology for assessing

[13] Asbestos Part 1: Chrysotile Asbestos; Regulation of Certain Conditions of Use Under Section 6(a) of the Toxic Substances Control Act (TSCA), Proposed Rule, 87 Fed. Reg. 21706 at 21712 (April 12, 2022).

animal carcinogenicity data. In the 2012 IRIS Assessment for perchloroethylene (PCE), EPA justified its conclusion that three bioassays on PCE showed increases in liver tumors in mice "Because hepatic adenomas and carcinomas are considered part of the same continuum of tumor development, and adenomas may be differentiated from carcinomas only on the basis of size, this analysis emphasizes the combined incidences of these two tumor types."[14] EPA further explained in the 2012 PCE IRIS Assessment that "EPA generally emphasizes combining hepatocellular adenomas and carcinomas in developing cancer risk values, for three reasons: (1) hepatocellular adenomas develop from the same cell lines as carcinomas and can progress to carcinomas; (2) adenomas are often distinguished from carcinomas only on the basis of size; and (3) histopathologic decision criteria may vary between laboratories or over time."[15] Thus, for EPA were to be consistent its approach with the evaluation of mouse liver tumors in the Nagano *et al.* (2007) study, the POD (NOAEL) must be 5 ppm because the incidence of combined adenomas and carcinomas were not statistically different from controls ($p>0.05$) at this exposure concentration. This is also consistent with the Substance Evaluation Conclusion for CTC prepared by France as part of the substance evaluation process under the REACH Regulation (EC) No 1907/2006, as noted in the attached Request for Correction.

A more complete evaluation of the data is provided in a memo from Dr. James Klaunig and Dr. Samuel Cohen, who are well-recognized experts in liver carcinogenesis and pathology (see Appendix 6). Both the historical control data for the BDF_1 mouse at the laboratory where the CTC two-year inhalation study was conducted and the lack of statistical significance in the combined liver adenomas and carcinomas should be taken into account is determining whether the 5 ppm CTC exposure concentration constitutes a LOAEL or a NOAEL for the female mouse liver tumors. Based on the evaluation of Drs. Klaunig and Cohen, the increase in liver tumors in the 5 ppm female mice in the Nagano *et al.* (2007) study is not treatment-related; thus, the NOAEL for liver tumors in this study is 5 ppm.

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[14] EPA Integrated Risk Information System (IRIS) Review of Toxicological Information on Tetrachloroethylene (Perchloroethylene) (2012), page 5-42.

[15] Ibid., page C-1.

II. Conclusion

In sum, TSCA mandates that EPA must complete a risk evaluation pursuant to the risk evaluation requirements in § 6(4) before it can proceed to § 6 risk management rulemaking. In this case, the underlying Risk Evaluation fails to comply with the § 6(b) risk evaluation requirements, including accounting for exposure under the conditions of use, describing the weight of the scientific evidence for the identified hazard and exposure, and using scientific information employed in a manner consistent with the best available science. To maintain the credibility of its regulatory efforts under TSCA, it is imperative that EPA build upon the available information to construct a more realistic risk evaluation before proceeding with rulemaking.

Respectfully submitted,

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Director, Scientific Programs

Appendices

January 26, 2021

Information Quality Guidelines Staff
Mail Code 2811R
Environmental Protection Agency
1200 Pennsylvania Avenue, N.W.
Washington, D.C. 20460

Re: Request for Correction
Risk Evaluation for Carbon Tetrachloride; EPA-HQ-OPPT-2019-0499

Dear Sir or Madam:

This request for the correction of information ("Request for Correction") is submitted under the Information Quality Act ("IQA")[1] and the implementing guidelines issued, respectively, by the Office of Management and Budget ("OMB")[2] and the Environmental Protection Agency ("EPA"),[3] on behalf of the Halogenated Solvents Industry Alliance, Inc. ("HSIA"). HSIA represents producers and users of carbon tetrachloride ("CTC") and other chlorinated solvents. As discussed below, HSIA seeks the correction of information disseminated in an EPA document "Risk Evaluation for Carbon Tetrachloride (Methane, Tetrachloro-); CAS RN: 56-23-5" issued pursuant to § 6 of the Toxic Substances Control Act (TSCA).[4]

This Request is organized as follows:

[1] Section 515(a) of the Treasury and General Government Appropriations Act for Fiscal Year 2001, P.L. 106-554; 44 U.S.C. § 3516 (notes).

[2] 67 Fed. Reg. 8452 (Feb. 22, 2002) ("OMB Guidelines").

[3] EPA, Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity, of Information Disseminated by the Environmental Protection Agency, EPA/260R-02-008 (October 2002) ("EPA Guidelines").

[4] EPA-740-R1-8014 (October 2020) (hereafter "Risk Evaluation"). HSIA notes that while TSCA § 21 provides for citizens' petitions, these are limited to proceedings for the issuance, amendment, or repeal *of a rule.* Nevertheless, we encourage EPA to treat this request as part of the process of "integrat[ing] and assess[ing] available information on hazards and exposures for the conditions of use of [CTC], including information that is relevant to specific risks of injury to health or the environment and information on potentially exposed or susceptible subpopulations" pursuant to TSCA § 6(b)(4)(F) (i) and "describ[ing] the weight of the scientific evidence for the identified hazard and exposure" pursuant to TSCA § 6(b)(4)(F)(v), and to add this Request to the captioned TSCA docket.

III. Dermal Exposure Assessment in the CTC Risk Evaluation
IV. Hazard Assessment in the CTC Risk Evaluation
V. Conclusion

I. Summary of Request for Correction

EPA selected CTC as one of the initial ten substances to be evaluated under TSCA as amended in 2016. CTC is an industrial chemical that was once in widespread use but is now tightly regulated under the Montreal Protocol on Substances That Deplete the Ozone Layer and Title VI of the Clean Air Act (CAA). Because of its ozone depletion potential, this regulatory program phased out the manufacture and import of CTC over 20 years ago, subject to limited exceptions such as use as a process agent or feedstock, where by definition it is used and entirely consumed, except for trace quantities.[5] Furthermore, facilities that manufacture CTC and use it as an intermediate are covered by National Emission Standards for Hazardous Air Pollutants (NESHAP) for the Synthetic Organic Chemical Manufacturing Industry (SOCMI),[6] which require closed systems where exposure is tightly controlled. And such facilities must meet workplace limits enforced by the Occupational Safety & Health Administration (OSHA).

HSIA requests correction of the CTC Risk Evaluation at this step of the TSCA process to correct two key deficiencies:

- The CTC Risk Evaluation fails to incorporate longstanding workplace practices recognized and required by EPA in the NESHAP. It instead relies on unrealistic assumptions about dermal exposure in the manufacturing sector, resulting in an amount of CTC absorbed by workers from skin contact that is thousands of times higher than from real world exposures.

- The CTC Risk Evaluation uses a linear non-threshold model coupled with an assumption that the principal study relied upon did not produce a no-observed-adverse-effect level (NOAEL), both in disregard of advice provided by outside peer reviewers, again resulting in estimates of risk thousands of times higher than reality.

These errors not only result in inaccurate findings but provide erroneous starting points for risk management. The implications for US manufacturing of EPA's findings based on incorrect information are enormous. For example, the Kigali Amendment to the Montreal Protocol, which mandates a global phase down of HFCs, is predicated on the widespread availability of low Global Warming Potential (GWP) HFO alternatives such as HFO-1234yf, -1234ze, and -1233zd. Carbon tetrachloride is the critical feedstock for US production of these low-GWP alternatives.

Accordingly, HSIA urges EPA to give full and prompt consideration to this Request for Correction.

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[5] Title VI of the Clean Air Act (implementing the Montreal Protocol) restricts the production and consumption of carbon tetrachloride. See also the implementing regulations at 40 C.F.R. Part 82, Subpart A.

[6] 40 C.F.R. 63 Subparts F, G, H, I (hereafter "the NESHAP").

II. EPA's IQA Guidelines

The CTC Risk Evaluation was among the first issued by EPA under TSCA as amended in 2016. This underscores the importance of the Risk Evaluation meeting EPA's key IQA Performance Goals of objectivity, utility, and integrity.[7] Because these TSCA evaluations will have such an impact on the manufacturing sector, it is imperative that they utilize accurate data.

A. Influential Scientific Information

As does OMB, EPA considers the "objectivity" inquiry for IQA purposes to be "whether the disseminated information is being presented in an accurate, clear, complete, and unbiased manner, and as a matter of substance, is accurate, reliable, and unbiased." To ensure the objectivity of "influential scientific risk assessment information," EPA adapted the quality principles from the Safe Drinking Water Act Amendments of 1996, as follows:

> "(A) The substance of the information is accurate, reliable and unbiased. This involves the use of:
>
> > (i) the best available science and supporting studies conducted in accordance with sound and objective scientific practices, including, when available, peer reviewed science and supporting studies; and
> >
> > (ii) data collected by accepted methods or best available methods (if the reliability of the method and the nature of the decision justifies the use of the data).
>
> "(B) The presentation of information on human health, safety, or environmental risks, consistent with the purpose of the information, is comprehensive, informative, and understandable."[8]

In calling for the use of "best available science," the EPA Guidelines expressly recognize that "scientific knowledge about risk is rapidly changing and … risk information may need to be updated over time."[9] Moreover, EPA recognizes that the "*influential* scientific, financial, or statistical information" it disseminates "should meet a higher standard of quality."[10] Under the EPA Guidelines, information is considered influential if "the Agency can reasonably determine that dissemination of the information will have or does have a clear and substantial impact (*i.e.,*

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[7] EPA Guidelines at 9. EPA's IQA Guidelines "contain EPA's policy and procedural guidance for ensuring and maximizing the quality of information [it] disseminate[s]" as well as specifically describing "new mechanisms to enable affected persons to seek and obtain corrections from EPA regarding disseminated information that they believe does not comply with EPA or OMB guidelines." *Id*. at 3.

[8] *Id.*at 22.

[9] *Id.* at 23.

[10] *Id.* at 19 (emphasis added).

potential change or effect) on important public policies or private sector decisions."[11] More specifically, information is "influential" if it is disseminated in support of top Agency actions (*i.e.*, rules…)."[12]

The EPA Guidelines further recognize that an "influential" risk assessment should be revised where, as here, the assessment will have a "clear and substantial impact" on private sector decisions.[13] The "clear and substantial impact" standard is met here, as otherwise the erroneous Risk Evaluation will result in rules requiring manufacturers to make decisions and expend significant resources to address non-existent risks.

B. Other IQA Performance Goals

EPA should also correct the errors identified to meet the IQA's second performance goal, one of integrating information quality "into each step of EPA's development of information, including creation, collection, maintenance and dissemination." In addition, the third performance goal in EPA's IQA Guidelines states that the means for correction should be "appropriate to the nature and timeliness of the disseminated information." As discussed above, addressing errors incorporated in the CTC Risk Evaluation is appropriate and necessary before EPA begins the risk management rule-making process.

C. Substantive TSCA Requirements for Scientific Information

TSCA, as amended in 2016, is entirely consistent with EPA's IQA Guidelines. TSCA §§ 6 and 26 expressly require that risk evaluations for existing chemicals be based on "best available science" and the "weight of the scientific evidence." As described in more detail below, the TSCA Science Advisory Committee on Chemicals (SACC) rejected EPA's concern that low-level exposures to carbon tetrachloride may somehow cause tumors through a genotoxic mode of action. The SACC expressly concluded that EPA's "underlying justification for using the "default" approach of applying a linearized model to the tumor mouse bioassay data in order to predict low-dose cancer-risk" is *not supported by the weight of the evidence*.[14]

III. Dermal Exposure Assessment in the CTC Risk Evaluation

The Risk Evaluation concludes that CTC presents unreasonable risks to workers under 13 of 15 conditions of use (COUs) with or without Personal Protective Equipment (PPE), as well as to occupational non-users (ONUs) without PPE.[15] For dermal exposure, although unsupported by

[11] *Id.*

[12] *Id.* at 20.

[13] *Id.*

[14] https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0499-0046 at 39.

[15] To be clear, while the focus of this section is dermal exposure, the flawed approach to the cancer mode of action criticized by the SACC underlies the unreasonable risk determinations for other COUs based on inhalation exposure as well. The problems with the hazard assessment are addressed in the following section.

actual data, EPA finds unreasonable cancer risks to workers under all 13 of these COUs even with the most protective glove use (Protection Factor of 20). In the absence of dermal exposure data for CTC, EPA relied on models to estimate the amount of CTC that is retained by workers from dermal contact. These "worst-case scenarios" assume unrealistic dermal exposure durations and fail to recognize basic industrial hygiene (IH) practices, as well as engineering controls required by the NESHAP. Thus, they are clearly inapplicable to facilities that manufacture CTC or use CTC as a process reactant or intermediate.

The manufacture of CTC and its use as in the production of other chemicals (*i.e.*, perchloroethylene, HFOs) are COUs that occur in closed system process units where potential dermal contact is limited to short-term tasks in the operation of unit activities. The typical tasks that could potentially involve contact with liquid phase CTC are handling of transfer lines for vessel charging/uncharging and collecting samples from process points for laboratory analysis. In general, these tasks would involve limited direct contact with liquid, and the duration of any potential contact with the liquid is very short (*i.e.*, minutes).

EPA estimated dermal exposure to CTC for workers using Kasting and Miller (2006)[16] with the following assumptions: (1) one dermal contact with undiluted CTC which coats fully one or both hands per work shift; (2) workers do not wash their hands at any point during the 8-hour work shift if gloves are not worn; and (3) a worker wears the same pair of gloves for the entire 8-hour work shift without stopping to wash their hands and/or change their gloves.[17] Incredibly, EPA provides no documentation or justification for these assumptions other than the intent to establish a theoretical "worst-case scenario." As a result of these assumptions, EPA has substantially overestimated worker exposure to CTC from dermal contact in facilities that manufacture and use CTC as a reactant or intermediate.

According to EPA, risk evaluations under TSCA § 6(b) are not screening level risk assessments, but are intended to "use scientific information, technical procedures, measures, protocols, methodologies and models consistent with the best available science." Therefore, EPA should consider in its dermal exposure models assumptions that are relevant and appropriate to actual workplace practices for the COUs being evaluated. Unfortunately, the CTC Risk Evaluation failed to acknowledge basic IH practices.

For CTC facilities with closed systems, any potential dermal exposures are for short durations and, combined with the industry standards for good IH practices at these facilities which require removal and disposal of potentially contaminated gloves and hand washing after each task completion, do not justify an 8-hour period for absorption of CTC through skin. Moreover, CTC will evaporate from the skin and gloves between exposure periods. A more realistic approach to estimating the dermal dose of CTC in workers in closed system facilities (manufacturing and

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[16] Kasting, BG, Miller, MA, Kinetics of finite dose absorption through skin 2: Volatile compounds. J. Pharm. Sci. 95: 268-280 (2006).

[17] Risk Evaluation, Supplemental Information on Releases and Occupational Exposure Assessment.

process reactant/intermediate use) can be obtained using the IH Skin Perm model.[18] This tool is commonly used by practitioners of IH and exposure assessment to produce reliable estimates of dermal exposure. And, as noted in the Risk Evaluation, "this model takes into account losses to evaporation and estimates the mass that is absorbed." In addition, IH SkinPerm can be used to evaluate the impacts of differing patterns of exposure on fractional and total dose of absorption, i.e., it allows for the incorporation of realistic exposure patterns.

Using the IH Skin Perm model and a more realistic, albeit still conservative, period for exposure and absorption after tasks, allowing for handwashing, and assuming skin exposure had occurred for up to 1 hour before removal, we can estimate the dermal absorbed dose for COUs involving manufacturing of CTC and its use as a reactant or intermediate in the production of other chemicals. For ungloved hands, the amount of CTC absorbed from exposure to two full hands is 2.78 mg/day. In comparison, EPA estimated the amount of CTC absorbed to be 90 mg/day for two full hands (high-end estimate). Thus, the impact of using a more realistic approach to estimating the high-end dermal CTC dose over one hour results in an approximately 32-fold reduction in the dermal dose.

This overestimate of dermal dose is expected also to hold true in the Risk Evaluation for gloved hands, the only difference being that there is reduced dermal uptake from glove use, and this is accounted for by a workplace protection factor. It is also important to note that these models assume that a worker is exposed to neat or undiluted chemical. Such exposure is highly unlikely in facilities that manufacture CTC or use it as a reactant or intermediate in closed systems. As a result of using unrealistic worst-case assumptions in its dermal exposure assessment, EPA has substantially overestimated worker exposure to CTC from dermal contact by at least several orders of magnitude. *Thus, if the revised scenarios were applied in the risk characterization, there would be no unreasonable risk to workers from dermal exposure!*

Recognition of standard work practices and reliance on reasonable and realistic exposure data are critical to meet the "objectivity" criterion of the IQA and the statutory requirements of TSCA. EPA's reliance on hypothetical assumptions for modeling of the amount of CTC that is absorbed by workers from dermal contact cannot be justified. Assumptions used for estimating worker exposures should be as relevant as possible for the COUs being evaluated. EPA's use of unrealistic dermal exposure assumptions has led to erroneous conclusions regarding the health risks to workers using CTC in closed systems. Because the Risk Evaluation is intended to determine whether CTC presents an unreasonable risk of injury to workers under TSCA § 6(b), which requires rulemaking to mitigate risks found to be unreasonable, it is imperative that it be revised to reflect the "best available science."

[18] IH SkinPerm is a peer-reviewed exposure assessment tool published by the American Industrial Hygiene Association (AIHA) Exposure Assessment Strategies Committee. Oddly this model was not used by EPA to estimate the dermal dose for workers in the Risk Evaluation, although Table 2-23 includes output data from it under various dermal exposure scenarios.

IV. Hazard Assessment in the CTC Risk Evaluation

The CTC Risk Evaluation uses a linear non-threshold model coupled with an assumption that the principal study relied upon did not produce a no-observed-adverse-effect level (NOAEL), both in disregard of advice provided by outside peer reviewers. As a result, as described in more detail below, the estimates are overly conservative by at least a thousand-fold.

The Risk Evaluation relies on Nagano *et al.,* (2007) to derive both the cancer inhalation unit risk (IUR) and the dermal slope factor. The IUR estimates based on Nagano *et al*. (2007) were calculated by the EPA IRIS Program in 2010. The IUR selected for carbon tetrachloride via the inhalation pathway was 6×10^{-6} $(\mu g/m^3)^{-1}$, which was associated with pheochromocytomas in the male mouse. The data set on pheochromocytomas in the male mouse was also judged by the EPA IRIS Program to yield the highest estimate of risk.[19]

As in the case of the dermal exposure assessment, this approach does not meet the "objectivity" criterion of the IQA (requiring "the best available science and supporting studies conducted in accordance with sound and objective scientific practices, including, when available, peer reviewed science and supporting studies"). Moreover, it patently departs from EPA's recognition, in calling for the use of "best available science," that "scientific knowledge about risk is rapidly changing and … risk information may need to be updated over time."[20]

In the IRIS CTC assessment, EPA concluded that there is insufficient information on the mode of action (MOA) of CTC for mouse liver tumors at low doses and the mouse pheochromocytomas to support a non-linear dose-response approach for assessing cancer risk. A majority (four out of six) of the external peer reviewers, however, recommended that potential CTC cancer risk should be based on a non-linear threshold method. To quote directly from the IRIS response to reviewer comments: "Two reviewers considered it appropriate to present a linear low-dose extrapolation approach as an alternative approach, but that based on available evidence, the nonlinear method seems more appropriate." A fifth reviewer stated that use of a linear dose-response model is "difficult to defend and is not a preferable approach" [and a] "sixth reviewer did not agree that a linear assessment is justified for carbon tetrachloride." Even one of the two reviewers who believed that a low-dose linear approach was the "most clear, prudent and scientifically defensible approach" noted that use of a nonlinear approach is "reasonable to consider," although noting that such an approach might use an additional, possibly 10-fold, uncertainty factor to assure protection of both cancer and non-cancer endpoints.[21]

The final Risk Evaluation included a nonlinear dose-response assessment, but departed from the advice of the TSCA Science Advisory Committee on Chemicals (SACC), which was quite clear that a threshold MOA should be used for CTC:

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[19] Risk Evaluation at 167.

[20] EPA Guidelines at 23.

[21] https://cfpub.epa.gov/ncea/iris/iris_documents/documents/toxreviews/0020tr.pdf at A-25.

"The Committee concluded that the weight of a considerable body of scientific evidence indicates that the relationship between carbon tetrachloride dose/exposure and its genotoxic response is nonlinear with a steep dose-response. Less is known about mechanisms underlying adrenal gland tumors in rodents or apparent glioblostomas [sic] in workers. Most of the Committee members recommended that the EPA consider adoption and implementation of a threshold MOA when estimating cancer risks."[22]

Indeed, the Committee highlighted the following recommendation:

"Recommendation 55: Consider adoption of a threshold-type MOA in estimating the carcinogenic risks of carbon tetrachloride.

"Mechanisms underlying the carcinogenicity of carbon tetrachloride in the rodent liver have been studied extensively. Using a WOE approach, it is likely that the relationship between carbon tetrachloride dose per exposure and its genotoxic response is nonlinear with a steep dose response. This conclusion is primarily based upon the MOA identified from numerous genotoxicity investigations, as well as several important factors that support/indicate a nonlinear dose-response. These include recognition that:

1. The primary site of carbon tetrachloride bioactivation and adverse effects is the smooth endoplasmic reticulum, a site removed from the nucleus and DNA;

2. The moieties which are formed are highly reactive and unlikely to travel far in the aqueous cytoplasm from their site of formation;

3. The observed genotoxic effects appear to result from indirect mechanisms related to oxidative and lipid peroxidation-mediated DNA damage, or damage occurring due to necrosis and apoptosis;

4. Carbon tetrachloride metabolite-induced lipid peroxidation is an exponential chain reaction, such that a single initiation event can lead to formation of many reactive species. Thus, the extent of damage can have a distinct nonlinear component;

5. High levels of hepatoprotective agents and antioxidants are present in hepatocytes;

6. A close relationship is manifest between cytotoxicity and genotoxicity;

7. Oxidative and lipoperoxidation-related DNA damage occurs spontaneously in untreated cells, and has been shown to be efficiently repaired; and

[22] https://www.regulations.gov/document?D=EPA-HQ-OPPT-2019-0499-0046 at 50.

8. Apoptosis and recognition and destruction of transformed cells by the immune system are additional protective mechanisms that argue against use of a linear dose-response model."[23]

The Committee concluded:

"[A]lthough the Evaluation claims to have 'Evaluated the weight of the scientific evidence based on the available human health hazard data for carbon tetrachloride,' the Committee noted that convincing support for this claim is lacking. In particular, the Evaluation refers repeatedly to a concern that low-level exposures to carbon tetrachloride may somehow act through genotoxic mechanisms (evidence for this notwithstanding); indeed, this concern is its underlying justification for using the "default" approach of applying a linearized model to the tumor mouse bioassay data in order to predict low-dose cancer-risk. But *the weight of evidence clearly indicates that any genotoxicity caused by carbon tetrachloride can occur only at exceedingly high levels of exposure, and is caused not by carbon tetrachloride directly, but only indirectly after high levels of lipid peroxide by-products (such as reactive aldehydes) have accumulated intracellularly. . . . No support is provided for EPA's designation of an 'alternate MOA' that combines cytotoxic mechanisms at relatively high CCl4 doses with 'alternate, non-cytotoxic mechanisms' at lower doses."*[24]

Although the Risk Evaluation includes cancer risk estimates derived using a non-linear approach, the calculations are based on a point of departure (POD) of 5 ppm. EPA interpreted the increase in liver tumors in the female mice at this concentration as a treatment-related lowest-observed-adverse-effect level (LOAEL). As noted by the SACC, however, the scientific justification for using a nonlinear approach here is that the MOA for CTC-induced liver tumors involves cytotoxicity and proliferation from the highly reactive radical metabolites of CTC. Thus, liver toxicity is a precursor key event to CTC-induced liver tumors. In the Nagano study there was no indication of liver toxicity in the livers of female mice exposed to 5 ppm. Accordingly, EPA's use of 5 ppm as a LOAEL for its derivation of cancer risk is incompatible with the underlying assumption regarding the MOA. Given the preponderance of science evidence for the cytotoxic-proliferative MOA for CTC carcinogenicity, the weight-of-the-evidence suggests that the increase in female mouse liver tumors at 5 ppm occurred by chance and that this exposure concentration is instead a NOAEL.

Indeed, the SACC stated:

"No support is provided for the EPA's designation of an "alternate MOA" that combines cytotoxic mechanisms at relatively high carbon tetrachloride doses with "alternate, non-cytotoxic mechanisms" at lower doses. What is meant by an

[23] *Id.*at 51-52.

[24] *Id.* at 39 (references omitted and emphasis added).

> "alternate non-cytotoxic mechanism" (Evaluation Page 124, line 4005)? This appears to be speculation that something must be occurring to produce an increased incidence in liver adenomas in the female mice dosed at five ppm. Consideration should be given to the possibility that this was a chance occurrence in a single study. The historical incidence of this benign tumor in control Crj:BDF1 mice is as high as 10%. Had three of 50 control females exhibited liver adenoma in this particular experiment, the difference between them and the five ppm dose group would not have been statistically significant. There was no increase in liver carcinoma incidence in the females dosed at five ppm and no significant increase over controls in combined benign and malignant liver tumors. It should also be noted there was no increase in hepatocellular adenoma or carcinoma in the male mice dosed at five ppm. Male mice metabolically activate more carbon tetrachloride and experience a higher incidence of liver cancer then do females."

The peer review excerpts quoted above make clear that the Committee disagreed with EPA and supported a non-linear assessment based on a 5 ppm NOAEL. Further, the Committee made clear its view that EPA was not using a weight-of-the-evidence approach. This is highly significant given the admonition in TSCA § 26(i) that "[t]he Administrator shall make decisions under sections 4, 5, and 6 based on the weight of the scientific evidence." It is unusual for peer reviewers to place so much emphasis on a recommendation, and even more unusual for EPA to disregard such a recommendation when it echoes earlier advice received from different external peer reviewers on the same subject.

Significantly, there is a recent and readily available Substance Evaluation Conclusion for CTC prepared by France as a part of the substance evaluation process under the REACH Regulation (EC) No 1907/2006 (enclosed). Unlike the EPA Evaluation, but consistent with the outside peer reviewers here, this weight-of-the-evidence review combines a nonlinear, threshold mode of action with a nongenotoxic mode of action:

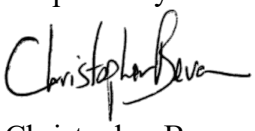
> "Taking into account the results of genotoxicity data, CCl4 [CTC] is not considered as a direct genotoxic agent but acts as a carcinogen by a threshold mode of action. Cytotoxicity and regeneration seem therefore to be a main factor in the apparition [sic] of (pre-)neoplastic lesions. In conclusion, CCl4 is considered to act as a carcinogen by a threshold mode of action."

Based on this conclusion, the French evaluation derives a NOAEL of 5 ppm (32 mg/m^3) for hepatoadenomas and carcinomas in both species after chronic exposure to CTC via the inhalation route. This is in line with the workplace limit enforced by OSHA (10 ppm) and that recommended by the American Conference of Governmental Hygienists (5 ppm), and some thousand times higher than the level deemed acceptable by EPA. HSIA strongly recommends that EPA recognize the 5 ppm NOAEL and use it, along with a nonlinear MOA, as the basis for a revised cancer risk assessment.

V. Conclusion

Prompt action on this Request for Correction is necessary in order for the EPA Risk Evaluation to comply with the IQA and TSCA, and to avoid EPA basing risk management regulations for CTC on erroneous scientific data and interpretation.

Respectively submitted,



Christopher Bevan, PhD, MPH, DABT
Director, Scientific Programs

Enclosure

cc: Deputy Assistant Administrator Michal Ilana Freedhoff
Mr. Mark Hartman
Mr. Joel Wolf
Mr. Erik Winchester
Mr. Douglas Parsons
W. Caffey Norman, Esq.

SUBSTANCE EVALUATION CONCLUSION

as required by REACH Article 48

and

EVALUATION REPORT

for

Carbon tetrachloride

EC No 200-262-8

CAS No 56-23-5

Evaluating Member State(s): France

Dated: December 2019

Evaluating Member State Competent Authority

France
Anses
14 rue Pierre et Marie Curie
94701 Maisons-Alfort Cedex

Year of evaluation in CoRAP: 2012

Before concluding the substance evaluation a Decision to request further information was issued on: 26.02.2014. This Decision was annulled by the Board of Appeal the 23rd of September 2015 (case A-005-2014).

Further information on registered substances here:

http://echa.europa.eu/web/guest/information-on-chemicals/registered-substances

DISCLAIMER

This document has been prepared by the evaluating Member State as a part of the substance evaluation process under the REACH Regulation (EC) No 1907/2006. The information and views set out in this document are those of the author and do not necessarily reflect the position or opinion of the European Chemicals Agency or other Member States. The Agency does not guarantee the accuracy of the information included in the document. Neither the Agency nor the evaluating Member State nor any person acting on either of their behalves may be held liable for the use which may be made of the information contained therein. Statements made or information contained in the document are without prejudice to any further regulatory work that the Agency or Member States may initiate at a later stage.

Foreword

Substance evaluation is an evaluation process under REACH Regulation (EC) No. 1907/2006. Under this process the Member States perform the evaluation and ECHA secretariat coordinates the work. The Community rolling action plan (CoRAP) of substances subject to evaluation, is updated and published annually on the ECHA web site[1].

Substance evaluation is a concern driven process, which aims to clarify whether a substance constitutes a risk to human health or the environment. Member States evaluate assigned substances in the CoRAP with the objective to clarify the potential concern and, if necessary, to request further information from the registrant(s) concerning the substance. If the evaluating Member State concludes that no further information needs to be requested, the substance evaluation is completed. If additional information is required, this is sought by the evaluating Member State. The evaluating Member State then draws conclusions on how to use the existing and obtained information for the safe use of the substance.

This Conclusion document, as required by Article 48 of the REACH Regulation, provides the final outcome of the Substance Evaluation carried out by the evaluating Member State. The document consists of two parts i.e. A) the conclusion and B) the evaluation report. In the conclusion part A, the evaluating Member State considers how the information on the substance can be used for the purposes of regulatory risk management such as identification of substances of very high concern (SVHC), restriction and/or classification and labelling. In the evaluation report part B the document provides explanation how the evaluating Member State assessed and drew the conclusions from the information available.

With this Conclusion document the substance evaluation process is finished and the Commission, the Registrant(s) of the substance and the Competent Authorities of the other Member States are informed of the considerations of the evaluating Member State. In case the evaluating Member State proposes further regulatory risk management measures, this document shall not be considered initiating those other measures or processes. Further analyses may need to be performed which may change the proposed regulatory measures in this document. Since this document only reflects the views of the evaluating Member State, it does not preclude other Member States or the European Commission from initiating regulatory risk management measures which they deem appropriate.

[1] http://echa.europa.eu/regulations/reach/evaluation/substance-evaluation/community-rolling-action-plan

Contents

Part A. Conclusion

1. CONCERN(S) SUBJECT TO EVALUATION

Carbon tetrachloride (CCl4) was originally selected for substance evaluation in order to clarify concerns about:

- potential mutagenicity, carcinogenicity and/or reprotoxicity;

- exposure of workers with a high aggregated tonnage even if only industrial use was reported (most of it as isolated intermediate or transported isolated intermediate).

2. OVERVIEW OF OTHER PROCESSES / EU LEGISLATION

CCl4 is regulated under Regulation (EC) No 1005/2009 of the European Parliament and of the Council on substances that deplete the ozone layer (OJ L 286, 31.10.2009, p. 1) which prohibits its use except as an intermediate, industrial processing agent and laboratory agent.

3. CONCLUSION OF SUBSTANCE EVALUATION

CCl4 was included in the Community rolling action plan (CoRAP) for substance evaluation pursuant to Article 44(2) of the REACH Regulation to be evaluated in 2012. CCl4 was originally selected for substance evaluation in order to clarify concerns about mutagenicity, carcinogenicity, reprotoxicity and occupational exposure (considering high aggregated tonnages). During the evaluation, an additional concern has been identified with regard to the waiving of two-generation study.

As a result of substance evaluation, CCl4 is not considered by eMSCA as a direct genotoxic agent, unless very high doses are used. DNA damages can be due to reactive oxygen species (ROS) and/or lipid peroxidation or related to a cytotoxic response since genotoxic effect was only observed at dose high where hepatic cytotoxicity occurred. The role of postulated reactive metabolites (including aldehydes, trichloromethyl or thrichloromethylperoxyl free radicals, phosgen) in DNA damage was also hypothetized.

In conclusion, CCl4 is considered to act as a carcinogen with threshold. The underlying carcinogenic mode of action is not clearly known. It is hypothesed that CCl4 is metabolized by CYP2E1 into radicals or other reactive species leading to lipid peroxidation with associated cell cytotoxicity / proliferation (Anses, 2017).

There are still some uncertainties related to potential reproductive toxicity due to contradictory data and low relevance of the available studies. However, given the current tonnages and uses of the substance and the risk management measures which should be already in place, considering the known toxicity of the substance, these uncertainties alone do not substantiate a potential risk to be addressed under substance evaluation. This substance evaluation can be concluded without a request for further information.

ECHA has checked the compliance with the standard information requirements under REACH for reproductive toxicity and considered it compliant at the currently registered tonnage levels. However, if the registered tonnage increases in future, the eMSCA recommends ECHA to consider this substance for prioritisation for compliance check.

Regarding occupational exposure, OELs recommended by the SCOEL (2009) could be used by registrants. Exposure data provided in registration dossier (both modelled and measured) do not exceed OELs recommended by SCOEL.

The evaluation of the available information on the substance has led the evaluating Member State to the following conclusions, as summarised in the table below.

Table 1

CONCLUSION OF SUBSTANCE EVALUATION	
Conclusions	**Tick box**
Need for follow-up regulatory action at EU level	x
Harmonised Classification and Labelling	x
Identification as SVHC (authorisation)	
Restrictions	
Other EU-wide measures	
No need for regulatory follow-up action at EU level	

4. FOLLOW-UP AT EU LEVEL

4.1. Need for follow-up regulatory action at EU level

As CCl4 is regulated under Regulation (EC) No 1005/2009 on substances that deplete the ozone layer, there is no identified consumer uses.

Regarding reproductive toxicity, there are still some uncertainties related to the to potential effects on fertility due to contradictory data and the low relevance of the available studies, however given the current tonnage and uses of the substance, clarification of these uncertainties is not considered a priority and therefore this substance evaluation can be concluded without a request for further information.

ECHA has checked the compliance with the standard information requirements under REACH for reproductive toxicity and considered it compliant at the currently registered tonnage levels. However, if the registered tonnage increases in future, the eMSCA recommends ECHA to consider this substance for prioritisation for compliance check.

4.1.1. Harmonised Classification and Labelling

CCl4 has the following harmonised classification:

-Acute Tox. 3* - H301, H311, H331
-Carc. 2 - H351
-STOT RE 1 - H372**
-Aquatic Chronic 3 - H412
-Ozone 1 - H420

The registrants added the following classification:
-Skin Sens. 1B - H317

The following hazard classes are in addition notified among the aggregated self-classifications in the C&L Inventory:
-Acute Tox. 2 – H310
-Skin Irrit. 2 – H315
-Eye Irrit. 2 – H319
-Carc. 1B – H350
-Repr. 2 - H361

After the evaluation of available data, eMSCA considers that the current EU harmonised classification of CCl4 could be updated for the following endpoints:
- Add Skin Sens 1B – H317
- Change Carc 2 – H351 to Carc 1B –H350
- Change Acute Tox. 3 to Acute Tox. 4

4.1.2. Identification as a substance of very high concern, SVHC (first step towards authorisation)

Not considered at this stage.

4.1.3. Restriction

Not considered at this stage.

4.1.4. Other EU-wide regulatory risk management measures

Not considered at this stage.

5. CURRENTLY NO FOLLOW-UP FORESEEN AT EU LEVEL

Not applicable.

6. TENTATIVE PLAN FOR FOLLOW-UP ACTIONS (IF NECESSARY)

Indication of a tentative plan is not a formal commitment by the evaluating Member State. A commitment to prepare a REACH Annex XV dossier (SVHC, restrictions) and/or CLP Annex VI dossier should be made via the Registry of Intentions.

Table 3

FOLLOW-UP		
Follow-up action	**Date for intention**	**Actor**
CLH report	2021- Scientifically justified but priorisation criteria under considerations	France

Part B. Substance evaluation

7. EVALUATION REPORT

7.1. Overview of the substance evaluation performed

CCl4 was originally selected for substance evaluation in order to clarify concerns about:

- mutagenicity, carcinogenicity, reprotoxicity,
- and exposure of workers with a high aggregated tonnage.

During the evaluation another concern was identified:

- waiving of two-generation study.

Table 4

EVALUATED ENDPOINTS	
Endpoint evaluated	**Outcome/conclusion**
Acute toxicity	Current harmonized classification as Acute Tox 3* Proposal to update as Acute Tox 4 - H332: harmful if inhaled
Corrosion / irritation	No further action
Skin / respiratory sensitisation	Proposal to add Skin Sens. 1B – H317 No concern identified for respiratory sensitisation
Repeated-dose toxicity	Liver identified as the most sensitive target organ. Current harmonized classification: STOT RE 1 - H372 (SCL = 1 %) after direct translation from the classification agreed under Directive 67/548/EEC. An update of this classification can be foreseen to add the route of exposure (oral; inhalation) and the target organ (liver)
Genotoxicity	Initial concern clarified. Not genotoxic: no further action
Carcinogenicity	Current harmonized classification as Carc. 2 Proposal to update as Carc. 1B – H350. As a result of substance evaluation, CCl4 is not considered by eMSCA as a direct genotoxic agent, unless very high doses are used. DNA damages can be due to ROS and/or lipid peroxidation or related to a cytotoxic response since genotoxic effect was only observed at dose high where hepatic cytotoxicity occurred. The role of postulated reactive metabolites (including aldehydes, trichloromethyl or

	thrichloromethylperoxyl free radicals, phosgen) in DNA damage was also hypothetized. In conclusion, CCl4 is considered to act as a carcinogen with threshold. The underlying carcinogenic mode of action is not clearly known. It is hypothesed that CCl4 is metabolized by CYP2E1 into radicals or other reactive species leading to lipid peroxidation with associated cell cytotoxicity / proliferation (Anses, 2017).
Toxicity to reproduction	There was not sufficient information to conclude on the integrity and performance of the male and female reproductive systems, and the effect on neonatal and postnatal developmental toxicity. Thefore there are still some uncertainties related to potential reproductive toxicity. However given the current tonnages and uses of the substance and the risk management measures which should be already in place, considering the known toxicity of the substance, these uncertainties alone do not substantiate a potential risk to be addressed under substance evaluation. This substance evaluation can be concluded without a request for further information. Prenatal developmental toxicity: no further action.

Regarding exposure scenarios, eMSCA identified inconsistencies in the chemical safety assessments provided by the registrants as mentioned in section 7.12.1.1 and detailed in the confidential annex, regarding the choice of some exposure concentrations for workers and the inhalation DNEL chosen for risk characterisation. Clarifications are needed from the registrants.

7.2. Procedure

CCl4 was included in the Community rolling action plan (CoRAP) for substance evaluation pursuant to Article 44(2) of the REACH Regulation to be evaluated in 2012. CCl4 was originally selected for substance evaluation in order to clarify concerns about mutagenicity, carcinogenicity, reprotoxicity and occupational exposure (considering high aggregated tonnages). During the evaluation, an additional concern has been identified with regard to the waiving of two-generation study. Indeed, at this time issue on CCH was to be sorted out during substance evaluation.

Following substance evaluation, a Decision dated 26 February 2014 requested the registrants to conduct an Extended One Generation Reproduction Toxicity Study by inhalation route (test method: OECD443). Specific Decisions were also addressed to some registrants regarding exposure scenarios (occupational and environmental exposure).

Regarding the main Decision, the Board of Appeal annuled the Agency's Decision on the substance evaluation of CCl4 the 23rd of September 2015 (case number A-005-2014). The Board of Appeal the Board of Appeal found that the Contested Decision was disproportionate on the grounds that an EOGRTS was not necessary to clarify a risk to

human health or the environment. In addition, the Agency had not adequately justified requesting information under substance evaluation, which was standard information requirement for one of the registrants under the REACH Regulation.

As a result of the specific Decisions regarding exposure scenarios, chemical safety reports have been updated by the main registrants in June 2016. Registered tonnage has been downgraded.

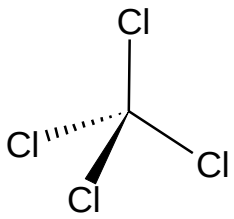
7.3. Identity of the substance

Table 5

SUBSTANCE IDENTITY	
Public name:	Carbon tetrachloride
EC number:	200-262-8
CAS number:	56-23-5
Index number in Annex VI of the CLP Regulation:	602-008-00-5
Molecular formula:	CCl4
Molecular weight range:	153.8227
Synonyms:	tetrachloromethane

Type of substance x Mono-constituent ☐ Multi-constituent ☐ UVCB

Structural formula:



The substance is considered, according to compositions submitted by the registrants, as monoconstituent according to REACH guidance for identification and naming of substances except for one composition considered by eMSCA as a multi-constituent substance (confidential annex).

Different manufacturing processes exist. They are based on the same chemical reaction but conditions (initiation, pressure, temperature…) and reactants differ. Moreover a purification step is performed or not, leading to different impurity profiles and different classifications of the substance (confidential annex).

Three registrants did provide analytical informations (UV/VIS, IR, NMR and GC chromatograms) to confirm the compositions and the structure of their registered substances. However, three registrants were not providing analytical data in their dossiers (confidential annex).

7.4. Physico-chemical properties

Table 7

OVERVIEW OF PHYSICOCHEMICAL PROPERTIES	
Property	**Value**
Physical state at 20°C and 101.3 kPa	**Value used for CSA: liquid at 20°C and 101.3 kPa** Data is available in a peer reviewed handbook (Merck Index 2006). Data is available in literauture which gives a consistent result.
Vapour pressure	**Value used for CSA: 12046 Pa at 19.8 °C** Data are available in a peer-reviewed handbook : 15.2 kPa at 25°C (CRC Handbook, 2009) and in a well described publication : 12046 Pa at 19.8°C and 14549 Pa at 24°C (Boublik, 1972). These values are consistent. Another supportive data from Handbook (Ullmann, 2002) gives a value of 11940 Pa at 20°C. This value has the same order of magnitude. Slight difference may be due to the difference of purity of the test material and to the accuracy of method used which are not specified. Carbon tetrachloride is volatile.
Water solubility	**Value used for CSA: 846.1 mg/L at 20 °C** A data has been generated according to OECD guideline 105 and GLP requirements which give a value of 846.1 mg/L at 20°C. The data reported in CRC Handbook (0.65 g/L at 25°C) has the same order of magnitude as the value generated in the study. Slightly difference may be due to the difference of purity of the test material, the difference of pH and to the accuracy of method used which is not specified. Carbon tetrachloride is moderately soluble.
Partition coefficient n-octanol/water (Log Kow)	**Value used for CSA: Log Kow (Pow): 2.83 at 25 °C** The reliability of 2 in the Klimisch scale is to be granted to the two peer reviewed experimental Handbook data being 2.64 and 2.83. The former used for the CRC handbook, which can, according to ECHA guidance, be regarded as peer reviewed, and the latter originally reported from Hansch et al (1995) and used for the training set of the validated QSAR software KOWWIN™ from the U.S. EPA EPI suite 4.0 package. A further experimental value of 2.75 at 23°C (Huels 1989) fits in the same range. The recommended value is logKow = 2.83

OVERVIEW OF PHYSICOCHEMICAL PROPERTIES	
Property	**Value**
Flammability	**Value used for CSA: non flammable** Carbon tetrachloride is a liquid at room temperature thus its primary value for ease of ignition is the flash point. In addition, based on experience in handling, carbon tetrachloride is not pyrophoric and is not flammable on contact with water.
Explosive properties	**Value used for CSA: non explosive** The substance does not contain any functional groups associated with explosive properties.
Oxidising properties	**Value used for CSA: non oxidizing properties** The substance does not contain any functional groups associated with oxidising properties
Granulometry	Not relevant. Carbon Tetrachloride has a melting point of -22.62 °C at 1013.25 hPa and therefore is a liquid at normal ambient temperatures.
Stability in organic solvents and identity of relevant degradation products	A study on the stability of carbon tetrachloride is not required as the stability of carbon tetrachloride in organic solvents is not regarded as critical.
Dissociation constant	The substance does not contain any relevant functional groups
Melting/freezing point	**Value used for CSA: -22.62 °C at 101.3 kPa** A study on the melting point/freezing point does not need to be conducted below a lower limit of -20°C. Available data from a peer-reviewed handbook (CRC Handbook, 2009) reports a melting point of -22.62°C at 1013.25 hPa. This value is in good agreement with the value (-22.99°C) found in an old publication (Dreisbach, 1949). Moreover these values are consistent with the Merck Index (2006) value which is -23°C.
Boilling point	**Value used for CSA: 76.8 °C at 101.3 kPa** Data is available in a peer reviewed handbook (CRC Handbook, 2009) and gives a boiling point of 76.8°C. The value given is in line with a value (76.75°C) found in the litterature (Dreisbach, 1949). These two values are consistent with the Merck Index (2006) value which is 76.7°C.
Relative density	**Value used for CSA: 1.59 at 20°C** Data for several temperatures are available in a peer-reviewed handbook (CRC Handbook, 2009). These values are in line with the density of 1594.7 kg/m^3 reported in another handbook at 20 °C (Ullmann's, 2002) and the relative density of 1.59 at 20/4°C found in an old publication (Dreisbach, 1949) and the relative density found in the Merck

OVERVIEW OF PHYSICOCHEMICAL PROPERTIES	
Property	**Value**
	Index (2006): 1.589. Thus the density of the substance is found to be 1.59 g/cm3 at 20°C.
Solubility in organic solvents	**Value used for CSA: soluble in acetone and ethanol** Data is available in a peer reviewed handbook (CRC Handbook, 2009)
Surface tension	An available publication reports a surface tension of 26.92 mN/m at 20°C for pure carbon tetrachloride. This value is in good agreement with the value found in an handbook and in another publication (26.7 mN/m at 20°C).
Viscosity	**Value used for CSA: 0.7676 mPa.s at 40°C; 0.9575 at 25°C** A detailed publication is available: the viscosity is reported to be 0.7676 mPa.s at 40°C and 0.9575 at 25°C. Value found in a peer-reviewed handbook (CRC Handbook of Chemistry and Physics): 0.908 mPa.s at 25 °C is consistent with the value provided in the publication. An Handbook (Ullmann) reports a viscosity of 1.35 mPa.s at 20°C. Slight difference may be due to the difference of purity of the test material and to the accuracy of method used which are not specified.

7.5. Manufacture and uses

7.5.1. Quantities

Table 8

AGGREGATED TONNAGE (PER YEAR)				
☐ 1 – 10 t	☐ 10 – 100 t	☐ 100 – 1000 t	☒ 1000- 10,000 t*	☐ 10,000-50,000 t
☐ 50,000 – 100,000 t	☐ 100,000 – 500,000 t	☐ 500,000 – 1000,000 t	☐ > 1000,000 t	☐ Confidential

There are 8 active registrants according to ECHA dissemination website (accessed on January 2019).

*During the compliance check performed by ECHA, the registered tonnage band of some registrants was downgraded so that at this point in time there are no full registrations ≥ 1000 tpa.

7.5.2. Overview of uses

Table 9

USES	Use(s)
Uses as intermediate	Use as chemical intermediate
Formulation	/
Uses at industrial sites	Use as a process agent / solvent according to Annex III of Regulation (EC) 1005/2009
Uses by professional workers	/
Consumer Uses	/
Article service life	/

CCl4 is regulated under Regulation (EC) No 1005/2009 on substances that deplete the ozone layer, which prohibits its use except as an intermediate, industrial processing agent and laboratory agent.

7.6. Classification and Labelling

7.6.1. Harmonised Classification (Annex VI of CLP)

Table 10: Harmonised classification – as stated by Regulation No 286/2011 amending, for the purposes of its adaptation to technical and scientific progress, Regulation (EC) No 1272/2008

HARMONISED CLASSIFICATION ACCORDING TO ANNEX VI OF CLP REGULATION (REGULATION (EC) 1272/2008)							
Index No	**International Chemical Identification**	**EC No**	**CAS No**	**Classification**		**Spec. Conc. Limits, M-factors**	**Notes**
				Hazard Class and Category Code(s)	**Hazard statement code(s)**		
602-008-00-5	carbon tetrachloride tetrachloromethane	200-262-8	56-23-5	Acute Tox. 3*	H301		
				Acute Tox. 3*	H311		
				Acute Tox. 3*	H331		
				Carc. 2	H351		
				STOT RE 1	H372**	STOT RE 1; H372: C ≥ 1 % STOT RE 2; H373: ,2 % ≤ C < 1 %	

HARMONISED CLASSIFICATION ACCORDING TO ANNEX VI OF CLP REGULATION (REGULATION (EC) 1272/2008)							
Index No	International Chemical Identification	EC No	CAS No	Classification		Spec. Conc. Limits, M-factors	Notes
				Hazard Class and Category Code(s)	Hazard statement code(s)		
				Aquatic Chronic 3	H412		
				Ozone 1	H420		

7.6.2. Self-classification

- In the registration(s):

Skin Sens. 1B - H317

- The following hazard classes are in addition notified among the aggregated self-classifications in the C&L Inventory:

Acute Tox. 2 – H310

Skin Irrit. 2 – H315

Eye Irrit. 2 – H319

Carc. 1B – H350

Repr. 2 - H361

7.7. Environmental fate properties

7.7.1. Degradation

Hydrolysis

All submitted studies are considered as supporting data. Nevertheless, based on the weight of evidence, they indicate that hydrolysis is not a relevant process for the degradation of CCl4 under environmental conditions.

Phototransformation/photolysis

Estimates of the atmospheric lifetime (the overall persistence of CCl4 in the troposphere and the stratosphere combined) range from 30 to 100 years, with 50 years (i.e. 18,250 days) generally being accepted as the most reasonable value. The atmospheric lifetime of CCl4 is assigned to 50 years.

CCl4 dissolved in water does not photodegrade in any measurable amounts. The carbon atom in CCl4 is in its most oxidized state; therefore it is much more likely to undergo reductive degradation. It may undergo reductive dechlorination in aquatic systems in the presence of free sulfide and ferrous ions.

Biodegradation

In water, under aerobic conditions, a negative result (0% biodegradation in 14 days) has been reported for a ready biodegradability test according to OECD TGD 301 C (MITI(I) test method). However, toxicity to bacteria may have prevented biodegradation at the high concentration used in the test (30 mg/l) so the study is considered to be unreliable. In an article reporting biodegradation studies on US priority chemicals, it was observed a rapid primary biodegradation at 5 and 10 mg/L under aerobic conditions (Tabak et al, 1981; Bunch et al, 1967).

Under anaerobic conditions, several studies have reported metabolization and mineralisation of CCl4 and it can be concluded that it is rapidly biodegradable in the corresponding compartments, as well as in digesters.

In view of the limited evidence for biodegradation in aerobic (oxidative) conditions but the observed mineralisation in anaerobic (reductive) conditions, it is proposed to conclude that CCl4 is inherently biodegradable, not fulfilling criteria for the risk assessment.

7.7.2. Environmental distribution

Adsorption/desorption

The mean Koc values from 7 determinations in 2 soils were 143.6±32.11 for the silt loam and 48.9±16.16 for the sandy loam, while the weighted mean K_{oc} value for both soils was calculated being 115.2.

Volatilisation

The value used for risk assessment is an Henry's law constant (H) at 20°C of 2370 (in Pa m^3/mol or dimensionless). These data indicates that CCl4 partitions easily from water to air.

7.7.3. Bioaccumulation

Several experimental determinations of BCF have been carried out on freshwater fish species. Only one of them is reported with enough details to be used in this assessment. Other data exist on fish or algae but too few experimental information is available to use these studies in the present assessment. A data on QSAR is also given and shows a correlation with data obtained in the key study.

Low bioconcentration factors have been measured in aquatic species. In freshwater fish, the BCF has been measured and documented in rainbow trout (BCF = 40) and bluegill sunfish (BCF = 30).

7.8. Environmental hazard assessment

7.8.1. Aquatic compartment (including sediment)

7.8.1.1. Fish

The lowest value for the short term toxicity is observed in a study using zebrafish *Brachydanio rerio* (OECD TG 203), with a LC50 (96 h) of 24.3 mg/L.

For the long term toxicity, the value is based on the effect observed at the lowest concentration in a study considered to be reliable using zebrafish Brachydanio rerio in a 14

days prolonged toxicity test using a flow-trough system. This protocol is not considered as a true chronic test but rather a subchronic one. The derived NOEC was 2.5 mg/L.

A second study (Black, 1992) using rainbow trout and fathead minnow in short term toxicity tests on embryo and 'sac fry' stages is considered unreliable. This study has been criticised for testing widely spaced concentrations and giving few details of control performance and the methods were non-standard and not well validated. However, they were conducted under flow-through conditions, with control of volatile loss and with concentration analysis. Therefore, the long-term LC50 values should not be used for endpoint derivation. The 9 day-LC50 (4 days post-hatch) for *P. promelas* was 4 mg/l; for *S. gairdneri*, the 27 day-LC50 (4 days post-hatch) was 1.97 mg/l.. The lowest concentration tested which had no discernible effect on survival of *S. gairdneri* (0.07 mg/l) is not valid as a NOEC, because of the wide interval between concentrations. The conclusion of the study is that the apparent NOEC was within the range 0.07 to 1.1 mg/l. However, the lower end of this range is approximately the same than the NOEC for freshwater algae. Therefore, the *S. gairdneri* study is sufficient to demonstrate that fish are no more sensitive than other trophic levels and the study can be used for that purpose without needing to define a NOEC for PNEC calculation.

7.8.1.2. Aquatic invertebrates

There is no fully reliable study available to assess the acute toxicity of CCl4 on daphnia. There is a *weight of evidence* that the EC50-48h must be in the range 10 to 100 mg/L, based on the majority of studies submitted in the registration dossier. The data published by the Japanese Ministry of the Environment (EC50-48h of 8.1 mg/L) seems below this range and should be considered with caution since, in a reliable chronic toxicity study, no mortality was observed among parent animals, during 21 days up to the highest tested concentration of 5.7 mg/L (measured). The measured NOEC is 3.1 mg/L. Moreover, there is not enough detail to validate the data published by the Japanese Ministry of the Environment.

Consequently, eMSCA uses the lowest concentration for the short-term toxicity to aquatic invertebrates: EC50 (48h) = 35 mg/L for daphnia, static (OECD TG 202).

The concentration used for the long term toxicity is based on a compliant and well conducted GLP OECD 211 study using *Daphnia magna* in a semi static 21 days reproduction test. Both growth and reproduction endpoints yielded the same values for NOEC (3.1 mg/L) and LOEC (5.7 mg/L).

7.8.1.3. Algae and aquatic plants

In order to take into account the volatility of the substance, an adapted algae experiment on *P. subcapitata* (OECD 201 compliant study) was carried out in stoppered flasks with no headspace, and using a medium buffered with HEPES in order to avoid pH drift. Good recovery of the test substance was demonstrated through analytical measurement (GC/MS) and other validity criteria were met. Consequently the values obtained in this study can be retained as reliable to assess algae toxicity: ErC50-72 = 20 mg/L, ErC10-72 = 6.3 mg/L and NOErC = 2.2 mg/L.

7.8.1.4. Sediment organisms

Due to its high volatility and its low adsorption properties, eMSCA considers negligible the risk of CCl4 to sediment.

7.8.2. Terrestrial compartment

Due to its high volatility and its low adsorption properties, eMSCA considers negligible the risk of CCl4 to soil organisms.

However, a PNEC value was calculated based on the aquatic toxicity with the equilibrium partitioning method.

7.8.3. Microbiological activity in sewage treatment systems

Inhibition of growth of cultures of *Pseudomonas putida* shows that the threshold of toxicity is 30 mg/L (BRINGMANN-G/KUHN-R, 1980b). This threshold of toxicity can be used in place of a NOEC.

7.8.4. PNEC derivation and other hazard conclusions

Table 11

PNEC DERIVATION AND OTHER HAZARD CONCLUSIONS		
Hazard assessment conclusion for the environment compartment	**Hazard conclusion**	**Remarks/Justification**
Freshwater	PNEC aqua (freshwater): 0.22 mg/L	Assessment factor: 10 Extrapolation method: assessment factor PNEC value is derived from the lowest long toxicity endpoint available for the most sensitive species: NOErC = 2.2 mg/L on *P. subcapitata*
Sediments (freshwater)	Not relevant	Due to the high volatility of CCL4 and its low adsorption properties, the risk for sediment toxicity to be inflicted by CCL4 is regarded negligible
Sewage treatment plant	PNEC STP: 30 mg/L	Assessment factor: 1 Extrapolation method: assessment factor PNEC value is derived from the available study on *S. putida*: NOEC = 30 mg/L
Soil	PNEC soil : 0.45 mg/kg wwt	Extrapolation method: Equilibrium partitioning method based on the PNEC aqua
Secondary poisoning	Not relevant	Considering the low potential for bioaccumulation of CCL4, the risk for secondary poisoning is regarded negligible

7.9. Human Health hazard assessment

7.9.1. Toxicokinetics

The water solubility (846.1 mg/L), the log Kow value (2.83) and the small size (153.82 g/mol) of CCl4 are favourable to absorption.

Most of following data come from the ATSDR Toxicological Profile of CCl4 (2005).

Absorption: CCl4 is readily absorbed from gastrointestinal and respiratory tracts, and more slowly through skin.

Results from animal studies indicate a gastrointestinal absorption of at least 85%. Influence of the vehicle used is noted with rapid and extensive absorption when water or other aqueous vehicles are used compared to corn oil (ATSDR, 2005).

The dermal absorption rate is 53.6 ± 9.30 nmol/min/cm² for the mouse (Tsuruta et al.,1975) and 1.246 µmol/min/cm² for the rat (Morgan et al., 1991).

By inhalation, the absorption across the lung was estimated to be about 60% in humans (ATSDR, 2005). CCl4 is absorbed readily in male rats (Sanzgiri et al., 1997).

Distribution: CCl4 is distributed in all organs. Because of its lipophilic properties, CCl4 mainly accumulates in fat-rich tissues (adipose tissue, liver, bone marrow, brain and kidney) (ATSDR, 2005; Sanzgiri et al., 1997).

In spite of its physico-chemical properties, the substance is not expected to have a bioaccumulation potential since half-lifes in organs are comprised between 4 and 12 hours.

Metabolism: About 50% of CCl4 is metabolised (ANSES, 2017). CCl4 was mainly metabolized by cytochrome P-450 enzymes (CYP 2E1 and CYP3A), with the production of the trichloromethyl radical (CCl_3*). This radical can be fixed in particular to lipids thus altering their metabolism or form DNA adducts.

Excretion: CCl4 is primarily excreted in exhaled air and in the faeces, relatively minimal amounts in the urine. Excretion of CCl4 and its metabolites may vary by species, dose and route of exposure. Fourty eight hours after 4h-nose-only inhalation, rats, mice and hamsters eliminated 65-83% of the initial body burden as CO_2 or volatile organic compounds in exhaled air (ATSDR, 2005).

7.9.2. Acute toxicity and Corrosion/Irritation

Acute toxicity:

Data are of low quality for acute toxicity by oral, inhalation and dermal exposure.

The acute oral, dermal and inhalation toxicity of CCl4 in rodents is mainly based on systemic effects in the liver (centrilobular necrosis) and some effects on the kidney. The lowest LD_{50} reported after oral and dermal administrations were about 2000 mg/kg bw. By inhalation, the LC_{50} are reported to be about 7000 ppm.

In humans, the main effects observed are depression of the central nervous system, hepatic disorders progressing to hepatic insufficiency (liver failure) and renal damage that may progress to reversible renal tubulopathy. These effects are observed regardless of the route of exposure. However, inhalation is the main route of exposure in the intoxications or accidents reported in the literature. Local effects are also reported after accidental or voluntary poisoning by the oral route and after dermal exposure.

This substance is currently classified according to CLP Regulation for acute oral, dermal and inhalation toxicities as followed:

Acute tox 3*

- H331: toxic if inhaled
- H311: toxic in contact with skin
- H301: toxic if swallowed

This classification is a direct translation from the classification agreed under Directive 67/548/EEC to CLP Regulation (CLP00).

Following substance evaluation, and though it is noted by eMSCA that this endpoint is not of high priority, eMSCA proposed to modify the classification regarding Acute toxicity as :

- Acute tox 4 H332: harmful if inhaled.

Corrosion / irritation

The data available are of low quality. Slight skin or eye irritations were reported in guinea pigs and rabbits.

In humans, gastric irritations have been reported following accidental or voluntary poisoning by the oral route. CCl_4 causes the formation of transient erythema via dermal route.

7.9.3. Sensitisation

The potential of CCl4 to induce skin sensitisation was evaluated using the murine Local Lymph Node Assay (LLNA) (unpublished study report, 2010).

A dose-related increase in the SI (stimulation index) was noted at all the concentrations (25 %: SI = 1.51; 50 %: SI = 2.39; 100%: SI =6.10).

In the absence of local irritation, the positive lymphoproliferative response observed was attributed to delayed contact hypersensitivity. The EC_3 value for CCl4 was equal to 58%.

Therefore, on the basis of this LLNA assay, CCl4 should be classified as skin sensitiser category 1B according to CLP regulation EU No. 286/2011. An update of the harmonised classification should be initiated.

7.9.4. Repeated dose toxicity

Repeated dose toxicity, oral:

No reliable study in humans was identified.

Many animal studies were available. All the studies were considered of reliability 3 or 4. None of them was performed according to GLP nor other official current guideline (Bruckner et al., 1986; Condie et al., 1986; Hayes et al., 1986; Koporec et al., 1995).

The lowest relevant NOAEL identified (NOAEL = 1 mg/kg bw /day) was based on effects observed in the liver of male rats at 10 mg/kg bw/day (Bruckner et al., 1986). Only a limited number of parameters were tested in comparison with the OECD TG 408. In this study, male rats were treated by gavage 5 days/week with 1, 10, 33 mg/kg bw of CCl4 in corn oil during 12 weeks. Three parameters of liver injury (OCT (ornithine carbamyl

transferase) activity, SDH (sorbitol dehydrogenase) activity and GPT (glutamic-pyruvic transaminase) activity) and one for kidney injury (blood urea nitrogen) were determined in addition to histopathology of liver and kidney. Slight but statistically significant increase of SDH value and mild hepatic centrilobular vacuolization were observed at 10 mg/kg bw. In the high dose group marked hepatotoxicity was noted including vacuolization, nuclear and cellular pleomorphism, bile duct hyperplasia and periportal fibrosis.

The other studies available support the above finding.

Condie et al. (1986) reported a similar NOAEL of 1.2 mg/kg bw/day when mice were exposed by gavage to CCl4 in corn oil at dose levels of 1.2, 12 or 120 mg/kg bw for 90 days (5 days/week). The primary target organ was the liver with fatty change as first noticeable effect followed by central lobular degeneration, fibrosis and finally cirrhosis. Liver toxicity was also apparent due to the rise of classical biochemical parameters (AST (aspartate aminotransferase), ALT (alanine aminotransferase), AP (alkaline phosphatase), SDH, LDH (lactate dehydrogenase), etc.).

Hayes et al. (1986) also identified liver as the most sensitive target organ in mice exposed by gavage. Indeed, effects on clinical chemistry were reported at all tested doses (between 12 to 1200 mg/kg bw/day for 13 weeks). In addition, the kidneys, thymus and spleen were identified as other target organs based on relative and absolute organ weight.

Similar findings were observed by Koporec et al. (1995) at all tested doses (25 or 100 mg/kg bw) of CCl4 administrated by gavage for 90 days in male rats.

Finally, Kutepov et al. (1968) stated a NOAEL of 0.15 mg/kg bw/day and a LOAEL of 1.5 mg/kg bw/day for rats exposed orally for 6 months, based on biochemical parameters (AST, ALT) and determination of liver excretion function. But this 6-month study presented some major deficiencies: dose spacing between the doses was high and the LOAEL was very close to the NOAEL determined in the Bruckner et al. (1986) study, no information concerning the type of administration (gavage or diet), the number of animals, and no detailed result. The presented information was so limited that this study was judged unreliable.

Mechanism of toxicity

Liver and kidney are especially vulnerable to the toxicity of CCl4 because of the abundance of CYP2E1 and various isoforms of CYP3A. Hepatic injury results from bioactivation of CCl4 into free-radical metabolites of CCl4 and lipid peroxidation.

Intrinsic tissue levels of antioxidants such as glutathione influence the degree to which oxidative damage progresses following exposure to CCl4. Another factor that may be of importance in CCl4-induced hepatotoxicity is the perturbation of normal cellular calcium homeostasis following exposure.

In conclusion, the NOAEL of 1 mg/kg bw/day from the Buckner et al. (1986) study is the most relevant value from the available studies considering the observed effects and the dose spacing.

Repeated dose toxicity, dermal:

No study was available for this endpoint.

Repeated dose toxicity, inhalation:

Several studies performed by inhalation are available for CCl4. The most relevant data come from studies carried out by Nagano et al. in 2007.

In a 13-week study, carried out according to OECD guideline 413 and with a Klimisch score of 1, Nagano et al. (2007a) administered CCl4 at 0, 10, 30, 90, 270 and 810 ppm (corresponding to 64, 192, 576, 1728 and 5184 mg/m^3) by inhalation (whole body) 6 hours per day, 5 days per week to male and female rats and mice. The most sensitive endpoint is liver toxicity, including liver fatty change with large droplets found at all concentrations in both species, as well as an increased relative liver weight only in male rats. Enhanced cytolytic release of liver transaminase into plasma was observed at medium (30 and 90 ppm) and high levels (270 and 810 ppm) of exposure. At high exposure levels (270 and 810 ppm), altered cell foci in the liver, fibrosis and cirrhosis were observed.

It should be noted that these findings are relevant for humans as reported by Gluchowski NL 2017.

Nephrotoxicity was also observed: increased relative kidney weight (at dose ≥ 90 ppm in male and female rats and at dose ≥ 30 ppm in male mice and ≥ 270 in female mice), increased urinary protein (in male rats at doses ≥ 270 ppm and in female at doses ≥ 90 ppm) and localized glomerulosclerosis in male and female rats exposed to 810 ppm.

Based on the effects reported at all concentrations in the liver, a NOAEC could not be derived; the LOAEC is 10 ppm (64 mg/m^3).

The liver effects were preneoplastic lesions of hepatocarcinogenesis which were studied in the 2-year study performed by Nagano et al. (2007b). In this study, male and female rats and mice were exposed by inhalation to 0, 5, 25 and 125 ppm (0, 32, 160 and 800 mg/m^3) of CCl4 for 2 years, 6 hours per day, 5 days per week. This study was assigned with a Klimisch score of 2 (lack in reporting of experimental data but well conducted; further details on this study are reported in section 7.9.6 of this document).

In mice, a LOAEC of 25 ppm (160 mg/m^3) and a NOAEC of 5 ppm (32 mg/m^3) were determined, based on the increase of organ weights (liver and adrenal gland) and biochemical parameters indicative of liver toxicity.

For rats, increased urinary protein levels was observed in the low dose groups (5 and 25 ppm). The kidney toxicity (increase blood urea nitrogen (BUN), creatinine…) was reported at exposure concentration of 25 ppm and more. While the increased severity of proteinuria could be related to the nephropathy at ≥ 25 ppm, the biological significance at 5 ppm was unknown. Proteinuria was found in essentially 100% of the rats (both control and CCl4 exposed) and 90% or more of the rats had proteins in urine. However, in the exposed animals, rats showed an increase in the severity of proteinuria compared to controls. After 2 years of exposure, proteinuria in rats treated with 5 ppm, did not progress (rats did not show treatment related increases in incidence or severity of renal changes that were observed at higher exposure). Furthermore, the F344 rat is known for its high incidence of spontaneous, age-related chronic progressive nephropathy (CPN). Therefore, the relevance of the effect reported at 5 ppm remains questionable.

The toxicity of CCl4 seems more influenced by the concentration than the duration of exposure as the LOAEC for systemic toxicity were in the same order of magnitude in the 90-day study and 2-year study of Nagano (2007 a & b).

Further studies, with low reliability, support the results reported by Nagano et al. (2007 a & b):

Smyth (1936) (klimisch score: 4) reported effects of CCl4 at all concentrations tested (from 25 ppm in guinea pigs with lactate treatment and from 50 ppm for rats, guinea pigs and monkeys) after exposure for 10.5 months 8h/d; 5d/w. Liver was identified as the most sensitive organ. In addition, granular swelling of the adrenals was observed in guinea pigs at 25 ppm and more.

The study of Adams (1952) presented a LOAEC of 10 ppm (64 mg/m^3) in rats and guinea pigs for subchronic repeated dose toxicity via inhalation exposure during 15-25 weeks. This LOAEC was also based in fatty change in the liver and liver weight increase. The corresponding NOAEC was 5 ppm (32 mg/m^3). However, a Klimisch score of 4 was assigned to this study as only a limited number of parameters were tested as compared to OECD TG 413. Nevertheless this result was in line with the subchronic inhalation 90-day study of Nagano (2007a) and could be used as supportive data.

A LOAEC of 62 mg/m^3 was identified after a subchronic continuous exposure to CCl4 (24h/day, 7d/week, 13 weeks) based on fatty change in the liver and increase liver weight in rats (Mac Ewen et al., 1966 – Klimisch score: 4). No NOAEC can be derived.

The study of Prendergast (1967)(Klimisch score: 4) where rats, guinea pigs, rabbits and monkeys were exposed continuously (24h/day, 7d/week) for 90 days to 6.1 mg/m³ and 61 mg/m³ (0.95 and 9.5 ppm) of CCl4 reported a NOAEC of 0.95 ppm based on fatty change in the liver and liver weigh increase. This NOAEC can correspond to a value of 34.2 mg/m^3 when converting this continuous exposure into an exposure of 6h/day; 5d/week as in the Nagano et al. (2007a) study. This is thus consistent with the NOAEC of 32 mg/m^3 identified from the Nagano study (2007b).

A LOAEC of 63 ppm was derived in rats after a 4-week exposure to CCl4; 6h/d; 7d/week based on fatty change in the liver, increased liver weight an biochemical findings (Bogers et al., 1987 – Klimisch score: 4). No NOAEC can be derived.

In conclusion, the most sensitive target organ of CCl4 toxicity is the liver. In addition, CCl4 has also a nephrotoxic potential at concentrations higher than those inducing hepatotoxicity (Nagano et al. 2007).

Human data:

Occupational exposure to unknown concentrations of CCl4 vapor for periods between 6 weeks and 3 months resulted in gastro-intestinal effects (nausea, vomiting, abdominal pain, anorexia), hepatic effects (observed as jaundice), and neurological effects (headache, dizziness) (Norwood, 1950).

Kazantis (1960) described symptoms in 17 workers exposed to CCl4 vapor at concentrations between 45 and 97 ppm, which were anorexia, nausea, vomiting, epigastric discomfort or distention, depression, irritability, headache, or giddiness. Symptoms typically occurred during the latter of the workweek and recovered at the end of week-end. One worker reporting these symptoms during a period of 2 years, had also an increased serum AST level.

Tomenson (1995) conducted a cross-sectional study of hepatic function in 135 CCl4-exposed workers in 3 chemical plants and in a control group of 276 unexposed workers. Blood samples were analysed for ALT, AST, alkaline phosphatase, gamma-glutamyl transferase, glutamate dehydrogenase, 5'-nucleotidase, total bile acids, cholesterol, triglycerides and hematological variables. The quantitative exposure levels associated with each of these categories were: ≤1 ppm for "low", 1.1-3.9 ppm for "medium", 4-11.9 ppm for "high". Exposed workers were also categorized according to length of time in job (<1, 1-5, >5 years). Overall, this study provided suggestive evidence of an effect from occupational CCl4 exposure on hepatic serum enzymes, indicating effects in human liver. Specifically, serum enzyme changes suggested an exposure-related effect in medium and high exposure categories. In the low exposure group, only the haematocrit was significantly decreased.

Classification:

The substance is currently classified according to CLP Regulation as STOT RE 1 (H372) with a specific concentration limit of 1 % after direct translation from the classification agreed

under Directive 67/548/EEC. Current harmonized classification should be updated to add the route of exposure (oral; inhalation) and the target organ (liver).

7.9.5. Mutagenicity

Many studies are available. However, a very limited number of these studies were conducted according to OECD guidelines and GLP. The data have been evaluated by different organisations (IARC, 1999; WHO, 1999; ATSDR, 2005; Afsset, 2009; US-EPA, 2010; Anses, 2017). Considering all the studies, it is possible to conclude by a *weight of evidence* approach that this substance is not genotoxic.

Genetic toxicity in *in vitro* microbiological systems:

The majority of mutagenicity assays for bacteria exposed to CCl4 gave negative results with or without metabolic activation, but volatilization of the chemical in standard plate incorporation methods using unsealed plates may have contributed to some negative findings.

In conclusion, positive slight effects were only observed at high dose and in particular in *E. Coli* strains which are more sensitive to oxidative mutagens (EPA, 2010; SCOEL, 2009).

Genetic toxicity in *in vitro* mammalian cell systems:

Various authorities (ATSDR 2005, EPA 2010, ANSES, 2017) reach similar conclusions regarding the *in vitro* tests in mammalian cells: some tests were positive, some were negative, some were ambiguous. In most of the positive tests, the effects can be explained more likely by oxidative DNA damage, secondary to cytotoxicity of CCl4.

In 2010, the EPA concluded that under certain conditions, CCl4 can induce genotoxic effects in mammalian cells exposed *in vitro*. Multiple studies indicated that at high dose, bioactivated CCl4 was able to cause DNA breaks leading, in some cases, to chromosome breakage. Multiple studies indicated that CCl4 was able to interfere with chromosome segregation resulting in modest levels of chromosome loss and aneuploidy. Both specific and non specific mechanisms were envisaged. In most tests with positive results, genotoxic effects were observed with significant toxicity.

Genetic toxicity in *in vivo* cell systems:

In general, studies analysing genotoxic effects of CCl4 with established methods (Suzuki 1997, Foureman 1994, Sawada 1991, Sasaki 1998, Barbin 1982, Bermudez 1982, Mirsalis 1982, Stewart, 1981 and Schwarz 1979), different species, strains and techniques gave negative results for the genotoxic potential of CCl4 *in vivo*.

In oral gavage studies, there were no increase in the frequencies of chromosomal aberration, sister chromatid exchange, or micronucleus formation in the liver of rats or in the frequency of micronucleus formation in bone marrow of mice (Sawada et al. 1991; Suzuki et al. 1997).

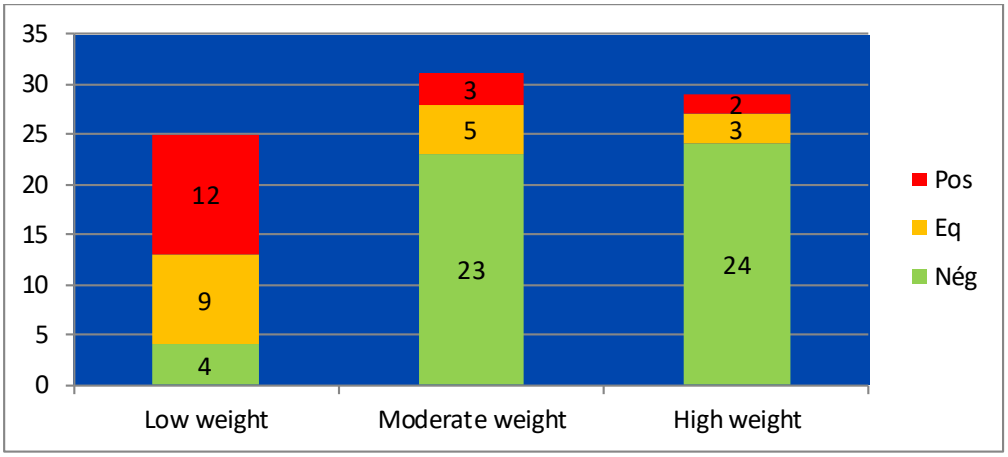
Covalent adducts of CCl4 metabolites in the liver had been reported in the literature but the amount of adducts was low as compared to the administered doses. Covalent adducts have no relevant significance if they are the only one sign of genotoxicity.

In conclusion:

The genotoxicity of CCl4 was evaluated by many international organisations (IARC, 1999; WHO, 1999; ATSDR, 2005; Afsset, 2009; US-EPA, 2010; Anses, 2017). In particular, Anses (2017) applied a *weight of evidence* approach on the results summarized by US EPA (2010)

to conclude on the genotoxic potential of CCl_4. It was concluded that most of the reliable studies (in particular Ames test, *in vivo* micronucleus assays, chromosomal aberrations tests, tests on transgenic animals) gave negative results. Positive results were rather obtained with tests assessing primary DNA damages. The summary of this assessment is provided in table 7.9.5-01.

Table 7.9.5-01. Summary of studies performed with CCl4 resulting to positive results (red), equivocal results (orange) and negative results (green) depending of the weight of the study (extracted from Anses, 2017).



Based on all these assessments, CCl4 is not considered as a direct genotoxic agent, unless very high doses are used (*in vitro* only). DNA damages can be due to ROS and/or lipid peroxidation or related to a cytotoxic response since genotoxic effect was only observed at dose high where hepatic cytotoxicity occurred. The role of postulated reactive metabolites (including aldehydes, trichloromethyl or thrichloromethylperoxyl free radicals, phosgen) in DNA damage was also hypothetized.

7.9.6. Carcinogenicity

For this endpoint, several studies were available (exposure by oral route and by inhalation). The main target organ (liver) was the same after oral or inhalation exposure.

Human data:

Industry-based studies are available with CCl4. According to IARC 1999, the risk of cancer has been examined in five occupational populations. In three out of four studies that collected information on non-Hodgkin lymphoma (two cohort investigations and one independent nested case–control study), associations with exposure to CCl4 were suggested. However, not all of these studies distinguished exposure to CCl4 specifically, and the associations were not statistically significant.

In the fourth study (another cohort investigation), few men were exposed to CCl4 and the risk of non-Hodgkin lymphoma was not reported. In addition, no association was found between exposure to CCl4 and non-Hodgkin lymphoma in a case-control study, although the power to detect an increased risk was low. There was no association between exposure to CCl4 and lung cancer (nested case-control study) or chronic lymphocytic leukaemia, brain cancer, female breast cancer and intraocular melanoma (population-based case–control studies) (IARC, 1999).

Carcinogenicity, oral:

Only non-reliable carcinogenicity studies by oral exposure were available (in particular due to non adequate duration of exposure). Available data however support the evidence of carcinogenic effects of CCl4 in the liver of rodents after oral exposure.

In the study of Eschenbrenner (1946), mice were treated with CCl4 in corn oil by oral gavage with 0, 10, 20, 40, or 80 mg/kg/d daily or 0, 40, 80, or 160 mg/kg bw/d every 4 days for 120 days. Based on the increase of hepatoma incidence, a NOAEL of 10 mg/kg bw/d was identified for the 120-daily exposure. A correlation between the severity of liver necrosis and the incidence of hepatomas in relation to the dose was observed in mice.

In the study of Page et al. (1976), rats and mice were orally treated for 78 weeks. Rats showed severe liver toxicity (fibrosis, bile duct proliferation and regenerative nodule) and a slight increase of the incidence of liver carcinomas and pre-neoplastic lesions for all treatment groups (males: 47 and 94 mg/kg bw/d; females: 80 and 159 mg/kg bw/d). Mice showed severe dose-dependent hepatotoxicity and hepatocellular carcinomas (at 1250 and 1500 mg/kg bw/d). No NOAEL can be derived from this study.

In the study of Weisburger et al. (1977), rats and mice were exposed by gavage to CCl4 for 78 weeks, with sacrifice at 90 weeks for mice and 110 weeks for rats. Hepatocellular carcinomas and adrenal tumours were observed in mice. In rats, moderate increase of neoplastic nodules and carcinomas of the liver were observed. No NOAEL can be derived from this study.

In contrast, no liver cell carcinoma was reported in hamsters treated once weekly for 30 weeks in corn oil at 19.81 mg/kg bw (Della Porta et al., 1960).

In conclusion, tumorigenic responses had been observed after oral administration of CCl4. The liver was the main target for tumours' occurrence. The lowest NOAEL identified was 10 mg/kg/d based on hepatomas in mice after exposure to CCl4 via gavage during 120 days (Eschenbrenner, 1946).

Carcinogenicity, inhalation:

CCl4 was tested for its carcinogenicity properties after inhalation in the rat and the mouse in a 2-year combined carcinogenicity/repeated dose study of Nagano et al. (2007b). Animals were exposed for 104 weeks, 6 h/d, 5 d/week to concentrations of 5, 25 or 125 ppm (0, 32, 160 and 800 mg/m^3). The study was performed in compliance with OECD TG 453 and GLP.

In both species, at 160 and 800 mg/m^3 (25 and 125 ppm), a marked to severe liver toxicity and an increase in incidences for liver adenomas (27/50 and 16/50 male mice; 17/50 and 5/49 female mice; 1/50 and 21/50 male rats; 0/50 and 40/50 female rats) and liver carcinomas (44/50 and 47/50 male mice; 33/50 and 48/49 female mice; 0/50 and 32/50 male rats; 3/50 and 15/50 female rats) were observed. The survival rates were decreased for both species at 125 ppm, causally related to various tumors including hepatocellular carcinoma in mice and rats and severe chronic progressive nephropathy in rats. At 32 mg/m^3 (5 ppm) the number of liver adenoma or carcinomas in both species were not raised and only minor toxic effects were apparent. In the female mice group at 32 mg/m^3 (5 ppm), an increased number of hepatocellular adenomas (8/49 compared to 2/50 in control) was reported but only with a low statistically significance (Fisher exact test, $p<0.05$). In addition, in mice, the incidence of phaeochromocytomas of the adrenal gland (0/50, 0/50, 16/50 and 31/50 males; 0/50, 0/49, 0/50 and 22/49 females) was increased in mid- and high-dose males and in high-dose females.

These data confirmed the liver as primary target for the carcinogenicity of CCl4. A NOAEL of 5 ppm (= 32 mg/m^3) for hepatoadenomas and carcinomas in both species after chronic exposure to CCl_4 via the inhalation route can be derived from this study.

Carcinogenicity, dermal:

No study was available for this endpoint.

General conclusion on carcinogenicity:

Studies in humans are inadequate to show an association between exposure to CCl4 and carcinogenicity (due to co-exposure for example). None of the human epidemiology studies reported associations to cancer of the liver, which is the main site of carcinogenicity in animal studies. Experimental studies clearly showed that CCl4 is carcinogenic in animals (in different species and for both sexes).

According to IARC (1999), there is inadequate evidence in humans for the carcinogenicity of CCl4 but there is sufficient evidence in experimental animals for the carcinogenicity of CCl4. Overall, IARC evaluation concluded that CCl4 is possibly carcinogenic to humans (group 2B).

Mecanism of action

The observed tumorigenic response of CCl4 seems directly linked to its metabolism and secondary to the cytotoxicity of the metabolites. The first step of metabolism by CYP2E1 is an homolytic cleavage of one carbon chlorine bond in CCl4 to yield chloride ion and the trichloromethyl radical.

In anaerobical conditions, the trichloromethyl radical may undergo several reactions:

- Direct binding to microsomal lipids and proteins
- Addition of a proton and an electron to form chloroform
- Dimerization to form hexachloroethane
- Further reductive dechlorination to form carbon monoxide.

Aerobically, the trichloromethyl radical may be trapped by oxygen to form trichloromethylperoxy radical which decomposes to phosgene (COCl2), which undergoes hydrolytic cleavage to form CO_2. The trichloromethylperoxy radical is more reactive than the trichloromethyl radical toward amino acid.

Both haloalkylation and lipid peroxidation contribute to loss of cellular functions and subsequent cell death.

Taking into account the results of genotoxicity data, CCl4 is not considered as a direct genotoxic agent but acts as a carcinogen by a threshold mode of action. Cytotoxicity and regeneration seem therefore to be a main factor in the apparition of (pre-)neoplastic lesions.

In conclusion, CCl4 is considered to act as a carcinogen by a threshold mode of action. The underlying carcinogenic mode of action is not clearly known. The hypothesis is that CCl4 is metabolized by CYP2E1 into radicals or other reactive species leading to lipid peroxidation with associated cell cytotoxicity / proliferation (Anses, 2017).

Classification

Appropriate experimental studies clearly shown that CCl4 is carcinogenic in animals (in different species and for both sexes). In humans, no reliable study allowed to conclude on an association between CCl4 and cancers.

The substance is currently classified as Carc. Category 2 (Suspected human carcinogen) - H351 according to EU Regulation (EC) No. 1272/2008 (CLP).

eMSCA will consider the opportunity to classify the substance as carcinogenic 1B – H350. Indeed, effects observed in animals may be relevant for humans as reported by Gluchowski NL 2017.

7.9.7. Toxicity to reproduction (effects on fertility and developmental toxicity)

Effects on fertility

There is no reliable study to adequately assess effects of CCl4 on fertility.

In a study performed by Alumot et al. (1976), the potential of CCl4 to adversely affect the health and the fertility of rats was analysed in a chronic 2-year feeding study with fumigated food at concentrations of 80 and 200 ppm CCl4. Females were mated with untreated males, 6 weeks after the start of the treatment, to test their basic reproductive capacity. At intervals of 2 months, 9 males of each dose group were mated with 2 treated females, the other 9 males mating with 18 sterile untreated females. The offspring was examined for litter size, viability, body weight and body weight gain. After study termination the parental animals were analysed for biochemical parameters of liver toxicity.

The treatment groups did not differ in any of the parameter from the control, except for the number of parturitions in the high dose group in the fourth mating. But this rate recovered to normal in the 5th.

However, this study was assigned with a Klimisch score of 4 due to extensive deviations from any available recognised guidelines/protocols for reproductive endpoints (neither OECD guidelines n°416/443 nor RACB (Reproductive Assessment by Continuous Breeding) protocol). The comparison of the protocol study with recognised protocols showed some deviations on the choice of tested doses, exposure design and data collected. Indeed, only two concentrations were tested instead of three as recommended in the protocol and at the highest dose no toxicity was observed. An expected difference in body weight of 10% compared to the controls should be observed, however it was not the case. Although the exposure seems (as the schedule of treatment is unclear) continuous, major differences from the RACB protocol were found, notably the cross mating (task 3 of protocol) and second generation (task 4) were not performed.

The parameters that were evaluated in the Alumot study are not sufficient to assess the capability of the animals to reproduce and to assess potential effects on fertility. In particular, only observations such as % pregnant, % with litters and % of mortality of young (all pregnancies mixed without detailed results) were reported. Several fertility parameters were not analysed such as: day of delivery, sex ratio, development of pups until weaning etc. Furthermore, gross and microscopic observations of all organs and body cavities, reproductive organs weights (ovary, testis, epididymis, seminal vesicle and prostate), oestrous cycle, testicular spermatid head and cauda epididymal sperm counts of the parents and pups should be observed and reported as recommended in the protocol but that is not the case in this study.

Human sperm production appears to be much closer to the infertility threshold; therefore, less severe sperm count reductions may cause human infertility. Indeed, male rats produce a number of spermatozoids that greatly exceed the minimum requirements for fertility, particularly as evaluated in reproductive studies that allow multiple matings. In some strains of rats and mice, sperm production can be drastically reduced (by up to 90% or more) without affecting fertility. It is therefore important to assess the sperm quality of the animals instead of assessing only female fertility index or gestation index. Negative

results in rodent studies that are limited to only fertility and pregnancy outcomes provide insufficient information to conclude that the test substance has no reproductive hazard in humans.

In the absence of a full reproductive toxicity study with CCl4, other toxicity studies can bring some information on the potential of CCl4 to affect reproduction. No effect on reproductive organs and tissues were clearly reported in the repeated-dose toxicity studies available. However, it is not clearly specified for these studies if the reproductive organs are analyzed. In this context, it is not possible to conclude if the absence of effect is due to a lack of toxicity or an absence of examination of reproductive organs.

In contrast, testicular atrophy, abnormality in the process of spermatogenesis, inhibition of estrous rhythm and weight and vascularization decreases of ovary and uterus, were reported in the litterature (Chatterjee et al., 1966; Chatterjee et al., 1968; Kalla and Bansal 1975). CCl4 was also used in several studies published in 2013 (Türk G. et al. 2013; Sönmez M. et al. 2013; Yüce A. et al. 2013) as an inductor of sperm damages (including abnormal sperm rate and decreased sperm concentration and motility) and testicular apoptosis in male rats treated weekly with 0.25 ml/kg of CCl4 in olive oil by gavage for 10 weeks. An oxidative stress mechanism is suspected by formation of free oxygen radicals which have high affinity to cell membrane lipids leading to tissue damage of testis and effects on sperm during maturation. But none of them are carried out or are comparable to current official guidelines.

Developmental toxicity

Several studies are available for this endpoint.

Only one study was available with inhalation exposure (Schwetz, 1974) in which Sprague Dawley rats were exposed to 300 or 1000 ppm CCl4 for 7h/day on days 6-15 of pregnancy. Evidence of maternal hepatotoxicity was seen in both groups; serum glutamic-pyruvic transaminase (SGPT) was significantly elevated during exposure but had returned to normal by day 21 of gestation when relative liver weights were significantly increased but absolute weights unchanged. There was no statistically significant effect on resorptions though 1/23 litters was fully resorbed in the 1000 ppm group. No gross external abnormalities were seen in any group. The data on internal and skeletal anomalies are difficult to evaluate: only information on the number and percentage of litters affected is given, with no data on the numbers of foetuses affected. However, no significant increases of anomalies are reported, except for subcutaneous oedema in the 300 ppm group and sternebral anomalies in the 1000 ppm group. These increases were judged unlikely to be of any biological significance since oedema was not significantly elevated in the 1000 ppm group and the incidence of sternebral anomalies varied considerably in the two control groups. Foetal body weight and crown-rump length were significantly decreased in a dose related manner but this is not unexpected in view of the severe effect on food consumption in the dams. Therefore, both maternal (hepatotoxicity) and developmental toxicity (body weight and crown-rump length decreased) were observed at a LOAEC of 300 ppm (2.11 g/m^3). No NOAEC could be derived.

Four studies by oral route are available.

Rats were treated with 0, 112.5 and 150 mg/kg bw/d of CCl4 via gavage on gestation days 6-19 (Narotsky et al., 1995). Maternal effects comprised piloerection and weight loss on gestation days 6-8 at both dose groups. An increase of resorption rate at 112.5 and 150 mg/kg bw/d was observed (44.4% and 71.4% compared to 0% in controls).

Litter resorption seems to be the most sensitive developmental toxicity effect of CCl4 in rats. In this context, Narotsky et al. (1997a) treated pregnant rats with 0, 25, 50 and 75 mg/kg bw/d via gavage on gestation days 6-15. Maternal effects comprised piloerection from 50 mg/kg and weight loss on gestation day (GD) 6-8 at 75 mg/kg bw/d. Embryotoxic effects characterized by full litter resorptions were obvious at 50 mg/kg bw/d and higher. Based on these results, a NOAEL of 25 mg/kg bw/d for developmental toxicity and maternal toxicity in rats was identified.

In order to identify the critical period of CCl4-induced pregnancy loss in rats, Narotsky *et al.* (1997b) administered the substance (single dose of 150 mg/kg bw) by gavage on gestation day 6, 7, 8, 10 or 12. Full litter resorptions were shown to occur early at GD 6-10 and were absent when rats were treated at GD12. Early in the pregnancy represents a period of susceptibility to acute exposures of CCl4.

No developmental toxicity was evident in surviving litters.

The following mechanism of action is hypothetized: progesterone could be involved in the full litter resorptions due to maternal hepatic toxicity since liver plays a role in the steroids synthesis and catabolism. This suggests that maternal toxicity could play a role on full litter resorptions. In follow-up investigations, Narotsky et al (1995, 1997)(US EPA, 2010) show association between the response and reduced levels of progesterone and luteinizing hormone. The authors found that after an administration of 150 mg/kg bw CCl4 on gestation day 8 the level of luteinizing hormone was drastically reduced during a phase of ca. 20 h post administration as compared to controls. Treated rats had significantly more full-litter resorptions (rarely seen in untreated rats of this strain). The effect could be rescued by coadministration of human choriongonadotropin, acting as LH surrogate. This suggests a specific mechanism causing full-litter resorptions.

In a review of the potential teratogenicity of substances emanating from landfill sites (Department of Health, 2001), CCl4 is suspected not to be embryotoxic by itself, but to cause litter resorptions by disrupting the endocrinal maintenance of pregnancy. The authors concluded "*Reproductive toxicity studies in rats have shown that reproductive effects are only observed at doses causing maternal toxicity. The only embryofetal toxicity reported with inhalation exposure at up to 1000 ppm (6410 mg/m^3) CCl4 during the period of organogenesis was reduced fetal bodyweight and retarded ossification, probably secondary to reduced maternal food intake and bodyweight gain. No fetal malformations were observed. At higher oral doses of 50 mg/kg bodyweight in rats around the time of implantation, complete resorption of litters may be observed which are very probably due to interference with maternal hormonal balance, and not due to a direct embryotoxic effect.*" The effect of subtle hormonal changes potentially induced by lower doses of CCl4 has not been studied.

Conclusion

There are still some uncertainties related to potential reproductive toxicity due to contradictory data and low relevance of the available studies. However, given the current tonnages and uses of the substance and the risk management measures which should be already in place, considering the known toxicity of the substance, these uncertainties alone do not substantiate a potential risk to be addressed under substance evaluation. This substance evaluation can be concluded without a request for further information.

ECHA has checked the compliance with the standard information requirements under REACH for reproductive toxicity and considered it compliant at the currently registered tonnage levels. However, if the registered tonnage increases in future, the eMSCA recommends ECHA to consider this substance for prioritisation for compliance check.

Classification:

There is no harmonized classification for this endpoint. But 8 notifiers declare a self-classification as Repr. 2 - H361.

Classification for reproductive endpoint could be re-assessed if new information becomes available.

7.9.8. Hazard assessment of physico-chemical properties

Not assessed.

7.9.9. Selection of the critical DNEL(s)/DMEL(s) and/or qualitative/semi-quantitative descriptors for critical health effects

Several toxicological reference values exist in the literature for repeated exposure to CCl_4 by inhalation (ATSDR, 2005; RIVM, 2001; OEHHA, 2000; US EPA, 2010).

For subchronic exposure, a MRL (minimal risk level) of 180 µg/m^3 was derived by ATSDR (2005). This value is based on liver effects with a NOAEC of 5 ppm issued from Adams et al. (1952) study.

For chronic exposure, threshold-based toxicological reference values range from 40 µg/m^3 (OEHHA, 2000) to 180 µg/m^3 (ATSDR, 2005). All these values were based on liver effects.

OEHHA (2000) and US EPA (2010) also derived non-threshold reference values of $4.2.10^{-5}$ $(\mu g/m^3)^{-1}$ and 6.10^{-6} $(\mu g/m^3)^{-1}$, respectively, based on the increase of liver tumours.

More recently, Anses (2017) derived a toxicological reference value of 0.11 mg/m^3 (0.0184 ppm) for carcinogenicity of CCl_4. This value is based on the increase of liver tumours (threshold mechanism assumed) and intends to protect general population. This value is recommended by eMSCA but is not expected to be used by registrants as no consumer uses are authorized under Regulation (EC) No 1005/2009.

Table 12

CRITICAL DNELS/DMELS					
Endpoint of concern	**Type of effect**	**Critical study(ies)**	**Corrected dose descriptor(s) (e.g. NOAEL, NOAEC)**	**DNEL/ DMEL**	**Justification/ Remarks**
Carcinogenicity, inhalation	Hepatocellular adenoma and carcinoma	Nagano et al. 2007	BMDL10%L95% = 2.6 ppm Adjusted BMDL = 2.6 ppm x 6/24 x 5/7 = 0.46 ppm = 2.91 mg/m^3	0.11 mg.m^{-3} (0.0184 ppm)	Uncertainties factors = 25 (interspecies = 2.5 x intraspecies = 10). General population.

7.9.10. Conclusions of the human health hazard assessment and related classification and labelling

Regarding acute toxicity, CCl4 is currently classified as Acute Tox 3* for oral, dermal and inhalation routes. The substance is slightly irritant to skin and eye and is a skin sensitizer.

Regarding repeated-dose toxicity by oral and inhalation routes, liver is the most sensitive target organ of the CCl4 toxicity. The lowest relevant NOAEL after oral administration is 1 mg/kg bw/day from a 12-week study (Bruckner et al., 1986). After inhalation, the lowest NOAEC is 5 ppm from a 2-year study (Nagano et al., 2007b). CCl4 is currently classified as STOT RE 1.

By a *weight of evidence* approach, CCl4 is not considered as a direct genotoxic agent but acts as a carcinogen by a threshold mode of action. Indeed, CCl4 induced liver adenoma and carcinoma after oral and inhalative routes of exposure in rodents. CCl4 is currently classified as Carc. Cat. 2.

Following the substance evaluation, eMSCA will consider an update of the classification of CCl4 in order to:

- remove the minimal classification for acute toxicity –Acute tox. 4 – H332;

- add a classification for skin sensitisation properties: Skin Sens. 1B – H317;

- update the classification STOT RE 1 – H372 to add the route of exposure (oral; inhalation) and the target organ (liver);

- update the classification Carc. Cat. 2 – H351 to Carc. Cat. 1B – H350.

7.10. Assessment of endocrine disrupting (ED) properties

7.10.1. Endocrine disruption – Environment

Not specifically assessed.

7.10.2. Endocrine disruption - Human health

Not specifically assessed.

7.10.3. Conclusion on endocrine disrupting properties (combined/separate)

Not specifically assessed.

7.11. PBT and VPVB assessment

Not assessed.

7.12. Exposure assessment

7.12.1. Human health

7.12.1.1. Workers

Considering the high aggregated tonnage, the eMSCA identified, based on the information provided in the chemical safety reports, a potential concern regarding the use of measured data instead of modelling (Tier 1 model TRA Workers 3.0).

In particular, for several contributing scenarios, the lead registrant used the average value of measured data, except in one case where the 90th percentile value is used

(recommended by R14 ECHA Guidance[2]). It appears that the registrants used the average values instead of the 90th percentile values when RCR were > 1 with exposure concentrations based on 90th percentile values, leading to risks possibly not adequately controlled. This is supported by the estimated concentrations of TRA Workers 3.0 giving RCR >1 with the DNEL proposed by the lead registrant (inhalation route, systemic, long-term). A refined assessment of the following contributing scenarios is therefore recommended:

- Closed manufacturing process (PROC 2);
- Loading of the substance / receiving and charging the substance (PROC 8b);
- Use in laboratory (PROC 15).

Overall, exposure data provided in registration dossier (both modelled and measured) do not exceed OELs recommended by SCOEL.

7.12.1.2. Consumers

The consumer uses are prohibited under Regulation (EC) No 1005/2009 on substances that deplete the ozone layer.

7.12.2. Environment

Exposure assessments provided by 2 registrants have been evaluated.

7.12.2.1. Registrant 1

<u>Exposure scenario 1: Manufacture</u>

CCl4 is produced on one site. Releases to environmental compartments are based on site specific information and monitoring data, taking into account the following assumptions:

- Water releases are collected and undergo a physico-chemical treatment (distillation with recycling into the process and settling tank) before being sent to an on-site waste water treatment plant.
- Gaseous vents are collected and send to a thermal oxidation treatment
- Wastes generated are collected and send for incineration

<u>Exposure scenario 2: Use at industrial site - Use as solvent</u>

The substance is used as a solvent on one site only, in a closed continuous process. At the use site (delivery by tank truck), CCl4 is unloaded into a storage tank and is then transferred into a closed reactor where the synthesis takes place. Releases to environmental compartments are based on site specific information and monitoring data, taking into account the following assumptions:

- Water releases are collected and undergo a physico-chemical treatment. The organic phase containing the substance and the aqueous phase are first separated in a settling tank. The organic phase is recycled into the process. A stripping (steam) is carried out on the aqueous phase that is sent to a sewage treatment plant afterwards.
- Gaseous vents are collected and sent to a thermal treatment for incineration. The combustion of these vents produces hydrogen chloride that is then recycled as an aqueous solution. An additional treatment of the vents by adsorption with activated charcoal has recently been implemented in the unit.

[2] Guidance on Information Requirements and Chemical Safety Assessment. Chapter R.14: Occupational exposure assessment. Version 3. 0 - August 2016.

- Wastes generated are collected and sent for incineration

Exposure scenario 3: Use at industrial site - Use as a process agent

The substance is used as a process agent on one site only, in a closed system. Releases to environmental compartments are based on site specific information and monitoring data, taking into account the following assumptions:

- Water releases of substance are minimal as the process operates without water contact and that the CCl4 resulting from this use is recycled in the process. Moreover, recovery systems are in place in the unit in case of drains/leak.
- Gaseous vents are collected and send to a thermal treatment for incineration.
- Wastes generated are collected and send for incineration. The assessment of environmental exposure was carried out by means of EUSES v2.1. Measured data for the environmental releases of CCl4 were taken into account for the refinement of the release fractions in air and wastewater.

7.12.2.2. Registrant 2

Exposure scenario 1: Manufacture - Manufacture & Dispatch

CCl4 is produced on one site. Manufactured in closed process and there is no likelihood of exposure. The process is optimized for highly efficient use of raw materials (very minimal environmental release). Volatile compounds subject to air emission controls. Wastewater emissions generated from equipment cleaning are collected in a central container and after neutralization treated by a steam stripper to remove the CCl4. This waste water is then treated in an onsite WWTP. There are negligible emissions via wastewater and negligible air emissions as the process operates in a contained system.

Risk assessment for manufacturing is based on ESVOC SpERC 1.1.v1. Site specific monitoring data is available and was used to refine the exposure assessment.

Exposure scenario 2: Use at industrial site - Use as intermediate under SCC

For this scenario, all reaction steps and transfers take place under 'strictly controlled conditions' as defined in Chapter 2, Article 18(4) of Regulation (EC) No. 1907/2006. Negligible emissions are assumed for this scenario.

Exposure scenario 3: Use at industrial site - Use as solvent (process agent)

Industrial use of solvent-borne polymer processing materials encompasses a wide range of activities such as material transfers, additives handling, moulding, curing, etc. Substance losses are reduced through use of general and site-specific risk management measures collected on the downstream user sites.

Risk assessment for this use is based on ESVOC SpERC 4.21a.v1 with refinement from site specific data and risk mitigation measures.

Exposure scenario 4: Use by professional worker - Use in laboratories by industrial and professional worker

Exposure assessment for industrial laboratory use is compared to scenario for professional laboratory use as available from the ESVOC SpERC library (ESVOC SpERC 8.17.v1).

7.12.3. Combined exposure assessment

Not assessed.

7.13. Risk characterisation

7.13.1. Environment

Based on site specific information and monitoring data, considering the conditions of use and risk mitigation measures applied for this phase, no environmental risks are identified.

More details are given in the confidential annex.

7.13.2. Human health

Not fully assessed. Regarding occupational exposure, OELs recommended by the SCOEL (2009) could be used by registrants. Exposure data provided in registration dossier (both modelled and measured) do not exceed OELs recommended by SCOEL.

7.14. References

Adams E. M., Spencer H. C., Rowe V. K., McCollister D. D., Irish D. D. (1952). Vapor toxicity of carbon tetrachloride determined by experiments on laboratory animals. A M A Arch Ind Hyg Occup Med, 1952, Vol. 6, No. 1, p. 50-66.

Alumot E, Nachtomi E, Mandel E, Holstein P. (1976). Tolerance and acceptable daily intake of chlorinated fumigants in the rat diet. Food Cosmet Toxicol., vol. 14, no. 2, p. 105-10.

Anses 2017. Élaboration de VTR chronique par voie respiratoire pour le tétrachlorure de carbone. Avis de l'Anses. Décembre 2017.

Barbin A., Bereziat J. C. Bartsch H. Evaluation of DNA damage by the alkaline elution technique in liver, kidneys and lungs of rats and hamsters treated with N-nitrosodialkylamines. Carcinogenesis 4: 541-545, (1983).

Bermudez E., Mirsalis J. C., Eales H. C. (1982). Detection of DNA Damage in Primary Cultures of Rat Hepatocytes Following in Vivo and In Vitro Exposure to Genotoxic Agents. Environmental Mutagenesis 4:667-679 (1982)..

Black A. (1982). The Aquatic Toxicity of Organic Compounds to Embryo-Larval Stages of Fish and Amphibians. University of Kentucky Research report No 133. Bogers M, Appelman LM, Feron VJ, Beems RB, Notten WR. (1987). Effects of the exposure profile on the inhalation toxicity of carbon tetrachloride in male rats. J Appl Toxicol., vol. 7, no. 3, p. 185-91.

BRINGMANN-G/KUHN-R (1980b). Comparison of the toxicity thresholds of water pollutants to bacteria, algae, and protozoa in the cell multiplication inhibition test. WATER-RES 14 231-241 1980.

Bruckner, J., V.; MacKenzie, W., F.; Muralidhara, S.; Luthra, R.; Kyle, G., M.; Acosta, D.; (1986). Oral toxicity of carbon tetrachloride: acute, subacute, and subchronic studies in rats. Fundamental and applied toxicology, vol. 6, p. 16-34.

Bunch RL, Chambers CW (1967). A biodegradability test for organic compounds. J Water Pollut Control Fed. 1967 Feb;39(2):181-7.

Chatterjee A (1966) Testicular degeneration in rats by carbon tetrachloride intoxication. Experientia(Basel), 226: 395-396.

Chatterjee A (1968). Effect of CCl4 on gonadal physiology in female rats. Acta Anat, 71: 82-86.

Condie, L., W.; Laurie, R., D.; Mills, T.; Robinson, M.; Bercz, J., P.; (1986). Effect of gavage vehicle on hepatotoxicity of carbon tetrachloride in CD-1 mice: corn oil versus Tween-60 aqueous emulsion. Fundamental and Applied Toxicology, vol. 7, p. 199 - 206.

Della Porta G., Terracini B. and Shubik P. Induction With Carbon Tetrachloride of Liver Cell Carcinomas in Hamster. Journal of the National Cancer Institute Vol 26, No 4, 855-863.

Department of Health (2001), A review of the potential teratogenicity of substances emanating from landfill sites, Sullivan FM, Barlow SM, McElhatton PR, Department of Health/Joint Research Programme on the Possible Health Effects of Landfill Sites.

EPA (2010). Toxicological review of carbon tetrachoride. EPA/635/R-08/005F.

Eschenbrenner A. B. and Miller E. (1946). Liver Necrosis and the Induction of Carbon Tetrachloride Hepatomas in Strain A Mice. J. Nat. Cancer Inst 6: 325 - 341, (1946). Testing laboratory: NCI, National Institute of Health, US Publich Health Service.

Faroon O, Taylor J, Roney N, Fransen ME, Bogaczyk S, Diamond G (2005). Toxicological profile for carbon tetrachloride. U. S. DEPARTMENT OF HEALTH AND HUMAN SERVICES, Public Health Service, Agency for Toxic Substances and Disease Registry (ATSDR), Division of Toxicology, Atlanta, GA, U. S. A. 358 p.

Foureman P., Mason J. M., Valencia R. and Zimmering S. (1994). Chemical Mutagenesis Testing in Drosophila. X. Results of 70 Coded Chemicals Tested for the National Toxicology Program. Environmental and Molecular Mutagenesis 23: 208-227 (1994).

de Fouw J (1999). Environmental Health Criteria 208 CARBON TETRACHLORIDE. ISBN 92 4 157208 6, ISSN 0250-863X, self-published WHO, Geneva, Switzerland, 199p http: //www. inchem. org/documents/ehc/ehc/ehc208. htm.

Gluchowski NL *et al.* (2017). Lipid droplets and liver disease: from basic biology to clinical implications. Nat Rev Gastroenterol Hepatol. 2017 June ; 14(6): 343–355. doi:10.1038/nrgastro.2017.32.

Hayes, J., R.; Condie, L., M., Jr.; Borzelleca, J., F.; (1986). Acute, 14-day repeated dosing, and 90-day subchronic toxicity studies of carbon tetrachloride in CD-1 mice. Fundam Appl Toxicol., vol. 7, no. 3, p. 454-63.

IARC 1999. IARC MONOGRAPHS VOLUME 71. Re-evaluation of Some Organic Chemicals, Hydrazine and Hydrogen Peroxide. https://monographs.iarc.fr/iarc-monographs-on-the-evaluation-of-carcinogenic-risks-to-humans-50/.

Kalla NR & Bansal MP (1975). Effect of carbon tetrachloride on gonadal physiology in male rats. Acta Anat, 91: 380-385.

KAZANTZIS G, BOMFORD RR. Dyspepsia due to inhalation of carbon tetrachloride vapour. Lancet. 1960 Feb 13;1(7120):360-2.

Koporec, K., P.; Kim, H., J.; MacKenzie, W., F.; Bruckner, J., V.; (1995). Effect of oral dosing vehicles on the subchronic hepatotoxicity of carbon tetrachloride in the rat. J Toxicol Environ Health, vol. 44, no. 1, p. 13-27.

Kutepov, E., N.; (1968). Experimental data for the establishment of standards for carbon tetrachloride in bodies of water. Gig Samit, vol. 33, p. 35-41.

MacEwen JD, Geckler RP. (1966). Comparative toxicity studies on animals exposed continuously for periods up to 90 days to NO2, O3, and CCl 4 in ambient air vs. 5 psia 100 per cent oxygen atmosphere. AMRL-TR-66-120. AMRL TR. 1966 Dec:238-59.

Mirsalis J. C., Tyson K. C., Butterwoth B. E. Detection of Genotoxic Carcinogens in the In Vivo-In Vitro Hepatocyte DNA Repair Assay. Environmental Mutagenesis 4: 553 - 562 (1982).

Nagano K, Umeda, Saito, Nishizawa, Ikawa, Arito H, Yamamoto S, Fukushima S; (2007a). Thirteen-week inhalation toxicity of carbon tetrachloride in rats and mice. J Occup Health 2007; 49: 249-259.

Nagano K, Sasaki T, Umeda Y, Nishizawa T, Ikawa N, Ohbayashi H, Arito H, Yamamoto S, Fukushima S; (2007b). Inhalation Carcinogenicity and Chronic Toxicity of Carbon Tetrachloride in Rats and Mice. Inhalation Toxicology, vol. 19, no. 13, p. 1089-1103.

Narotsky MG, Kavlock RJ. (1995). A multidisciplinary approach to toxicological screening: II. Developmental toxicity. J Toxicol Environ Health, no. 45, vol. 2, p. 145-71.

Narotsky MG, Brownie CF, Kavlock RJ. (1997a). Critical period of carbon tetrachloride-induced pregnancy loss in Fischer-344 rats, with insights into the detection of resorption sites by ammonium sulfide staining. Teratology, vol. 56, no. 4, p. 252-61.

Narotsky MG, Pegram RA, Kavlock RJ. (1997b). Effect of dosing vehicle on the developmental toxicity of bromodichloromethane and carbon tetrachloride in rats. Fundam Appl Toxicol., vol. 40, no 1, p. 30-36.

Norwood, W.D., P.A. Fuqua, and B.C. Scudder. 1950. Carbon tetrachloride poisoning: More regulation, more education needed. Arch. Ind. Hyg. Occup. Med. 1(1):90-100.

Sasaki Y. F., Safa A., Akasaka M., Ishibashi S., Yoshida K., Su Y. Q., Matsusaka N. and Tsuda S. (1998). Detection of in vivo genotoxicity of haloalkanes and haloalkenes carcinogenic to rodents by the alkaline single cell gel electrophoresis (comet) assay in multiple mouse organs. Muatation Research 419, 13 - 20 (1998).

Sawada S., Yamanaka T., Yamatsu K., Furihata C. and Matsushima T. (1991). Chromosome aberrations, micronuclei and sister-chromatid exchanges (SCEs) in rat liver induced in vivo by hepatocarcinogens including heterocyclic amines. Mutation Research, 251, 59-69 (1991).

Schwarz M., Hummel J., Appel K. E., Rickart R. and Kunz W. (1979). DNA Damage induced in vivo evaluated with a non-radioactive alkaline elution technique. Cancer Letters, 6, 221-226, (1979).

Schwetz B. A., Leong B. K. J., Gehring P. J. (1974). Embryo- and Fetotoxicity of Inhaled Carbon Tetrachloride, 1,1-Dichloroethane and Methyl Ethyl Ketone in Rats. Toxicology and Applied Pharmacology, vol. 28, p. 452-464.

Smyth SF, Carpenter CP, (1936). The chronic toxicity of carbon tetrachloride; Animal exposures and field studies. The Journal of industrial hygiene and toxicology. vol. 18, no. 5, p. 277- 298.

Sönmez M. et al. (2013). Quercetin attenuates carbon tetrachloride-induced testicular damage in rats. Andrologia. 2014 Oct;46(8):848-58.

Stewart B. W. Generation and Persistence of Carcinogen-induced Repair Intermediates in Rat Liver DNA in vivo. Cancer Research 41: 3238 - 3243.

Suzuki H., Hirano N., Watanabe C. and Tarumoto Y. (1997). Carbon tetrachloride does not induce micronucleus in either mouse bone marrow or peripheral blood. Mutation Research 394, 77-80 (1997).

Tabak HH, Quave SA, Mashni CI, Barth EF (1981). Biodegadability studies with organic priority pollutant compounds. J Water Pollut Control Fed. 53(10): 1503-17.

Tomenson JA, Baron CE, O'Sullivan JJ, Edwards JC, Stonard MD, Walker RJ, Fearnley DM. (1995). Hepatic function in workers occupationally exposed to carbon tetrachloride. Occup Environ Med, vol. 52, no. 8, p. 508-14.

Türk G *et al*. (2013). Ameliorating effect of pomegranate juice consumption on carbon tetrachloride-induced sperm damages, lipid peroxidation, and testicular apoptosis. Toxicol Ind Health. 2016 Jan;32(1):126-37

Weisburger E. K. (1977). Carcinogenicity Studies on Halogenated Hydrocarbons. Environmental Health Perspectives 21: 7-16, 1977.

Yüce A *et al.* (2013). Effectiveness of cinnamon (Cinnamomum zeylanicum) bark oil in the prevention of carbon tetrachloride-induced damages on the male reproductive system. Andrologia. 2014 Apr;46(3):263-72.

7.15. Abbreviations

CCH / DEV: complicance check / dossier evaluation

CCl4: carbon tetrachloride

EOGRTS: Extended One Generation Reproduction Toxicity Study

PNDT: Prenatal developmental toxicity

Confidential annex is removed from the public version.

SOPs for Personal Protection at CTC Manufacturing Sites

As conveyed to EPA during the Risk Evaluation process, carbon tetrachloride (CTC) is tightly controlled under the federal Clean Air Act and its use is regulated under Title VI of the Clean Air Act (implementing the Montreal Protocol). CTC is also the critical feedstock for US production of Low-Global Warming Potential (GWP) alternative fluorocarbon products which serve as the basis for the Kigali Amendment to the Montreal Protocol's phase down of hydrofluorocarbons (HFCs).

This summary discusses four topics relating to personal protection at CTC manufacturing sites that are in place in addition to the environmental regulations currently imposed upon and benefits generated by CTC manufacturing and processing. This information is provided to EPA for consideration during the Risk Management rule development process for carbon tetrachloride:

1) OSHA standards applicable to Personal Protective Equipment (PPE) selection for dermal protection that protect against potential dermal exposure, and inhalation protection that protect against vapor exposure.
2) Minimum PPE requirements for operational and maintenance personnel at CTC manufacturing facilities.
3) CTC manufacturing practices only present a potential risk of an intermittent, short term exposure (The CTC Risk Evaluation assumed an 8-hour potential exposure which overestimates any potential dermal risk.)
4) Standard Operating Procedures (SOPs) examples for short-term tasks such as loading, minor maintenance and sampling that document the required steps to ensure the safe operation of task and the proper use of the selected PPE to prevent potential dermal and vapor inhalation exposure.

1. OSHA STANDARDS FOR DERMAL AND INHALATION PROTECTION

OSHA standards have specific Hazard Assessment requirements for personal protection and training requirements for PPE selection and use. This section lists OSHA regulations relating to personal protection that are implemented at each CTC manufacturing site.

Glove selection must meet the OSHA Hazard Assessment requirements in 29 CFR Part 1910:

- 1910.1000 Toxic and Hazardous Substances
- 1910.132(a) General Requirements
- 1910.132(d) Hazard Assessment and PPE Equipment Selection
- 1910.132(e) Prohibition of use of defective or damaged equipment
- 1910.132(f) PPE Training
- 1910.133 Eye and Face Protection
- 1910.134 Respiratory Protection
- 1910.138 Hand Protection

As a part of the OSHA PPE regulations, OSHA Standard (29 CFR 1910.138) specifically addresses hand protection:

> (a) Appropriate hand protection must be worn when hands are exposed to hazards such as skin absorption of harmful substances, severe cuts, lacerations or abrasions, punctures, chemical or thermal burns and harmful temperature extremes.

(b) Employers must base the selection of appropriate hand protection on an evaluation of the performance characteristics of the hand protection relative to the task(s) to be performed, conditions present, duration of use and the hazards and potential hazards identified.

In addition to chemical protection, the OSHA regulation for hand protection, quoted above, requires that the glove selection must be appropriate for task. Selection of glove types and materials are based on the potential exposure risk and nature of the hazards that are likely to be encountered when performing job tasks. OSHA guidelines recognize that consideration should be given to other factors when selecting the appropriate PPE for a task. 29 CFR Part 1910 Subpart I Appendix B.11. The following list provides an example of factors that are evaluated when selecting the most appropriate glove for a particular application:

- Permeation/degradation/breakthrough data provided by the manufacturer or through independent testing
- Degree of dexterity required to perform task (i.e. use of fine motor skills)
- Expected contact with chemical (incidental with little or no direct contact with chemical or extended contact with chemical)
- Compatibility of glove type and material with one or more chemicals that may be encountered
- Feasibility (i.e. availability)
- Length of glove (i.e. gauntlet style)
- User fit, function, and comfort
- Reusability of glove
- Temperature considerations (i.e. glove textures, finishes, linings)
- Duration/frequency of job tasks requiring the use of gloves

Glove selection and use cannot be solely determined by permeation, degradation, and breakthrough data. All of the factors listed above may need to be considered when identifying a glove for a specific type of task.

Many manufacturers test glove materials by immersing the glove material in the chemical. Immersion data may provide the user with “worst case scenario” data. The assumption may be made that glove materials may perform for longer periods of time without permeation or degradation occurring in situations where incidental, intermittent, or splash contact is expected.

2. Minimum PPE Requirements

Chemical manufacturers conduct evaluations on hazards present in the workplace by knowledgeable experts to ensure that PPE used in the workplace will protect against the hazards present and work as expected. These evaluations address worker exposures to chemical, physical, biological and ergonomic hazards with potential health significance in the workplace. While the evaluations normally concentrate on specific facility tasks. Attention is also be paid to exposures resulting from general, non-specific tasks such as "making plant rounds".

The level of PPE required for general nonspecific tasks in a plant is often referred to as "plant minimum PPE". This is the minimum requirement for PPE specified for any Operations or Maintenance personnel, visitors or contractors, to enter designated process areas. See Figure 2.

Additional levels of PPE are then required based on the task to be conducted, or demarcation of specific areas within the facility that have been identified to contain increased risk (e.g. “acid handling area”, or "hearing protection required" area, etc.).

Access to the process area of each plant is controlled through the control room. Anyone needing to access the process area must inform the control room prior to entering the area. Minimum PPE is expected to be worn when entering the area. Any additional PPE would be specified by the control room.

Figure 2 – Typical Minimum PPE Requirements at CTC Manufacturing Facilities

(A.) Operations and Maintenance Personnel - Minimum Facility PPE Requirements:

- **Head:** Safety Glasses with side shields, Hard Hat, Monogoggles (must carry on person), Hearing Protection (muffs or ear plugs)
- **Respiratory Protection**: Mouthbit Organic Vapor Respirator (must carry on person) or Half Face Air Purifying Respirator
- **Body:** Fire Retardant Clothing (area or task specific requirement)
- **Feet:** Safety Shoes with Steel Toes
- ***Goggles and work gloves are required anytime valves are operated**

(B.) Line and Equipment Opening (LEO) Activities with minimal risk of exposure – PPE Requirements:

- **Head:** Safety Glasses with side shields, Hard Hat, Monogoggles (must carry on person), Hearing Protection (muffs or ear plugs)
- **Respiratory Protection**: Full or Half Face Air Purifying Respirator
- **Body:** Fire Retardant Clothing (area or task specific requirement)
- **Gloves**: Chemical Resistant Gloves (i.e. Nitrile)
- **Feet**: Chemical Resistant Boots with Steel Toes

(C.) Major LEO Activities or those with increased risk of exposure – PPE Requirements:

- **Head:** Safety Glasses with side shields, Hard Hat, Monogoggles (must carry on person), Hearing Protection (muffs or ear plugs)
- **Respiratory**: Full Face Respirator with Supplied Air Line (can also include a 5 minute Escape Pack)
- **Gloves**: Chemical Resistant Gloves (i.e. Nitrile)
- **Body**: Chemically Resistant Suit
- **Feet**: Chemical Resistant Boots with Steel Toes

3. INTERMITTENT TASKS

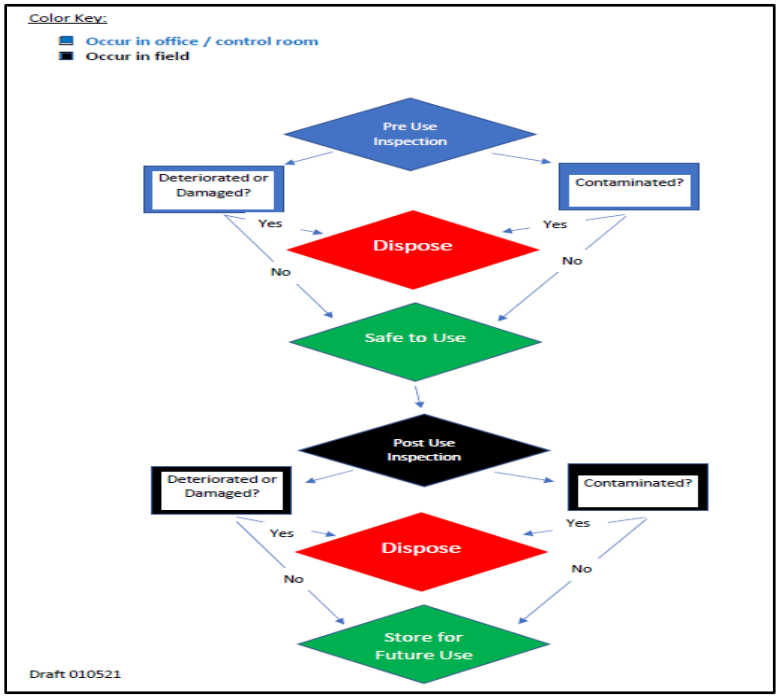
The glove use, and the hazard assessments, for manufacturing CTC are based upon activities where the potential risks for exposure are extremely short term (ranging from approximately 5 - 30 min.), *i.e.*, sampling, loading/unloading preparation, connections and disconnections. The CTC Risk Evaluation assumed a longer 8-hour glove use and/or exposure period for potential exposure which is not applicable to these tasks.

Tasks with potential CTC exposure in manufacturing, such as collecting samples, loading and unloading carbon tetrachloride, require the use of gloves for a duration of approximately 15 – 30 minutes. Sample collection occurs daily; gloves are donned before the sampling round begins and are removed after the round is completed. For loading/unloading activities, which varies weekly, the gloves are donned before the connection is made and are removed after disconnection. Although not expected, should accidental contact with carbon tetrachloride occur during the performance of these tasks, concentrations and amounts are minimal. Incidental, intermittent, or splash contact may only occur if there is an accidental spill, overspray conditions, or unexpected failure of a control device.

It is also important to note that employees are trained to inspect gloves before and after use to look for signs of swelling, cracking, shrinking, or discoloration of the material, as these are evidence of chemical contact and signs the glove material may no longer provide adequate chemical protection. Employees are trained to look for holes, tears, or punctures and remove the gloves from service if any are found. If an employee suspects any incidental or intermittent chemical contact, gloves will be discarded and replaced with new gloves. Refer to the PPE Pre and Post Task Inspection Process diagram in Figure 3.

The glove material must have the fit and thickness to protect against any potential intermittent exposure during these short term tasks, but just as importantly, the gloves must allow the appropriate dexterity to take samples and unhook loading lines without adding to the risk of exposure due to a reduced ability to conduct the task.

Figure 3: PPE Inspection Process



4. STANDARD OPERATING PROCEDURE EXAMPLES FOR TASKS IN CTC MANUFACTURING.

This section includes example Standard Operating Procedures (SOPs) for short-term tasks such as loading transport equipment, conducting minor maintenance and line openings, packaging wastes, and collecting process samples. These SOPs are provided to document examples of existing process steps taken and controls employed to safely conduct the task and prevent potential dermal and inhalation exposure. OSHA regulations require that the SOP include instructions for conducting activities safely, including the "Precautions necessary to prevent exposure, including engineering controls, administrative controls, and personal protective equipment." (40 CFR §68.69 and 29 CFR §1910.119(f)). Additionally, EPA regulates facilities that manufacture CTC through the National Emission Standards for Hazardous Air Pollutants (NESHAP) for the Synthetic Organic Chemical Manufacturing Industry (SOCMI). 40 C.F.R.§63 Subparts F, G, H, I.

The SOPs incorporate both the use of PPE and the procedures to properly operate the engineering controls for these tasks.

It is critical to note that these SOPs are examples only as each facility must account for specific protections for its unique facility operational footprint and process.

The various SOPs are listed in Appendix 1. Each section contains a flowchart of the SOP and an overview of the typical procedures employed by manufacturers.

Appendix 1

Standard Operating Procedures for CTC

A. Rail Tank Car Loading

B. Tank Truck Loading

C. Process Sampling

D. Waste Packaging

E. Minor Maintenance and Line Openings

Each section contains a flowchart of the SOP and an overview of the typical procedures employed by manufacturers.

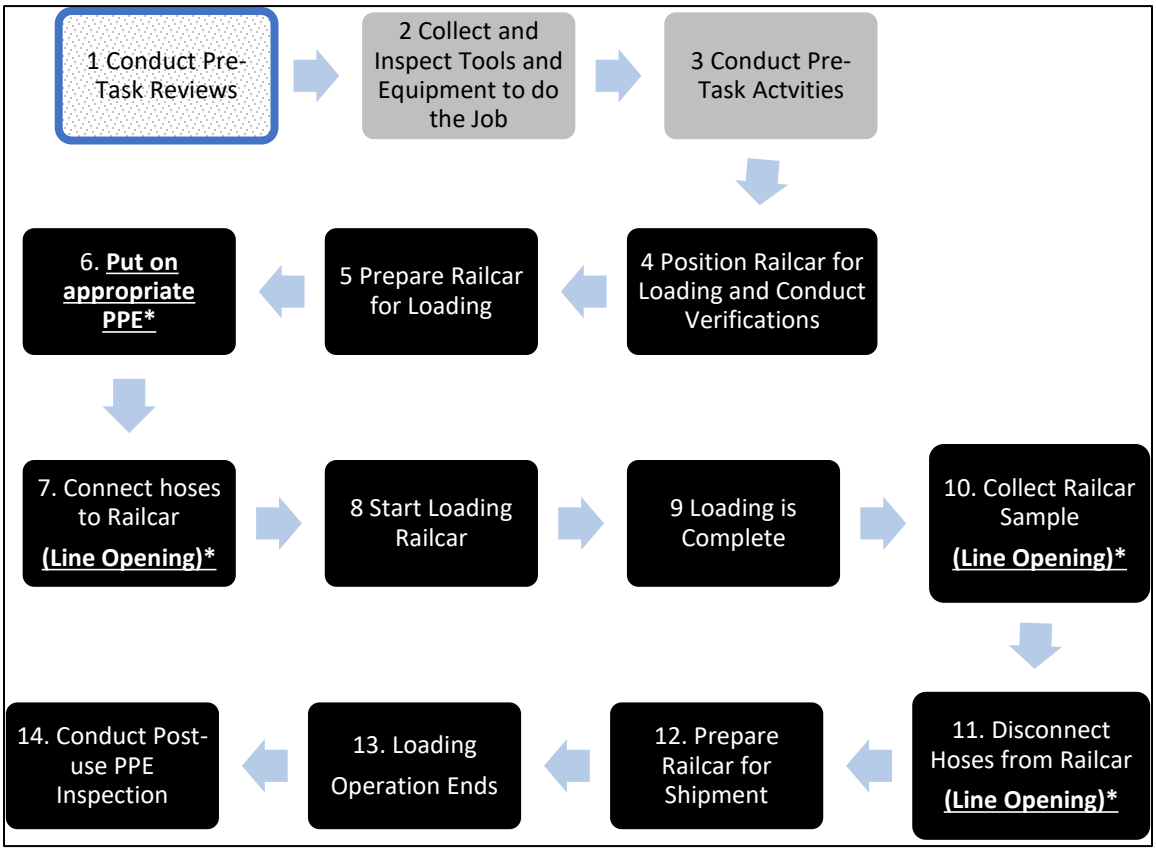
As stated above, it is critical to note that these SOPs are examples only as each facility must account for specific protections and procedures for its unique facility operational footprint and process. Due to the timeline of the Risk Management proposal, additional information may be necessary to provide details on a site-specific basis and/or address specific questions from EPA.

A. Rail Tank Car Loading SOP

1. SOP Flow Chart

Color Key:

- **Occur in office / control room**
- **Occur in both office/control and field**
- **Occur in field**



Underline text denotes steps that require additional PPE, and/or when additional PPE is donned or removed

A. Rail Tank Car Loading SOP (Continued)

2. SOP Overview

1. Conduct Pre-Task Reviews
    a. Scope & Risk Assessment
    b. Safety, Health and Environmental and Ergonomic Considerations
    c. Determine Proper PPE Requirements
    d. Consequences of Deviation from Procedure
2. Collect and inspect tools and equipment necessary to do the job
3. Conduct Pre-Task Activities
    a. Review Plant Safety Standards
    b. Visual inspections of rail tank car to be loaded
    c. Verify safety equipment operational
    d. Inspect tools, hoses, sample equipment
    e. Evaluate spill potential and verify emergency procedures in place (spill response, evacuation)
4. Position Railcar for loading
    a. Derail, Blue Flag & Light in place
    b. Chock Railcar and set Brake
    c. Conduct Railcar Verifications
        i. Car is spotted at correct spot to load CTC
        ii. Adequate CTC in storage tank to load rail tank
        iii. Correct rail car type for product, status, net weight
5. Prepare Railcar for loading
    a. Calculate weight of CTC to be loaded.
    b. Lower load ramp and platform onto railcar
    c. Conduct Elevated Work pre-task analysis
    d. Secure loading area and move all non-essential personnel outside of barricade
    e. Test high level probe and alarm (if equipped)
6. **Put on protective equipment (PPE) for loading operation***
7. **Connect loading hoses to Tank Car**
    a. Open railcar dome lid and inspect railcar valves
    b. Connect vent hose from railcar to Thermal Treatment Unit
    c. Depressurize railcar
    d. Connect CTC liquid loading hose to railcar
    e. Line opening ends – Extra PPE can be removed if conditions permit
    f. Pressure test the CTC liquid load line
    g. Set CTC load meter – it will close the automatic block valve when load amount has been reached.
8. Start loading Rail Tank Car
    a. Open manual liquid fill and vent valves on railcar. **The CTC is now loading**
    b. Inspect hoses, rail tank car and piping for leaks during the loading process
9. When load is complete:
    a. Close liquid loading valve
    b. Notify control room that loading is complete.
    c. Blow any remaining liquid in loading hose back into the railcar using nitrogen
    d. Close nitrogen valve
10. **Collect Railcar Sample**
    a. Put on protective equipment (PPE) for sample collection*
    b. Ensure all personnel are away from the railcar
    c. De-pressure sample point into a waste collection container
    d. If sample is taken from the load line, allow liquid to flow from railcar into load line
    e. Fill sample container 75% full from sample valve on load line.
    f. Blow any remaining liquid in loading hose back into the railcar using nitrogen (or air)and close nitrogen (or air)valve.
11. Disconnect load and vent hoses from railcar
    a. Remove high level probe
    b. Close railcar vent valve and manual load valve
    c. De-pressure vent and load hoses and disconnect from railcar
    d. Install plugs in all railcar valves
    e. Secure load and vent hoses to load rack
    f. Line opening ends – Extra PPE can be removed if conditions permit
12. Prepare railcar for shipment
    a. Inspect dome area for cleanliness
    b. Close dome
    c. Attach product tags
    d. Apply tamper evident seal to dome, Record seal numbers
    e. Raise and secure load ramp
    f. Attach DOT placards on railcar
    g. Remove derail, blue flag, blue light
    h. Remove chocks
    i. Input load data and note end time
13. Loading Operation ends
14. Conduct Post-Use PPE inspection and store for future use or discard PPE if not suitable for reuse

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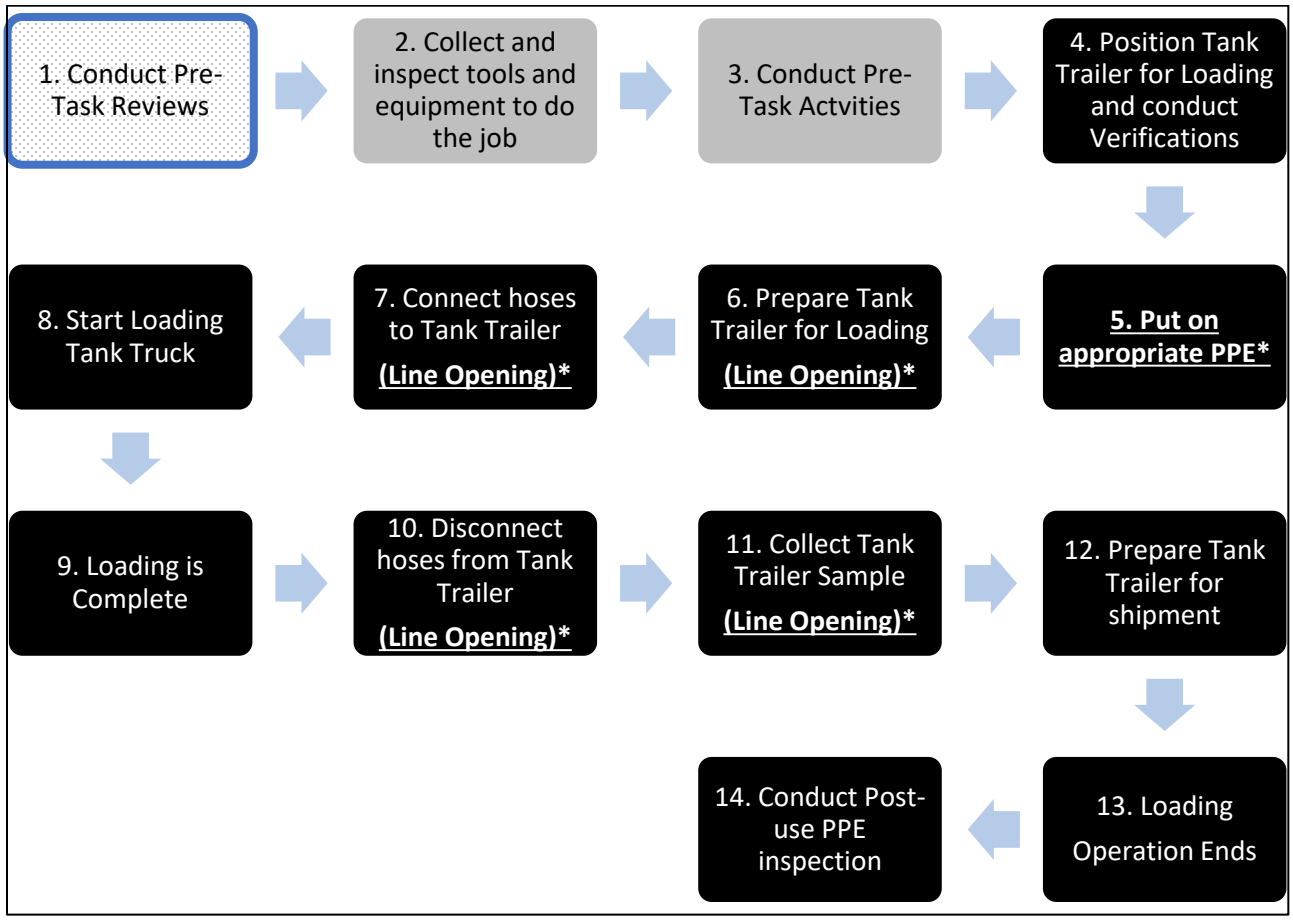
*At a minimum, Line and Equipment Opening Activities require additional PPE: Full or Half Face Air Purifying Respirator and Chemical Resistant Gloves. Some LEO tasks with higher risk of exposure require Chemical Suit and Supplied Air Respirator

B. Tank Truck Loading SOP

1. SOP Flow Chart

Color Key:

- Occur in office / control room
- Occur in both office/control and field
- Occur in field



Underline text denotes steps that require additional PPE, and/or when additional PPE is donned or removed

B. Tank Truck Loading SOP (Continued)

2. SOP Overview

1. Conduct Pre-Task Reviews
    a. Scope & Risk Assessment
    b. Safety, Health and Environmental and Ergonomic Considerations
    c. Determine Proper PPE Requirements
    d. Consequences of Deviation from Procedure
    e. Confirm current DOT training for loading personnel
2. Collect and inspect tools and equipment necessary to do the job
3. Conduct Pre-Task Activities
    a. Review Plant Safety Standards
    b. Verify safety equipment operational
    c. Inspect tools, hoses, sample equipment
    d. Evaluate spill potential and verify emergency procedures in place (spill response, evacuation)
    e. Conduct Elevated Work pre-task analysis
4. Collect general information prior to loading
    a. Verify that an order has been placed and the vehicle has arrived at CTC load area
    b. Review the trailing loading papers
    c. Spot tank truck at the CTC loading rack
    d. Verify correct DOT classification and capacity of the trailer.) Apply wheel chocks and place sign in windshield.
    e. Lower the ramp and fall protection in place over dome.
5. **Put on protective equipment (PPE) for loading operation***
6. **Prepare Tank Trailer to Load**
    a. Inspect dome area of tank trailer
    b. Check pressure on trailer
7. **Connect hoses to Tank Trailer**
    a. Connect vent hose and depressurize tank trailer to Vapor Recovery Unit (VRU)
    b. Connect load line to tank trailer.
    c. Verify pressure test of tank trailer and loading/vent hoses.
    d. Place CTC placards on trailer
    e. Line opening ends – extra PPE can be removed if conditions permit
    f. Set CTC load meter – automatic block valve closes once load amount reached.
8. Start loading Tank Trailer
    a. Open manual liquid fill and vent valves on tank trailer
    b. Notify control room ready to load CTC.
    c. Open CTC loading valves in field.
    d. **The CTC is now loading**
    e. Inspect hoses, tank trailer and piping for leaks during the loading process
9. When load is complete,
    a. Put on protective equipment (PPE) for loading and sampling operation*
    b. Close liquid loading valve
    c. Blow any remaining liquid in loading hose back into the tank trailer.
    d. Verify tank trailer is depressurized.
    e. Close vent valve to VRU
10. **Disconnect loading and loading hoses**
    a. Place caps on end of each hose.
11. **As needed, Collect Tank Trailer Sample**
    a. Ensure all personnel are away from the area
    b. Collect samples.
    c. Line opening ends – extra PPE can be removed if conditions permit
12. Prepare tank trailer for shipment
    a. Inspect dome area for cleanliness
    b. Close dome
    c. Attach product tags
    d. Apply tamper evident seal to dome, Record seal numbers
    e. Raise and secure load ramp
    f. Inspect tank trailer for leaks.
    g. Remove chocks and windshield sign
    h. Verify trailer sample analyses meet sales specifications
    i. Give completed load sheet and keys to driver
    j. Record end time.
13. Loading operation ends
14. Conduct Post-Use PPE Inspection and store for future use or discard PPE if not suitable for reuse

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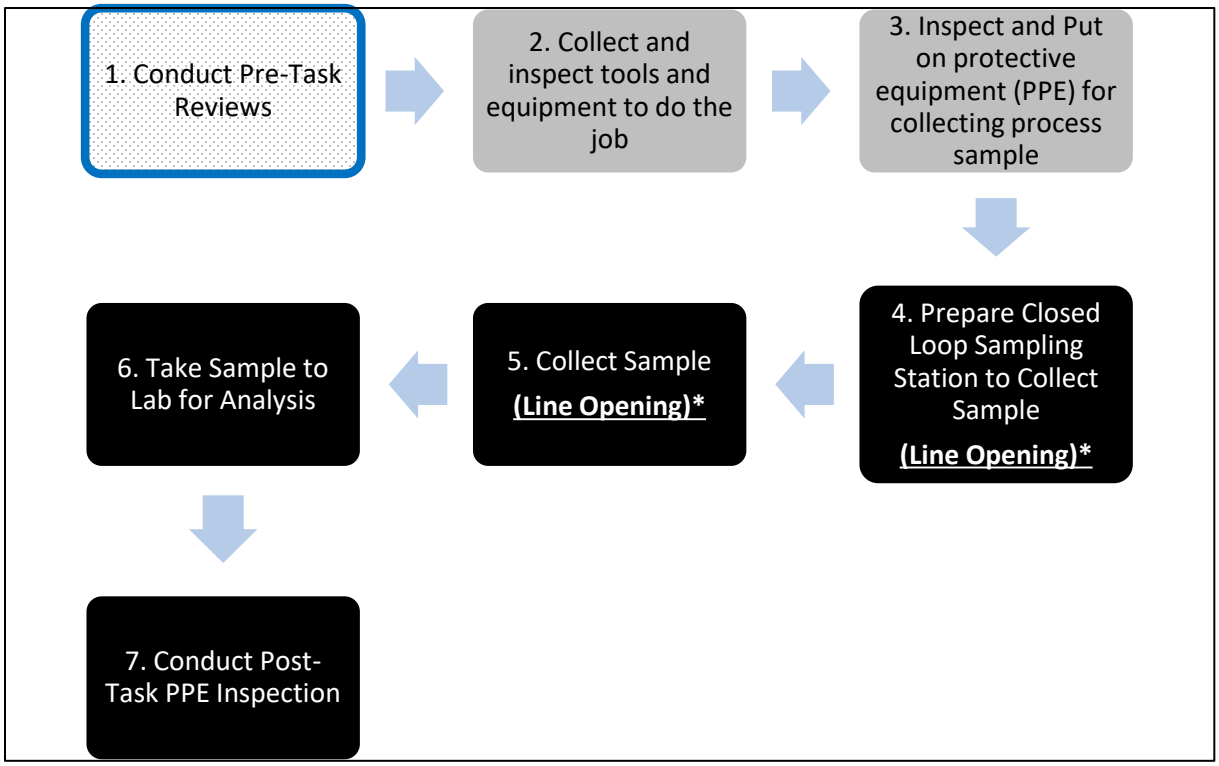
*At a minimum, Line and Equipment Opening Activities require additional PPE: Full or Half Face Air Purifying Respirator and Chemical Resistant Gloves. Some LEO tasks with higher risk of exposure require Chemical Suit and Supplied Air Respirator

C. CTC Process Sampling SOP

1. SOP Flow Chart

Color Key:

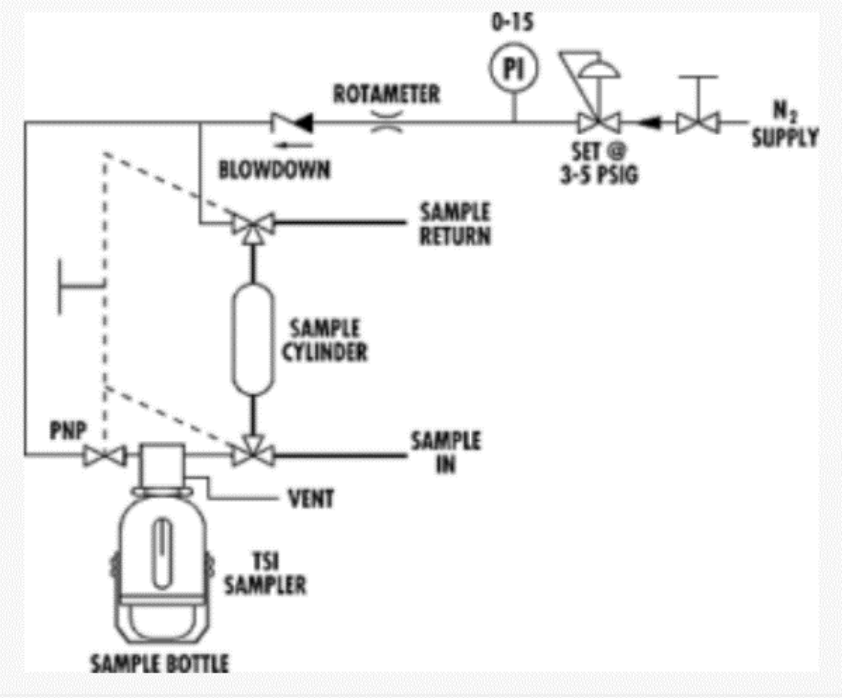
- Occur in office / control room
- Occur in field
- Occur in both office/control and field



Underline text denotes steps that require additional PPE, and/or when additional PPE is donned or removed

C. CTC Process Sampling SOP (Continued)

Note: This SOP example includes the use of a Closed Loop Sampling Station, such as those commercially available from Texas Sampling[1] or similar vendors. Diagram is shown below:



[1] https://www.texassampling.com/fixed-volume-sample-systems/#1587512857215-8489adfc-4187

C. CTC Process Sampling SOP (Continued)

2. SOP Overview

1. Conduct Pre-Task Reviews
    a. Scope & Risk Assessment
    b. Safety, Health and Environmental and Ergonomic Considerations
    c. Determine Proper PPE Requirements
    d. Consequences of Deviation from Procedure
2. Collect and inspect tools and equipment necessary to do the job
    a. Sample bottles
    b. Sample carrier
    c. Label bottles for each sample to be collected
3. **Inspect and put on protective equipment (PPE) for collecting process sample***
4. If closed loop, prepare Closed Loop Sampling Station to Collect Sample
    a. Verify valves on Sampling Station are in proper position to collect sample
    b. Circulate fresh material through the sampling system for 20-30 seconds
5. Collect Sample
    a. Insert clean sample bottle into the Sampling Station
    b. Fill the sample bottle through the septum, leaving adequate vapor space.
    c. Relieve pressure on sampling system back into the process
    d. Verify valves on Sampling Station are in proper closed positions
    e. Remove full sample bottle and place into Sample Carrier
    f. Line Opening Ends, additional PPE can be removed if conditions permit
6. Take samples to Lab for analyses
7. Conduct PPE post-use inspection and store for future use or discard PPE if not suitable for reuse

*At a minimum, Line and Equipment Opening Activities require additional PPE: Full or Half Face Air Purifying Respirator and Chemical Resistant Gloves. Some LEO tasks with higher risk of exposure require Chemical Suit and Supplied Air Respirator

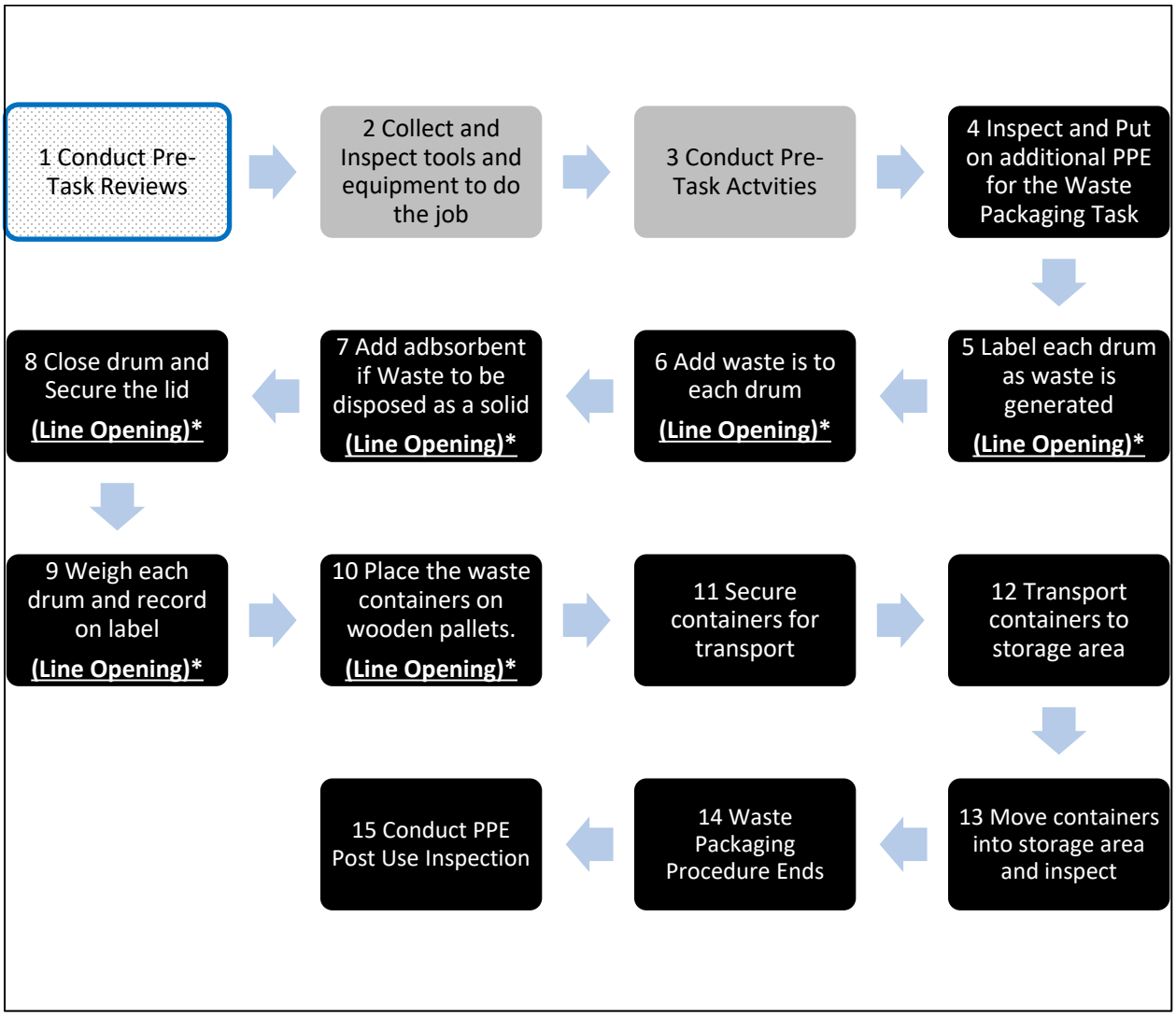
D. CTC Waste Packaging SOP (Solvent Waste/Retains)

1. SOP Flow Chart

Color Key:

Occur in office / control room **Occur in both office/control and field**

Occur in field



Underline text denotes steps that require additional PPE, and/or when additional PPE is donned or removed

D. CTC Waste Packaging SOP (Solvent Waste/Retains) (Continued)

2. SOP Overview

1. Conduct Pre-Task Reviews
    a. Scope & Risk Assessment
    b. Safety, Health and Environmental and Ergonomic Considerations
    c. Determine Proper PPE Requirements
2. Collect and inspect tools and equipment necessary to do the job
3. Conduct Pre-Task Activities – identify the following:
    a. Origin of the waste
    b. Waste Designation
    c. Container needed
    d. Compatible absorbent
    e. Intended disposal method
    f. Proper labels
4. **Inspect and Put on additional protective equipment (PPE) for Waste Packaging**
5. As the waste is generated, package and label the container as per the requirements determined in Step 1.
6. Add the waste to the drum.
    a. Note: The drum can only be open when waste being added or removed.
    b. If the waste will be disposed of as a solid offsite, all liquid must be completely absorbed.
    c. If the waste will be disposed of as a liquid, do not add any absorbent to the waste.
7. Close the drum and secure the lid.
8. If weighing the drum, write the weight on the drum or the drum label.
9. Place the waste containers on wooden pallets.
10. **Line Opening Ends – additional PPE can be removed if conditions permit**
11. Containers must be secured while in transport.
12. Transport the waste drums to the proper storage area.
13. Move the waste drums into the proper storage area and inspect the waste containers:
    a. If any part of the waste label is illegible or obscured in any form or fashion, re-label the drum
    b. If the label is not visible from the aisle space of the storage area, rotate the drum until the label is visible from the aisle space
    c. If the label is not dated, date the label with the date waste was generated
    d. If the exterior of the drum is contaminated, clean the exterior of the drum
    e. Ensure there is at least a minimum 24 inch aisle space between rows of drums
14. Conduct post-use PPE inspection and store for future use or discard PPE if not suitable for reuse

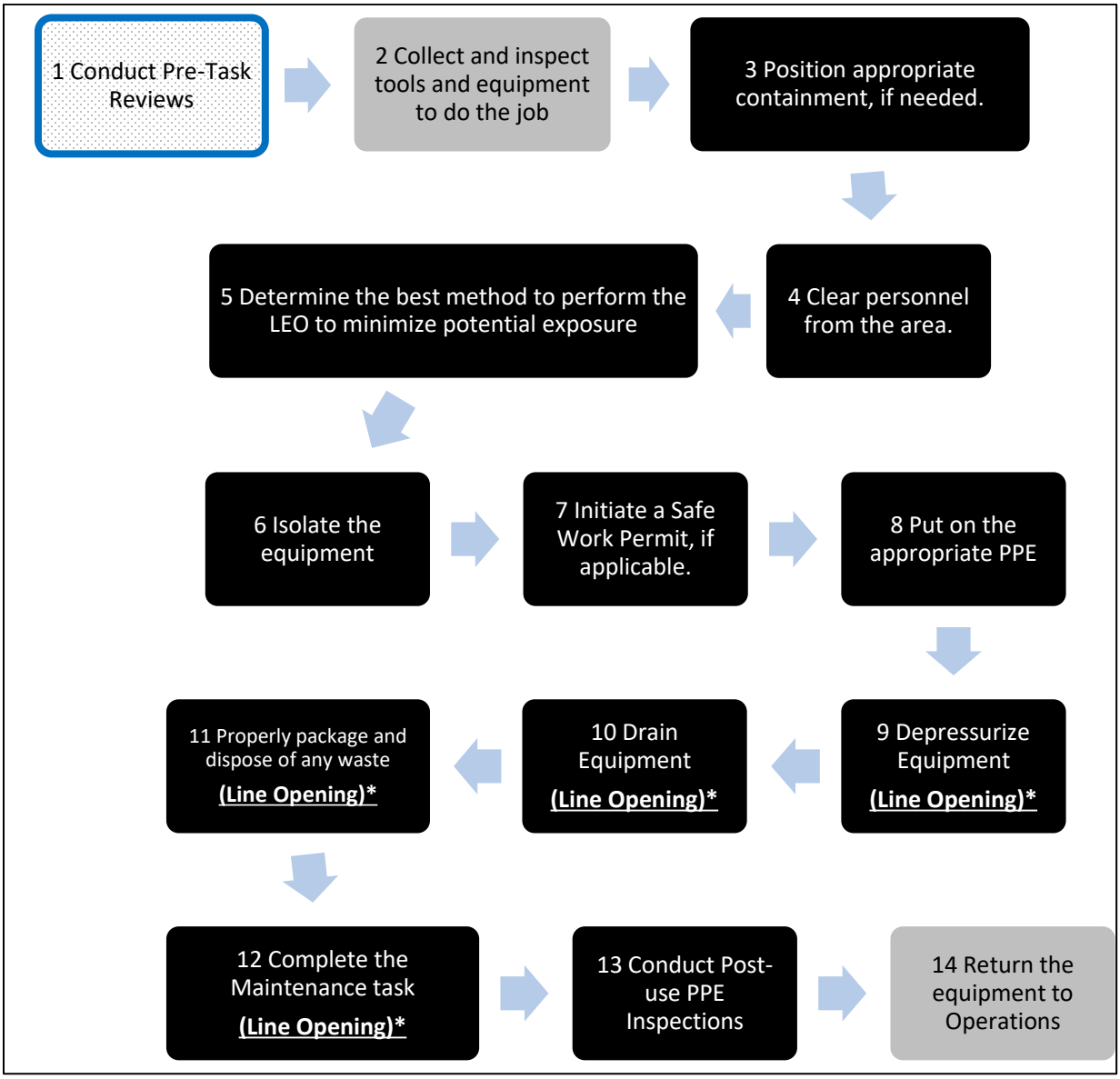
*At a minimum, Line and Equipment Opening Activities require additional PPE: Full or Half Face Air Purifying Respirator and Chemical Resistant Gloves. Some LEO tasks with higher risk of exposure require Chemical Suit and Supplied Air Respirator

E. CTC Minor Maintenance and Line Openings SOP

1. SOP Flow Chart

Color Key:

- Occur in office / control room
- Occur in field
- Occur in both office/control and field



Underline text denotes steps that require additional PPE, and/or when additional PPE is donned or removed

E. CTC Minor Maintenance and Line Openings SOP (Continued)

2. SOP Overview

1. Conduct Pre-Task Reviews
    a. Scope & Risk Assessment
    b. Safety, Health and Environmental and Ergonomic Considerations
    c. Determine Proper PPE Requirements
    d. Describe methods to Prepare and Confirm Line and/or Equipment is ready for Maintenance (Isolation, Depressurization, Draining/Disposal)
    e. Identify the exact location of the LEO.
2. Assemble and inspect equipment needed to perform the work.
3. Position appropriate containment, if needed.
4. Clear unnecessary personnel from the area.
5. Determine the best method to perform the LEO that minimizes potential exposure (regardless of PPE in use).
6. Isolate the process equipment.
7. Initiate a Safe Work Permit, if applicable.
8. **Don the appropriate PPE for the Line Opening Task***
9. As possible, clear process fluids from equipment into other process vessels
10. Perform the LEO.
    a. Depressurize equipment to vent recovery device
    b. Drain Equipment
11. Properly package and dispose of any waste associated with the LEO.
12. Complete the maintenance task associated with the LEO.
13. **Line Opening Task is complete – extra PPE can be removed if conditions permit**
14. Conduct Post-Use PPE inspection and store for future use or discard PPE if not suitable for reuse
15. Return the process equipment to Operations as per the plant policies

*At a minimum, Line and Equipment Opening Activities require additional PPE: Full or Half Face Air Purifying Respirator and Chemical Resistant Gloves. Some LEO tasks with higher risk of exposure require Chemical Suit and Supplied Air Respirator

HSIA halogenated solvents industry alliance, inc.

September 27, 2021

HSIA Response to EPA's Questions on Standard Operating Procedures (SOPs) at Carbon Tetrachloride and Other Solvent Manufacturing Sites

Carbon Tetrachloride Docket #EPA-HQ-OPPT-2020-0592; EPA-HQ-OPPT-2016-0733
Trichloroethylene Docket #EPA-HQ-OPPT-2020-0642; EPA-HQ-OPPT-2019-0500; EPA-HQ-OPPT-2016-0737
Perchloroethylene Docket #EPA-HQ-OPPT-2019-0502; EPA-HQ-OPPT-2016-0732
Methylene Chloride Docket #EPA-HQ-OPPT-2019-0437; EPA-HQ-OPPT-2016-0742

EPA posed several questions to HSIA on August 5, 2021 via email in preparation for meeting with HSIA and the EPA Carbon Tetrachloride (CTC) risk management team. As a part of that request, EPA asked for written responses that also noted when the information or answers applies to trichloroethylene, perchloroethylene, and methylene chloride. EPA's questions are presented in italics below followed by HSIA's response.

EPA: *What administrative controls (e.g., training, signs designating process areas, etc.) are in place to ensure SOP requirements are followed?*

HSIA: Employees, both new and seasoned, at our facilities are highly trained on a regular basis to ensure SOP requirements are followed. The following outline highlights some training sessions that focus on SOPs and information included in SOPs for new operator orientation, area training for experienced operators new to a process area, and additional training for specific tasks within a process area.

<u>Orientation Training of approximately 60 hours depending on the complexity of the unit and experience of the operator</u>

Orientation training for new operators includes, but is not limited to:

a. An overview of safety process systems and how employees will participate, be trained and tested on the safety systems;
b. Basic PPE requirements of the facility, the type of PPE used at the facility and how the task and/or area specific PPE is identified and required;
c. Training on the Hazard Communications Program required by 29 CFR 1910.1200, including the labeling system, how to obtain hazard information and review safety data sheets, the physical and health hazards they may encounter in the workplace, measures taken to prevent exposures such as work practices; and
d. Initial training on site-wide key procedures such as line break procedures.

Process specific area training of approximately 160 hours depending on the complexity of the unit and experience of the operator.

For experienced operators new to a process area, area training includes testing their knowledge of SOPs. This specific process training and testing requires that the operator demonstrates knowledge of:

a. The process area systems and operation guidelines;
b. The hazards of the process(es), and
c. The methods used to control those hazards specific to the plant area (e.g., information included in SOPs such as engineering controls, administrative controls, personal protective equipment).

The process specific area training is module-based training, followed by testing exercises to confirm process knowledge. A documented field walk through will be given by the unit process supervisor to determine if the trainee has the required knowledge of the unit.

Specific task training of approximately 360 hours depending upon the complexity of the unit and experience of the operator.

Additional job/task specific training is generally conducted on-the-job, on shift, on a one-on-one basis and focuses on the plant procedures and practices specific to the task expected to be performed within an area. Materials covered include training and testing an operator's knowledge of SOPs. Specific task training includes:

a. Field-based training with a transition towards taking the lead on specific tasks or duties based on demonstrated competence. Until a trainee reaches full qualification, the trainer maintains full accountability and responsibility for: 1.) the operation of the unit; 2.) the trainee's understanding; and 3.) managing the trainee's learning as they progress towards qualification;
b. Testing to ensure the operator can demonstrate an understanding of the training;
c. A job performance talk-thru must be performed or explained for every task. The walk-thru must be witnessed by a unit qualified technician and a supervisor. The trainer/supervisor will use a task check off list to verify that the trainee has completed all steps of the task correctly; and
d. Testing on each of the following applicable units: 1.) troubleshooting; 2.) safety procedures; and 3.) hazard assessments.

Refresher/Requalification Training

All employees who perform work under an SOP are trained on that SOP with refresher sessions on a regular basis. Retraining includes both a process-specific training refresher course that is conducted every six to twelve months after initial qualification and requalification and every three years at a minimum.

Additional Administrative Controls

Personnel entering certain process areas must sign in and out of the area. All personnel entering a process area must go through site orientation training that includes annual hazard communication/PPE training, which informs the employees about the hazards they work with in the facility, including all chemicals. The personnel must wear the minimum PPE required for entering the process area.

Signs are used within the plant to list the PPE required to enter a process area. In areas where additional PPE is routinely required, PPE requirements are posted in that area.

Finally, all SOPs must be readily available in hardcopy or electronically to employees that work in the unit.

EPA: *The SOP states that googles and work gloves are required anytime valves are operated and Figure 2 mentions nitrile gloves, which is consistent with some of the information provided during the risk evaluation process. Some work gloves do not offer chemical protection or offer limited protection. Are nitrile gloves the only gloves used? Is there a specific standard (e.g. ASTM) that is used or the manufacturer uses to determine the type of gloves?*

HSIA: Nitrile gloves are the primary gloves approved and listed in the PPE Hazard Assessments for tasks with potential exposure/contact with CTC. Nitrile gloves are also used for Perc and butyl gloves are used for TCE. In some cases, a specific PVC glove many be approved for tasks based on the hazard assessment. Other work gloves, such as cotton or leather, are not approved for any task where contact with CTC, Perc, Methylene Chloride or TCE is expected to occur (e.g., opening valves, etc.)

Glove permeation testing is typically performed by the glove manufacturers to make a preliminary decision of appropriateness of the glove materials for protection against chemical exposure. Chemical permeation testing is performed according to the American Society of Testing and Materials (ASTM) F739 total immersion and ASTA F1383 intermittent contact methods.

The ASTM F1383 is an intermittent test with one minute of immersion followed by nine minutes of no immersion, and then repeated up to a maximum of four hours or 240 minutes. The test was designed for showing reasonable use of gloves with highly volatile chemicals where limited contact was involved and not total immersion.

Other glove selection factors are considered such as length of task, type of task performed, and expected exposure. Many of the glove recommendations made are for tasks where incidental contact, i.e., no contact (or at worst very little contact), with a chemical is anticipated. The gloves specified are intended to prevent chemical contact with the skin during an unanticipated event – such as a spill or splash to the hand. Based upon the controls and standard operating practices in place, chemical contact is rarely seen with the glove, and these practices have been successful in

making actual hand contact with the chemical during the task practically unseen as a risk to hands protected by gloves. If there is a rare situation that creates contact with the glove or with gloved hand, the gloves are removed and the hands are washed.

EPA: *How are the PPE selections modified when the chemical hazard involves a mixture of chemicals compared to a single individual chlorinated solvent hazard?*

HSIA: The PPE is selected that best provides protection against the chemical of highest concern or the chemical that presents the most likelihood/potential for exposure to the worker in the mixture. The chemical hazard determination for each chemical in the mixture is made using the permeation data for that chemical published by the manufacturer (ATSM F739). This is the standard for liquids and gases. The Hazard Assessment provides the glove selection information to employees or those personal purchasing gloves.

EPA: *The document states that gloves are donned before sampling and loading/unloading activities. In addition, we understand tasks take 5-30 minutes. How many times are gloves reused and how is the number of reuses calculated based on breakthrough time and other workplace factors? How are the employees trained to recognize that a glove can no longer be used?*

HSIA: Employees are trained on how to inspect PPE used as part of unit orientation/SOP training as outlined in the PPE self-inspection guideline. If the gloves used for sampling/loading/unloading or line opening do not pass inspection (e.g., by showing any sign of discoloration or deformity) or have otherwise been in contact with a chemical, the gloves are disposed of per PPE policy.

Use or reuse of gloves vary based upon the task but are typically disposed of quickly. Cost is not considered in glove reuse. If the gloves do not pass inspection, they are disposed and replaced. In some cases, gloves are disposed of after a task or at the end of a shift. While there is training that requires when gloves should be disposed of, there are no restrictions on obtaining a new set of gloves after a single use or as needed or identified by the operator.

EPA: *If concentrations and amounts of accidental contact are minimal, how does the facility determine if the gloves should be replaced? Is it simply based on employee inspection or evidence? Have you considered using charcoal patch testing?*

HSIA: The PPE disposal decision is based on the employee's inspection or implemented policies, such as a single use for specific tasks. If the gloves used for sampling/loading/unloading or line opening do not pass inspection (e.g., by showing any sign of discoloration or deformity) or have otherwise been in contact with a chemical, the gloves are disposed of per PPE policy.
There are no incident trends that indicate the current methods of protection, inspection and glove replacement are not protective. Charcoal patch testing is not an industry standard.

In addition to the engineering controls and PPE use that prevents exposure, any minimal accidental exposure is also mitigated by the highly evaporative nature of the solvents. As mentioned above, although glove inspection and disposal in certain cases is mandatory, there are no restrictions on obtaining a new set of gloves after a single use.

EPA: *Can you clarify what is entailed in the step "extra PPE can be removed if conditions permit".*

HSIA: PPE can be removed if conditions permit although it is not typical to remove or downgrade PPE. For respiratory protection to be removed, it must be validated that exposures are below applicable exposure limits and/or within the protection factor of the respiratory protection type being downgraded to. Direct read instrumentation is often used to establish baseline concentrations during the performance of a task and/or to clean an area after a task has been performed. There must be sufficient evidence to suggest that exposures do not exceed exposure limits and PPE (including respiratory protection) is no longer needed. If there is any potential for the employee to come into contact with any liquid, splash, overspray, etc., then PPE would not be removed.

One example of when PPE requirements can be modified for a specific task, if conditions permit, would be a line opening task that requires full body PPE and a respirator for a "first break", when the individual begins to loosen bolts on a flange to break the line apart. Prior to this, the line has been cleared for maintenance. Once it has been verified using direct read instrumentation that the equipment is clear of all liquids, then the PPE requirements may be modified.

Other examples would be when a worker leaves the area where the potential exposure exists, a line opening task is completed and the equipment is closed up and returned to normal operations; or if the real time air monitoring with a direct reading instrument for specific chemicals shows that the level is below the exposure limit, then the PPE may be modified for that specific task. Permission from the environmental health and safety department, the operations permit writer or a supervisor may be required to make this decision. The full PPE must be put back on before the worker reenters the work area, for example, where the risk of solvent exposure exists until the specific task if completed and the risk of exposure no longer exists.

EPA: *Do you use any tools in addition to gloves, such as glove bags, tongs, funnels, SafeTainers®, etc. for any of the tasks that may lead to contact with CTC or other solvents? If not, have you considered these tools? If these tools are mot helpful or feasible, could you explain why not?*

HSIA: The tools listed in the question are not applicable to the CTC, TCE, Perc or Methylene Chloride manufacturing or feedstock processes. Closed loop sampling systems are used to collect process samples. Emission control devices are used to collect and dispose of vapors for rail car loading and unloading. If additional tools are used (wrenches, etc.), then they would need to be

evaluated for use on a task-by-task basis and decontaminated after the task is completed prior to reuse or be disposed of.

There are no incident trends that would lead us to research alternatives or additional methods of protection such as those listed. Our typical activities don't currently necessitate use of the tools listed in the question above.

EPA: *What circumstances trigger the need for the lower and the higher range of PPE when documentation suggests a range?*

HSIA: The potential for exposure to a chemical while performing a task determines the level of PPE required. This is based on the engineering controls in place for the task/process, the industrial hygiene data, and an assessment of the task to determine what the exposure level and frequency of exposure might be. In some cases, PPE may not be needed based on the exposure assessment, yet it is required by the hazard assessment to be worn as an additional backup layer to protect the worker.

EPA: *The waste packaging SOP has a step for cleaning. "If the exterior of the drum is contaminated, clean the exterior of the drum." Could you clarify how the drum is cleaned and what PPE is used during this step?*

HSIA: The drum is cleaned using a solvent chosen for the type of contamination. For CTC wastes, it would likely be perchloroethylene. In that instance, the required PPE would be full body protection and a full-face respirator with supplied air. For Perc wastes, it's most likely that perc is used to clean the drum. For methylene chloride wastes, it's most likely that methylene chloride is used to clean the drum, and for TCE wastes, it must likely that TCE is used.

EPA: *We understand that the NESHAPs require management practices consisting of quarterly inspection for leaks. Are there any additional inspections, for example, due to process changes or equipment updates, and if so, how often do they occur?*

HSIA: In addition to the quarterly inspections referenced above, HSIA's CTC, perc, TCE and methylene chloride manufacturing, processing and feedstock facilities implement the following multi-layered inspection program, management of change (MOC) procedures and pre-start up safety reviews (PSSR) requirements.

Operator Rounds
Operator audible, visual and olfactory (AVO) rounds occur at least twice each shift. During this time, operators are walking through the process area looking for leaks, drips and odors while they are taking readings from field instruments.

Mechanical Integrity Inspections
EPA's RMP (40 CFR 68.73) and OSHA's PSM (29 CFR 1910.119(j)

a. These regulations impose performance-based mechanical integrity programs that apply to the manufacturing and processing equipment. In certain cases, these standards allow/require site-specific inspection practices, maintenance and replacement based upon process knowledge and experience.

b. Industry standards for mechanical integrity incorporate Generally Accepted Good Engineering Practices (RSAGAGEP) for the process safety/mechanical integrity program (including design, fabrication, installation, inspection, testing and repair.

c. Performance-based standards and site-specific implementation for testing, inspection and repair begins with API industry standards. For example, (i.) API 653 for Tanks; (ii) API 570 and 574 for Pipes; and (iii) API 510 and API RP 572 for pressure vessels.

Management of Change (MOC)
(40 CFR 68.75) and (29 CFR 1910.119(1))

d. The MOC process reviews any changes proposed for existing processes prior to the implementation to minimize the occurrence of unplanned events. The MOC provides a mechanism for documenting changes and tracking all follow-up activities resulting from changes.

e. Supplemental training is implemented based upon each site's MOC program and training is presented when needed and upon the MOCs in place.

Pre-Startup Safety Review (PSSR)
(40 CFR 68.77) and (29 CFR 1910.119(i)

PSSR reviews the installation of new processes (new facilities), significant modification to processes, or a change to process safety information. This review is to ensure that all process safety system(s) affected by the change have been reviewed to verify that they are in place and adequate prior to the introduction of chemicals or energy to the process.

Reportable Quantity

The mechanical integrity inspections, quarterly inspections and AVO rounds described above are actions taken to both prevent and detect any releases early. The reportable quantity levels (per the Clean Water Act Section 311, CERCLA and DOT) represent additional regulatory programs in place to detect and end any potential release.

Reportable quantities for the substances discussed in this response are listed below.

	CWA Section 311 40 CFR § 117.3	**CERCLA 40 CFR § 302.4**	**DOT 40 CFR § 172.101 Table 1 to Appendix A**
Carbon Tetrachloride 56-23-5	Not listed	10 lbs	10 lbs
Perchloroethylene 127-18-4	Not listed	100 lbs	100 lbs
Methylene Chloride 75-09-2	Lot listed	1,000 lbs	1,000 lbs
Trichloroethylene 79-02-6	100 lbs	100 lbs	100 lbs

EPA: *Upon entering the production area or designed process area, at what point do respirator use requirements take effect?*

HSIA: The production areas for CTC, TCE, Perc and Methylene Chloride are all located outside and the equipment is a closed process system. Respirators are not required to be worn in the process area under normal operating conditions but are required per the task.

This is supported by the industrial hygiene data collected for employees working in the process area. Full shift and task-based samples are evaluated against the applicable occupational exposure limits. When precautionary protection is required for certain tasks, that requires respiratory protection. If another employee is going to enter the area where an SOP task is being conducted, they too would have to don the appropriate PPE for that SOP.

Appendix 4

HSIA halogenated solvents industry alliance, inc.

Meeting with EPA on Chlorinated Solvent Feedstocks in HFC/HFO Production and Cross Cutting Issues

May 25, 2021

Agenda

halogenated solvents industry alliance, inc.

1. Implications of Restricting Feedstock Use
2. Cross Cutting Concerns
    i. Hazard Assessment
    ii. Inhalation Exposure
    iii. Dermal Exposure
3. Examples: Conditions of Use should Consider existing Layers of Protections
    i. Manufacture
    ii. Feedstock Use

Overarching Issues

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1) The hazard assessments were not based upon best available science and weight of evidence. As an example, these concerns are documented in the Request for Correction submitted to EPA for CTC.

2) Conditions of Use in the Risk Evaluation did not incorporate standard engineering and workplace industrial requirements for dermal or inhalation potential exposure, as implemented under NESHAP and OSHA regulatory requirements.

3) These errors in the Risk Evaluations do not provide a scientific or practical basis for the Risk Management Rule and should be remedied before or during the Risk Management Phase.

Implications of Restricting Feedstock Uses

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- CTC, PERC and TCE are used as a feedstock for refrigerant gases and other critical uses such as automotive and stationary air conditioning.

- The implications of these unreasonable risk determinations are enormous for the environment as well as the US economy.
  - For example, the Kigali Amendment to the Montreal Protocol, which mandates a global phase down of HFCs, is predicated on the widespread availability of low-GWP alternatives such as HFO-1234yf and related HFOs which rely on these substances as feedstock.
  - The importance of this transition was recognized by the inclusion of HFC phase down provisions in the omnibus spending bill approved in December 2021, hailed as the most important measure to fight climate change ever enacted by Congress

- CTC feedstock is required for production of HFOs, the critical low-GWP alternatives.

- The transition to HFOs will take over a decade, and during this time HFCs will still be very much in demand. Restricting the use of TCE and perc as HFC feedstocks could cause severe disruptions in important user sectors such as refrigeration, HVAC, and mobile A/C.

Issues with Hazard Assessments

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- Decisions not based on weight of the scientific evidence
- Deficiencies in the use of best available science
- Carbon tetrachloride (CTC) cancer hazard assessment
  - EPA disregarded advice from scientific advisory committees (IRIS, SACC) on CTC cancer mode-of-action (MOA) and derivation approach for a cancer toxicity/risk value
  - EU concluded CTC acts as a carcinogen by a threshold MOA with a Derived-Minimal-Effect-Level (DMEL) based on a No-Observed-Adverse-Effect-Concentration (NOAEC) of 5 ppm for mouse liver tumors
- Similar problems also exist for the cancer hazard assessments of TCE and PCE

Issues with Hazard Assessment

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- Considerable objectivity concerns with the systematic review of TCE (and PCE) cancer epidemiology studies.
  - Similar view by the NAS committee review of the TSCA systematic review process.
- Significant scientific validity problems with key TCE autoimmune study (Keil *et al.*, 2009) for the chronic non-cancer toxicity endpoint.
- Inaccurate and misleading interpretation of one of the key PCE studies (Cavelleri *et al.*, 1994) for the chronic non-cancer toxicity endpoint.

Inhalation Exposure Assessment Concerns in TSCA Risk Evaluations

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- Lumping all worker exposure data together for a condition of use
  - Does not differentiate tasks or similar exposure groups (SEGs)
  - Tasks are combined having an array of exposure profiles: differences in processes, frequency of exposure, exposure duration, etc.
  - Matching non-routine vs. routine tasks with inappropriate health benchmarks
    - Impacts risk characterization and determination of Existing Chemical Exposure Limits (ECELs)
    - Workers/ONUs that have infrequent or rare exposure potential should be benchmarked with an 8-hr TWA based on acute effects, not an 8-hr TWA based on cancer and/or non-cancer effects that require repeated daily exposures.
- Bias due to considerable amount of worker/ONU monitoring data below the Level of Quantitation (LOQ)

Dermal Exposure Assessment Concerns in TSCA Risk Evaluations

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- Engineering controls (CAA MACT standards) are designed to prevent industrial emissions and exposures.
- TSCA risk evaluations excluded consideration of EPA-mandated MACT standards in dermal exposure models for closed system production/feedstock use facilities.
- Instead, EPA dermal exposure model assumed open process assuming both hands on both sides have liquid contact. Moreover, EPA assumed liquid stayed on unwashed hands (if gloves used, not removed) for the entire 8-hr work shift.
- Splash exposures are not allowed at these facilities and worst-case exposure (rare) are reduced to drops from, for example, transfer lines.

Dermal Exposure Assessment

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Closed, hard-piped systems, engineering controls and procedures for manufacturing and processing prevent the type of dermal exposure scenarios assumed in the risk evaluations.

EPA Assumption in dermal model	Actual Condition of Use for intermittent tasks such as loading, unloading, sampling and line openings with any potential dermal exposure
Undiluted, full hand CTC contact each shift.	Tasks are 15 min., approximately once a shift, engineering controls and PPE protect from potential exposure. Rare, worst-case exposures are reduced to drops, not full hand contact.
Workers do not wash hands during a shift.	Any liquid prompts immediate glove removal and hand washing. Hands are washed after the task. (Not an infinite dose).
Workers wear the same gloves for 8 hours.	The integrity of gloves are inspected both before the task and when removed immediately after the task.

The dermal assumptions used in the risk evaluation for manufacturing and processing do not reflect the actual condition of use.

Dermal Exposure Assessment

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- Final risk evaluation drastically overstates the dermal risk for chlorinated solvents in closed processes used in production and feedstock use.
  - Skin loading (2.1 vs. 0.2 mg/cm2)
  - Skin area for contact (1070 vs 134 cm2)
  - Fraction absorbed (versus evaporation)
- Dermal exposure in final risk evaluations does not account for rapid evaporation of these highly volatile substances. (evaporation time for 2 g ranges from 0.5- 2min at 25 degrees C)
- 2 grams deposited on the hand is more representative of dermal exposure to water from consumer washing dishes
- 2 grams deposited on the glove would evaporate in under 5 min. The gloves are impervious to the solvent for short exposure time
- Using a more realistic yet still conservative approach results in exposures 40-250x lower depending on the substance properties

The Manufacturing and Processing Conditions of Use should consider Existing Layers of Protection

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FACILITY DESIGN

ENGINEERING CONTROLS

- Closed Vent System – hard piping into control devices or recycled
- Emission controls such as scrubbers, thermal oxidizers or flares with a required destruction efficiency
- Vapor recovery units, vapor balancing to a control device
- Caps and/or double valves so no single layer to a potential open line
- Closed loop sampling
- Welding fittings

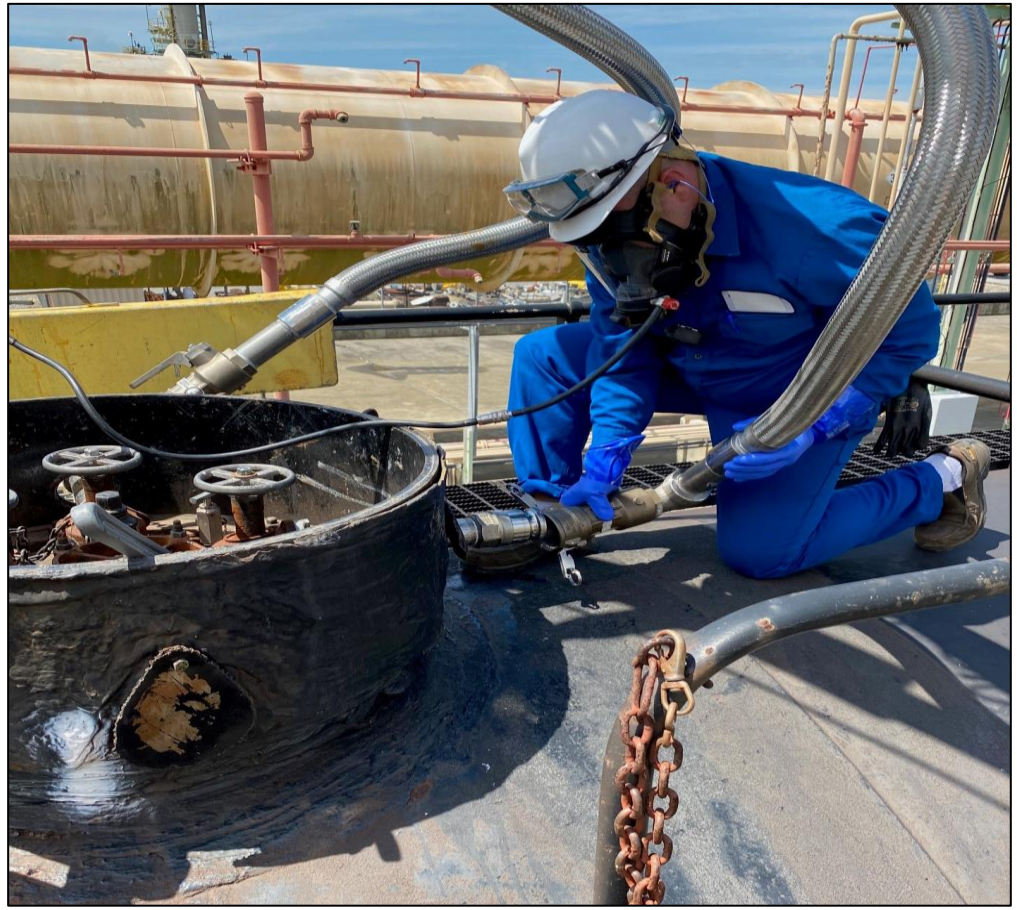
ADMINISTRATIVE CONTROLS

- Employee Training and Qualification
- Standard Operating Procedure
- Permitting Requirements
- Access Controls
- Leak Detection and Repair
- Distributive Control Systems

PERSONAL PROTECTIVE EQUIPMENT (PPE)

- Standard Plant PPE is typically hard hat, safety glasses, steel-toed shoes, earplugs (as required by signage). Chemical gloves, chemical resistant suit and respirator use is required based upon task.
- Full shift and task-based sampling confirms engineering controls and administrative controls are protective
- Monitored by Specific Exposure Groups
- Exposure data does not account for half-face or air-supplied respirator worn during monitoring periods (personal monitor device is worn “outside” PPE).

Layers of Protection Loading/Unloading



Engineering Controls: NESHAP Controls for loading/unloading, transfer racks (40 CFR 63.126-130, 2475, 2525) *e.g.*, vapor recovery units, vapor balancing, incineration with a required destruction efficiency.

Administrative Controls: Standard Operating Procedures includes the procedures to use the engineering controls and the necessary PPE for the task.

PPE: chemical resistant gloves, clothing and footwear; air supplied respirator.

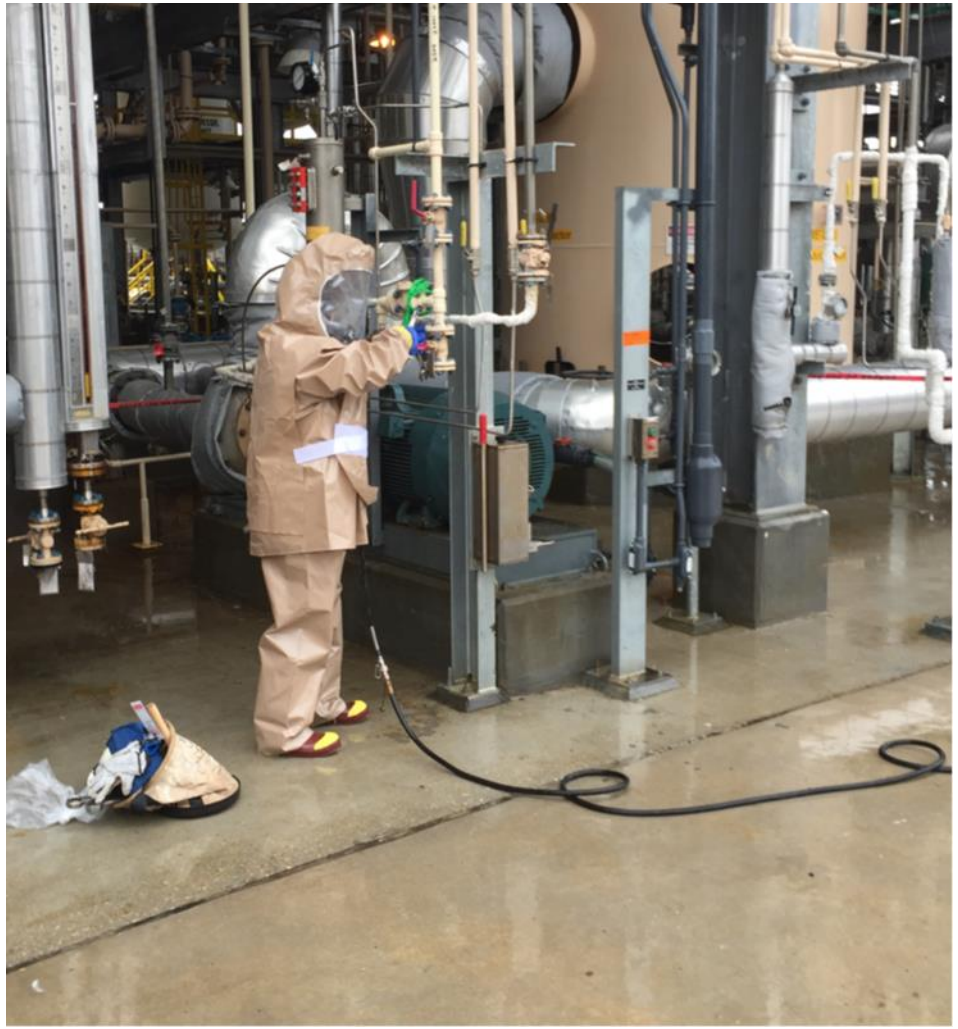
Layers of Protection Sampling

Engineering Controls: Process sampling systems for CTC prevents releases or potential personnel exposure.

Administrative Controls: Standard Operating Procedure (SOP) includes the procedures to use the engineering controls and the necessary PPE for the task.

PPE requirements: Goggles, hand protection and air purifying respirator

Layers of Protection Line Opening



Administrative Controls: Standard Operating Procedure and Permitting requirements before each task:

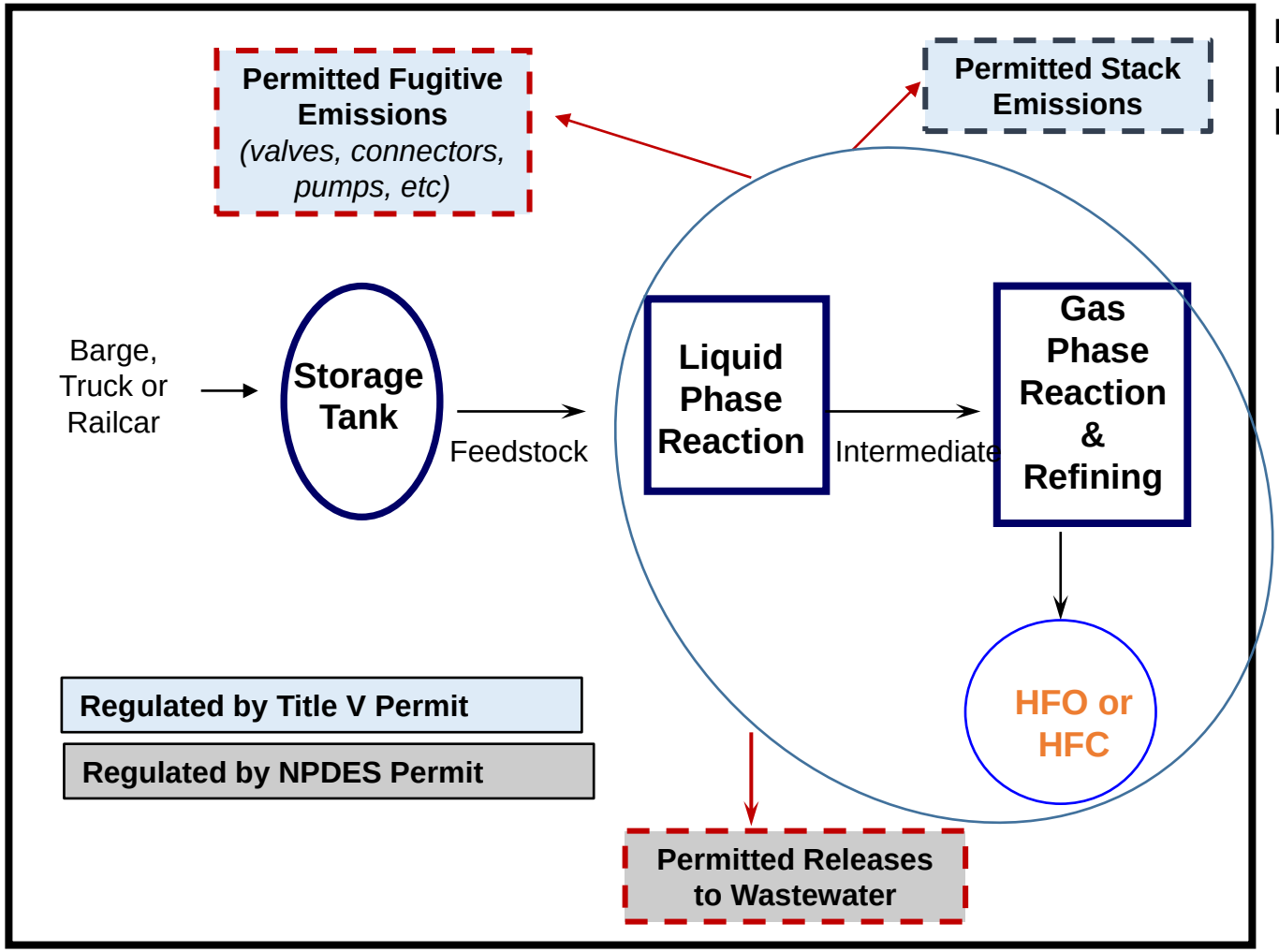
- Required hazard analysis
- Communication tool between maintenance and operations
- Ensure that work hazards are identified and mitigated prior to the work beginning
- Barricade

Engineering Controls: two layers of protection for the duration of the task for example, for a line break:

- Line clearing
- multiple layers of isolation

PPE: chemical resistant gloves, clothing and footwear; air supplied respirator

Use of Chlorinated Solvent as a Feedstock



Loading/unloading operations should include the following protections required by regulations in the manufacturing and processing condition of use:

i. **NESHAP regulations/Engineering Controls:** The HON NESHAP requires engineering controls such as vapor collection, balancing and/or controls to control emissions during unloading/loading. (40 CFR 63.126-130, 2475, 2525)

ii. **SOPs/Administrative Controls:** As required by OSHA, each site implements Standard Operating Procedures (SOPs) to ensure the engineering controls are effectively and safely used in the unloading/loading process. (29 CFR 1910.119(f))

iii. **PPE:** PPE (respiratory and dermal) is identified and required for unloading/loading operations. For dermal, gloves are selected based upon potential exposure and nature of potential hazards for the task. (OSHA 29 CFR 1910.138.) OSHA also recognizes factors, *e.g.,* required dexterity, length of glove, temperature, and duration of task, that may be evaluated for use when selecting the proper dermal protection. (29 CFR Subpart I Appendix B.11)

HFC Allocation Proposed Rule

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- Proposal published a week ago.
- EJ section is rooted in these TSCA evaluations: focus is entirely on solvent feedstocks: “known to present an unreasonable risk of injury to the health of workers or occupational non-users in processing as a reactant or intermediate in industrial gas manufacturing.”
- The TSCA Evaluations are also impeding transition to HFOs where solvents now presented as risk at fenceline as well as to workers.
- NESHAPs adopted under §112(d) of the Clean Air Act specifically “to provide an ample margin of error of safety to protect public health” in fenceline communities should be focus of EJ analysis but are not mentioned.

Key Takeaways

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- EPA must use the best available science in assessing risks, consistent with peer reviewer advice.
- Dermal exposure is not an issue for these conditions of use.
- EPA must look at NESHAP requirements in assessing workplace exposures and fence line risk.
- Failure to reflect foregoing will offshore HFO/HFC manufacturing.

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Carbon Tetrachloride Risk Management Rule August 17, 2021

Docket EPA-HQ-OPPT-2016-0733
EPA-HQ-OPPT-2019-0499

Carbon Tetrachloride Agenda

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1. Environmental Benefits
2. Federal CAA Emission Controls
3. Layers of Protection in Facilities
4. Risk Evaluation and Exposure Concerns
5. EPA Questions

CTC Feedstock Use Has Environmental Benefits

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- CTC is the feedstock for all the low GWP HFO alternatives that will enable compliance with the Kigali Amendment and the AIM Act, including the refrigerant HFO-1234yf.

- Example: HFO-1234yf, refrigerant replacing R-134a for auto A/C, has a low GWP:

  R-134a: 1,300 GWP

  HFO-1234yf: 4 GWP

TSCA Section 6(c)(A)(iii) considers the benefits of a chemical substance in the Risk Management Rule process.

CTC is a critical building block for low GWP refrigerants.

Implications of Restricting Feedstock Uses

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Eliminating CTC as a feedstock use would threaten major production facilities just opened in Louisiana and Texas, along with a projected additional 33,000 new American manufacturing jobs, $12.5 billion increase in direct output per year by 2027, and 25 percent boost in US exports of refrigerants and related equipment.

TSCA §6(c)(A)(iv) considers the economic consequences of a chemical substance in the Risk Management Rule process.

Industry has heavily invested in the transition to low GWP refrigerants using CTC.

The transition to low-GWP refrigerants will take over a decade, eliminating the manufacture or use of CTC as a feedstock would cause severe disruptions in the transition to low GWP refrigerants.

CTC Emissions Controlled by Federal CAA

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National Emission Standards for Organic Hazardous Air Pollutants (NESHAP) imposes standards and controls on CTC facilities.

- Synthetic Organic Chemical Manufacturing Industry (HON) 40 CFR Part 63 Subparts F, G, H, and I, and/or
- Miscellaneous Organic Chemical Manufacturing (MON) 40 CFR Part 63 Subpart F

CAA Title VI (Montreal Protocol)
Protection of Stratospheric Ozone

- 40 CFR Part 82

TCSA §6(c)(A)(i) requires consideration of exposure in the Risk Management Rule process.

Existing federal Clean Air Act requirements currently reduces exposure with controls, standards and use limitations.

NESHAP Emission Standards and Controls

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HON and MON NESHAPs. Impose standards and controls to prevent emissions and exposure from CTC manufacturing and processing facilities:

- Process Vents
- Wastewater
- Storage Tanks and Vessels
- Loading/Unloading transfer racks
- Fugitives - Leak Detection and Repair

CAA Residual Risk Review (CAA §112(f)(2)). EPA determined that no changes were required for CTC controls under the HON (71 Fed. Reg. 76603 (Dec. 21, 2006)) or the MON (85 Fed. Reg. 49084 (Aug. 12, 2020)) because the regulations impose CTC controls that:

- Reduces HAP emissions to levels that present an acceptable level of risk, and
- Protects the public health with an ample margin of safety.

Montreal Protocol Limits Uses of CTC

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Protection of Stratospheric Ozone, 40 CFR Part 82.3, limits the use of CTC to the following:

(1) the manufacture of a controlled substance that is subsequently 100% transformed (*i.e.,* used as a feedstock);
(2) the reuse or recycling of a controlled substance;
(3) amounts that are destroyed by approved technologies; and
(4) amounts of CTC that are unintentionally vented or spilled.

In addition to the HON and the MON NESHAPs, these use limitations require additional engineering and emission controls, as well as recordkeeping and reporting requirements, to maintain compliance.

Layers of Protection
CTC Manufacturing or Processing

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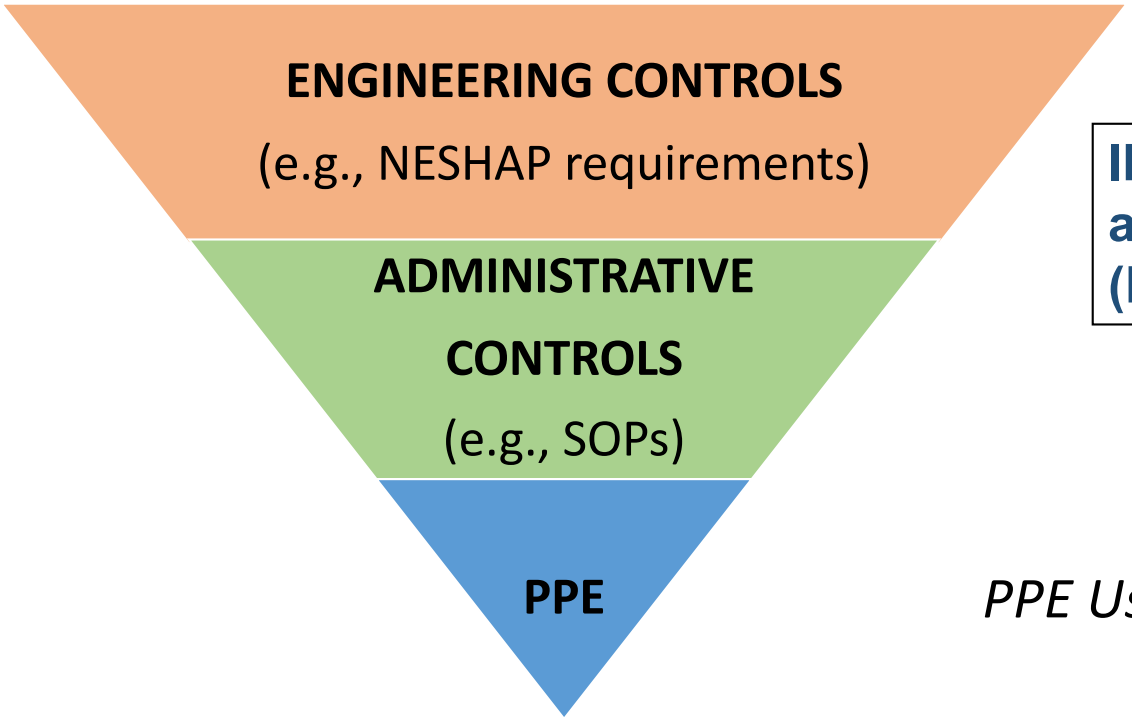
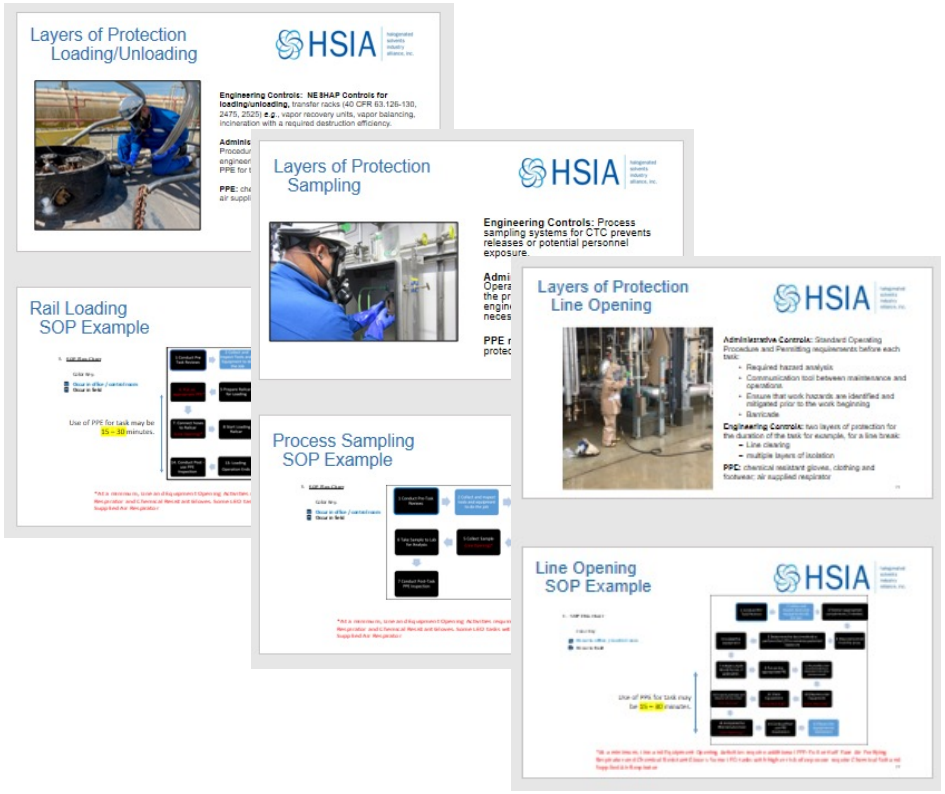


IH Monitoring Confirms Control and SOP Effectiveness. (Measured Outside of PPE.)

PPE Use Does Not Equal Exposure

Layers of Protection by Task



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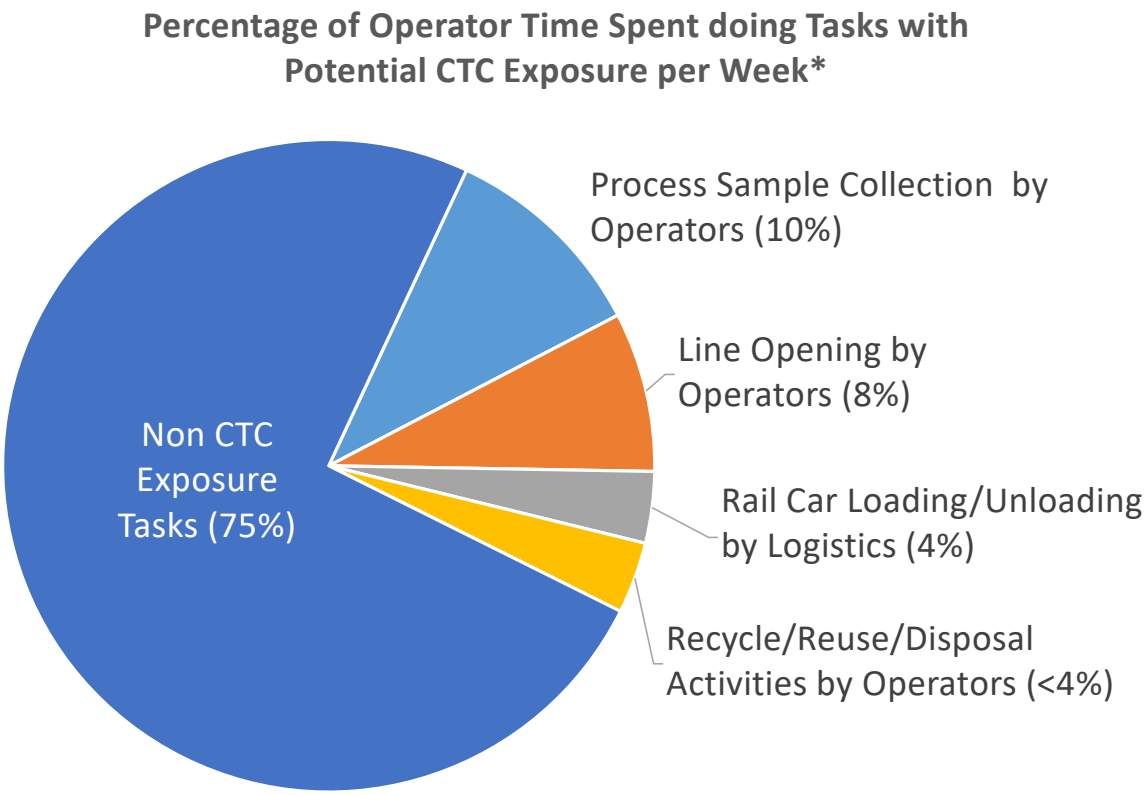
- Risks are mitigated by standard detailed SOPs for all tasks
- Operators in Manufacturing and Feedstock Facilities spend most of their time out of the process area

Analysis of CTC Tasks



Majority of Operator Task Time Don't Involve CTC Exposure Potential

**All tasks not necessarily conducted by a single operator; could be spread across multiple groups*

**Line Opening, Loading/Unloading, and Recycle etc tasks are performed weekly. Process Sampling is a daily task.*

Risk Evaluation Concerns

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Hazard Assessment

- The Risk Evaluation uses a linear non-threshold model coupled with an assumption that the principal study relied upon did not produce a no-observed-adverse-effect level (NOAEL) for mouse liver tumors.
- This approach disregards the advice provided by outside peer reviewers, resulting in estimates of risk thousands of times higher than reality.

ONUs as defined in the Risk Evaluation do not exist

- PPE is required by task, not job title.
- Any person/worker is subject to PPE requirements imposed on a specific location and/or task.

Exposure Assessment

- The ONU category is overestimated in Risk Evaluation.
- The CTC dermal exposure modeling overestimates exposure

Screening Assessment

- Fenceline assessments were conducted for the NESHAP HON and MON Residual Risk Review.
- The NESHAP Standards and Residual Risk Reviews should be utilized for the review in accord with TSCA §9.

"ONU" Risk Concerns

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"ONU" as defined in the Risk Evaluation does not exist in Manufacturing and Processing Facilities.

- PPE requirements are driven by task and potential exposure, not job classification.
- If a supervisor is in the area of a SOP-covered task, the supervisor must don appropriate PPE.
- SOPs implement a restricted area & removal of all nonessential personnel before tasks begin.

The Risk Evaluation overestimates exposure for ONU-like workers.

- All exposure values for ONU-like workers were less than the limit of detection (<LOD)
- For workers not performing certain SOP tasks, it is expected that exposure will be <LOD.

Dermal Modeling Overestimates Exposure

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- Facilities employ closed, hard-piped systems, engineering controls and procedures
- Tasks are infrequent and typically of short duration during a shift
  - Engineering controls and PPE protect from potential exposure.
  - Rare, worst-case exposures are reduced to drops, not full hand contact.
- Any liquid prompts immediate glove removal and hand washing. Hands are washed after the task. (Not an infinite dose).
- The integrity of gloves are inspected both before the task and when removed immediately after the task.
  - Contaminated or damaged gloves are replaced

TSCA Section 6(c)(A)(i) requires the Risk Mitigation Rule to take into account the magnitude of exposure. The Risk Evaluation overestimates dermal exposure.

Risk Mitigation Rule Summary

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1. CTC is the building block for the next-generation low GWP alternatives.
   A. Environmental Benefits
   B. Economic Benefits

2. The Risk Mitigation Rule should recognize, but not unnecessarily duplicate, federal controls:
   A. NESHAPs established by EPA to reduce CTC and other HAP emissions to levels that present an acceptable level of risk and protect public health with an ample margin of safety.
   B. Workplace limits enforced by OSHA
   C. OSHA's Process Safety Mgmt (PSM) and EPA's Risk Mgmt Program (RMP) performance-based requirements, including facility specific:
      1. Operating instructions (SOPs)
      2. Emission control instructions
      3. PPE requirements
      4. Mechanical Integrity
      5. Mgmt of Change
      6. Pre-Startup Safety Review (PSSR)

Questions from EPA

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1. The SOP states that goggles and work gloves are required anytime valves are operated and Figure 2 mentions nitrile gloves, which is consistent with some of the information provided during the risk evaluation process. Some work gloves do not offer chemical protection or offer limited protection. Are nitrile gloves the only gloves used?
    - Is there a specific standard (e.g. ASTM) that is used or the manufacturer uses to determine the type of gloves?
2. How are the PPE selections modified when the chemical hazard involves a mixture of chemicals (compared to a single individual chlorinated solvent hazard)?
3. The document states that gloves are donned before sampling and loading/unloading activities. In addition, we understand tasks take 5-30 mins. How many times are gloves reused and how is the number of re-uses calculated based on breakthrough time and other workplace factors? How are employees trained to recognize when a glove can no longer be reused?

Questions from EPA…

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4. If concentrations and amounts of accidental contact are minimal, how does the facility determine if the gloves should be replaced? Is it simply based on employee inspection of evidence? Have you considered using charcoal patch testing?
5. Could you clarify what is entailed in the step “Extra PPE can be removed if conditions permit”?
6. Do you use any tools in addition to gloves, such as glove bags, tongs, funnels, SafeTainersTM, etc. for any of the tasks that may lead to contact with CTC? If not, have you considered these tools? If these tools are not helpful or feasible, could you explain why not?
7. What circumstances trigger the need for the lower and the higher range of PPE when documentation suggests a range?

Questions from EPA…

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8. The Waste Packaging SOP has a step for cleaning: “If the exterior of the drum is contaminated, clean the exterior of the drum.” Could you clarify how the drum is cleaned and what PPE is used during this step?
9. We understand that the NESHAPs require management practices consisting of quarterly inspections for leaks. Are there any other additional inspections, for examples due to process changes or equipment updates, and, if so, how often do they occur?
10. Upon entering the production area or designated process area, at what point do respirator use requirements take effect?
11. What administrative controls (e.g. training, signs designating process areas, etc.) are in place to ensure SOP requirements are followed?

BACKUP INFORMATION

- The next few slides were also shown in today's meeting

Layers of Protection
CTC Manufacturing or Processing

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FACILITY DESIGN

ENGINEERING CONTROLS (e.g., NESHAP requirements)

- Closed Vent System – hard piping into control devices or recycled
- Emission controls such as scrubbers, thermal oxidizers or flares with a required destruction efficiency
- Vapor recovery units, vapor balancing to a control device
- Caps and/or double valves so no single layer to a potential open line
- Closed loop sampling
- Welding fittings

ADMINISTRATIVE CONTROLS (e.g., SOPs)

- Employee Training and Qualification
- Standard Operating Procedure
- Permitting Requirements
- Access Controls
- Leak Detection and Repair
- Distributive Control Systems

PERSONAL PROTECTIVE EQUIPMENT (PPE)

- Standard Plant PPE is typically hard hat, safety glasses, steel-toed shoes, earplugs (as required by signage).
- Chemical gloves, chemical resistant suit and respirator use is required based upon task.
- Full shift and task-based sampling confirms engineering controls and administrative controls are protective
- Monitored by Specific Exposure Groups

IH Monitoring Confirms Control and SOP Effectiveness. (Measured Outside of PPE.)

Layers of Protection Loading/Unloading

Engineering Controls: NESHAP Controls for loading/unloading, transfer racks (40 CFR 63.126-130, 2475, 2525) *e.g.*, vapor recovery units, vapor balancing, incineration with a required destruction efficiency.

Administrative Controls: Standard Operating Procedures includes the procedures to use the engineering controls and the necessary PPE for the task.

PPE: chemical resistant gloves, clothing and footwear; air supplied respirator.

Rail Loading SOP Example

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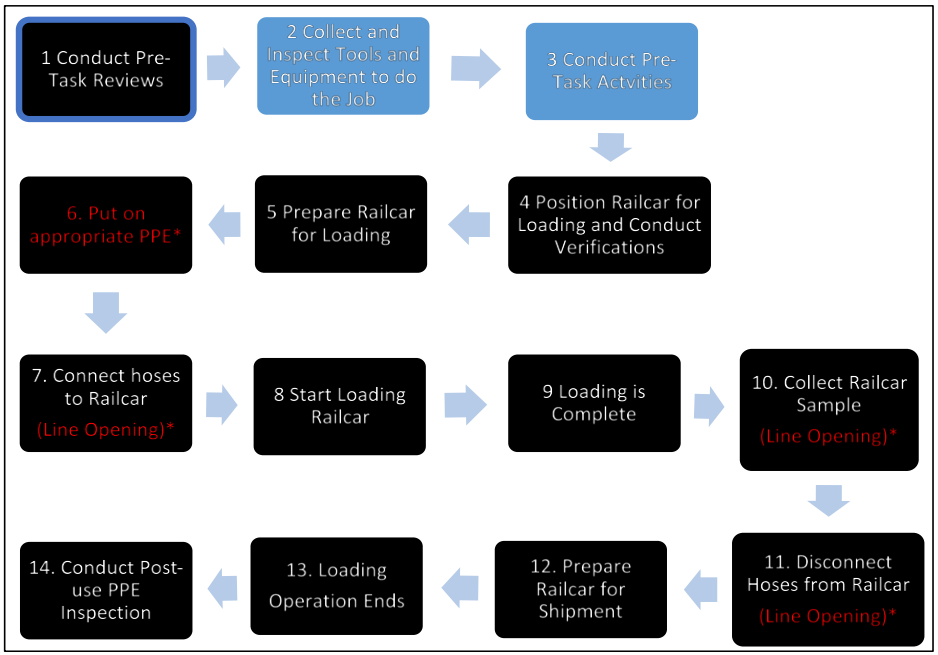
1. **SOP Flow Chart**

Color Key:

- **Occur in office / control room**
- **Occur in field**



*At a minimum, Line and Equipment Opening Activities require additional PPE: Full or Half Face Air Purifying Respirator and Chemical Resistant Gloves. Some LEO tasks with higher risk of exposure require Chemical Suit and Supplied Air Respirator

Layers of Protection Sampling

Engineering Controls: Process sampling systems for CTC prevents releases or potential personnel exposure.

Administrative Controls: Standard Operating Procedure (SOP) includes the procedures to use the engineering controls and the necessary PPE for the task.

PPE requirements: Goggles, hand protection and air purifying respirator

Process Sampling SOP Example

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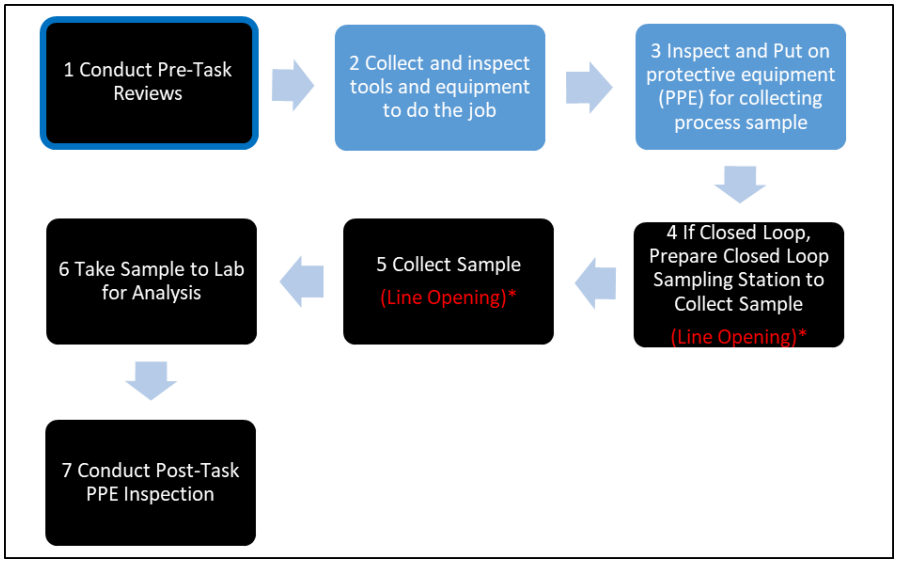
1. **SOP Flow Chart**

Color Key:

- **Occur in office / control room**
- **Occur in field**



*At a minimum, Line and Equipment Opening Activities require additional PPE: Full or Half Face Air Purifying Respirator and Chemical Resistant Gloves. Some LEO tasks with higher risk of exposure require Chemical Suit and Supplied Air Respirator

Layers of Protection Line Opening

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Administrative Controls: Standard Operating Procedure and Permitting requirements before each task:

- Required hazard analysis
- Communication tool between maintenance and operations
- Ensure that work hazards are identified and mitigated prior to the work beginning
- Barricade

Engineering Controls: two layers of protection for the duration of the task for example, for a line break:

- Line clearing
- multiple layers of isolation

PPE: chemical resistant gloves, clothing and footwear; air supplied respirator

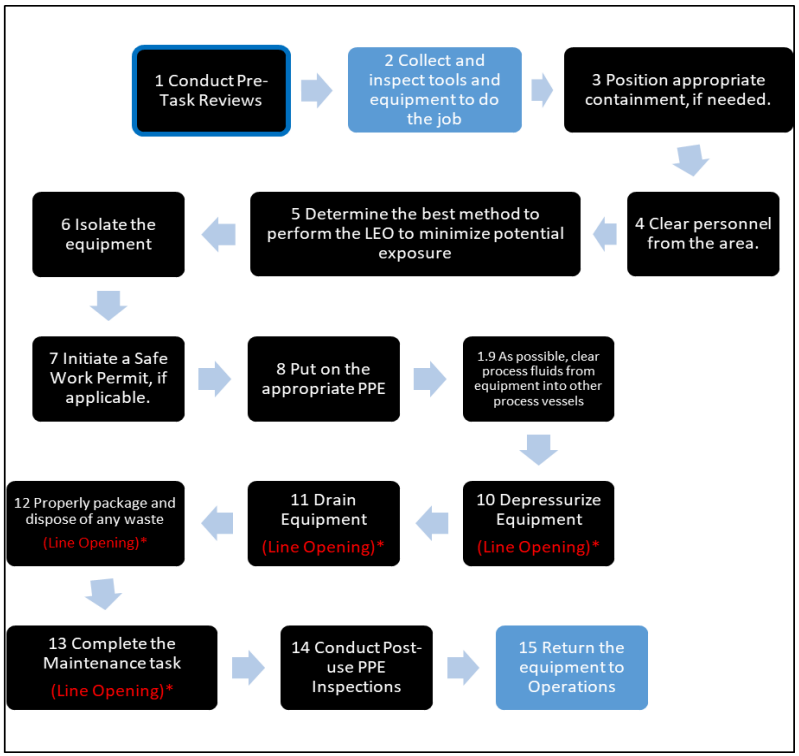
Line Opening SOP Example

halogenated solvents industry alliance, inc.

1. **SOP Flow Chart**

Color Key:

- **Occur in office / control room**
- **Occur in field**



*At a minimum, Line and Equipment Opening Activities require additional PPE: Full or Half Face Air Purifying Respirator and Chemical Resistant Gloves. Some LEO tasks with higher risk of exposure require Chemical Suit and Supplied Air Respirator

Dermal Modeling Overestimates Exposure

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Closed, hard-piped systems, engineering controls and procedures for manufacturing and processing prevent the type of dermal exposure scenarios modeled in the risk evaluations.

EPA Assumption in dermal model	Actual Potential Dermal Exposure for intermittent tasks such as loading, unloading, sampling and line openings
Undiluted, full hand CTC contact each shift.	Tasks are 15 min. Engineering controls and PPE protect from potential exposure. Rare, worst-case exposures are reduced to drops, not full hand contact.
Workers do not wash hands during a shift.	Any liquid prompts immediate glove removal and hand washing. Hands are washed after the task. (Not an infinite dose).
Workers wear the same gloves for 8 hours.	The integrity of gloves are inspected both before the task and when removed immediately after the task.

TSCA Section 6(c)(A)(i) requires the Risk Mitigation Rule to take into account the magnitude of exposure. The Risk Evaluation overestimates dermal exposure.

September 26, 2022

To: Christopher Bevan, PhD, DABT
Halogenated Solvents Industry Alliance, Inc.

Evaluation of the liver tumors of the 5 ppm-exposed female mice in the two-year carcinogenicity study on carbon tetrachloride by Nagano *et al.* (2007a)

Several bioassays have been performed in rodents to assess the carcinogenicity of carbon tetrachloride (CTC). The results of many of these studies have been criticized for not meeting the currently accepted bioassay standards or by using routes of administration that do not consider the major route of human exposure in an occupational setting *i.e.*, inhalation. particularly in an occupational setting. A two-year bioassay in rats and mice exposed by inhalation to CTC was performed by the Japan Bioassay Research Center (JBRC) (Nagano *et al.*, 2007a). This study has been used by regulatory agencies for assessing carcinogenicity of CTC. In the JBRC study using F344 male and female rats and male and female BDF_1 mice (cross between female C57BL/6 and male DBA/2 mice), the liver proved to be the most sensitive target organ for tumor formation in both species. Liver adenomas and carcinomas were detected in both rats and mice. In rats, the incidence of liver adenomas and carcinomas were increased only at the highest exposure concentration examined (125 ppm) in both males and females. The incidence of hepatic adenomas and carcinomas was increased over control at the two highest exposure concentrations (25 and 125 ppm) in both male and female mice. In addition, a slight increase in liver adenomas (8/49) but not carcinomas or combined adenomas and carcinomas was reported at 5 ppm in female mice. In a reexamination of the results from the JBRC study, concern has been raised on the significance and validity of this observation (female mouse liver tumors at 5 ppm). In reviewing the significance of the adenoma incidences at the 5 ppm-exposed female mice, several points need to be considered.

Point 1: Statistical analysis

Nagano *et al.* (2007a) reported a statistically significant increase ($p \leq 0.05$) in liver adenomas compared to controls using the Fisher's exact test. A re-examination of the results showed that using the Fisher's exact test results in a p value of 0.05112, which is not significant at the p = 0.05 level of significance.

Point 2: Haseman Rule

The statistical significance of the liver adenomas seen in the Nagano *et al.* (2007a) bioassay should be reconsidered. As Haseman (1983) stated, for common tumors, statistical significance for tumor incidences should be based on the probability of $p < 0.01$ rather than $p < 0.05$ because of the multiple comparisons and to avoid the high probability of false positives. Certainly, liver cell hepatocellular tumors in mice are a common tumor (as defined by Haseman as tumors with spontaneous incidence of >1%). This statistical standard has been adopted by pharmaceutical regulatory agencies (FDA, 2001), and was extended by the U.S. FDA to have the

trend test be significant only if $p < 0.005$, rather than 0.01. OECD (2012) has also accepted this standard of $p < 0.01$ for comparison of incidences of common tumors. Thus, on a purely statistical basis, these tumors (even adenomas alone) were not significant and are considered not treatment related.

Point 3: Historical Control data

Historical control incidence data on female BDF_1 mouse liver tumors from two-year carcinogenicity studies conducted at JBRC are presented in the tables below.

Liver Adenomas

Source	Details	Historical Control Group Incidence (%)
Yamate *et al.* (1990)	1 study (≤1988); 50 animals	12%
Katagiri *et al.* (1998)	10 studies (over ten years); 499 animals	Range: 2-8%
Nagano (2004); cited in EPA (2011)*	20 studies (dates and number of animals not provided)	Range: 2-10%
Nagano *et al.* (2007a)**	17 studies (1990-2006); 849 animals	Maximum: 12%
Fukushima (2022)	1348 animals	Range: 2-20%

*Historical control data provided to EPA from Kasuke Nagano (JBRC) in letter dated March 8, 2004, and email dated March 9, 2004).
**2-year inhalation studies only.

Liver Carcinomas

Source	Details	Historical Control Group Incidence (%)
Yamate *et al.* (1990)	1 study (≤1988); 50 animals	0%
Katagiri et al. (1998)	10 studies (over ten years); 499 animals	Range: 0-4%
Nagano (2004); cited in EPA (2010)*	20 studies (dates and number of animals not provided)	Range: 0-8%
Nagano *et al.* (2007a)**	No data provided.	-
Fukushima (2022)	1348 animals	Range: 0-8%

*Historical control data provided to EPA from Kasuke Nagano (JBRC) in letter dated March 8, 2004, and email dated March 9, 2004).
**2-year inhalation studies only.

Liver Adenomas and Carcinomas (Combined)

Source	Details	Historical Control Group Incidence (%)
Yamate *et al.* (1990)	1 study (≤1988); 50 animals	12%
Katagiri *et al.* (1998)	10 studies (over ten years); 499 animals	Not specified.
Nagano (2004); cited in EPA (2010)*	20 studies (dates and number of animals not provided)	Not specified.
Nagano *et al.* (2007a)**	17 studies (1990-2006); 849 animals	Maximum: 12%

Fukushima (2022)	1348 animals	Range: 2-20%

*Historical control data provided to EPA from Kasuke Nagano (JBRC) in letter dated March 8, 2004, and email dated March 9, 2004).

**2-year inhalation studies only.

The mean incidence of liver adenomas was found to be in a range from 2- 8 % (Katagiri *et al.*, 1998). Similarly, Yamate *et al.* (1990) reported a control incidence of 12% liver adenomas, 0% incidence of carcinomas and 12% incidence in combined adenomas and carcinomas in untreated female BDF1 mice. Finally, the information provided by Dr. Shoji Fukushima (personal communication), the former Director of JBRC and the senior author on the publications of the 13-week and two-year inhalation CTC studies (Nagano *et al.*, 2007a; Nagano et al., 2007b), indicated that the range of incidences of hepatocellular adenomas in female BDF1 mice in the JBRC was 2 - 20%. The range was 0 - 8% for hepatocellular carcinomas and 2-20% for combined adenomas and carcinomas.

Based on this information and the reported studies, the observed incidences of hepatocellular adenoma, hepatocellular carcinoma, and combined hepatocellular adenomas plus carcinomas seen in the female mice treated at 5 ppm in the CTC bioassay of Nagano *et al.* (2007) were <u>within the historical range for this laboratory</u> and for this strain of mice.

<u>Point 4: Combined Adenomas and Carcinomas Analysis</u>

While the CTC bioassay by Nagano *et al.* (2007) reported a slight increase in liver adenomas at 5 ppm in the female BDF_1 mice, the incidence of total tumors (adenomas and carcinomas combined) was not statistically significant. Comparison of hepatocellular tumors should be made on the basis of total tumor incidences (adenomas plus carcinomas), not on adenomas and carcinomas separately. It is well known that the sequence of events for hepatocellular tumors in rats and mice involves the formation of altered cell leading to adenomas leading to carcinomas. Although these are defined entities, they are continuous, and there is often difficulty in discerning lesions that are at the border between these different diagnoses. Adenomas have the potential to evolve into carcinomas. Based on these considerations, it is best to make statistical comparisons of incidences between groups based on the incidences of animals with adenomas and/or carcinomas, rather than evaluating each one separately (Quist *et al.*, 2018). One of the co-authors, Dr. R. Maronpot, on this paper was the former director of pathology at the National Toxicology Program (NTP) and is widely considered an international authority on rodent liver tumors. This approach is confirmed by the U.S. EPA in the IRIS Assessment document for perchloroethylene where it is stated “EPA generally emphasizes combining hepatocellular adenomas and carcinomas in developing cancer risk values, for three reasons: (1) hepatocellular adenomas develop from the same cell lines as carcinomas and can progress to carcinomas; (2) adenomas are often distinguished from carcinomas only on the basis of size; and (3) histopathologic decision criteria may vary between laboratories or over time” (EPA, 2012).

Thus, given the development and progression of liver adenomas and carcinomas in rodents, the combined tumor incidence is a more accurate measurement of the actual tumor incidence.

Conclusion

Thus, based on statistical considerations, evaluation of combined adenomas plus carcinomas, and taking into account the historical controls, the incidences of hepatocellular adenomas, carcinomas, and combined hepatocellular tumors in the 5 ppm female mice group should not be considered treatment related.

References

EPA (2010). Toxicological Review of Carbon Tetrachloride (CAS No. 56-23-5) In Support of Summary Information on the Integrated Risk Information System (IRIS), EPA/635/R-08/005F. https://iris.epa.gov/static/pdfs/0020tr.pdf.

EPA (2012). Toxicological Review of Tetrachloroethylene (Perchloroethylene) (CAS No. 127-18-4) In Support of Summary Information on the Integrated Risk Information System (IRIS), page C-1, EPA/635/R-08/011F. https://iris.epa.gov/static/pdfs/0106tr.pdf.

FDA (2001). Guidance for Industry. Statistical Aspects of the Design, Analysis, and Interpretation of Chronic Rodent Carcinogenicity Studies of Pharmaceuticals, Draft Guidance. https://www.fda.gov/media/72296/download.

Fukushima, S. (2022), personal communication

Haseman, J. K. (1983). A reexamination of false-positive rates for carcinogenesis studies. Fundam. Appl. Toxicol. 3: 334-339.

Katagiri, T., Nagano, K., Aiso, S., Senoh, H., Sakura, Y., Takeuchi, T., and Okudaira, M. (1998). A pathological study on spontaneous hepatic neoplasms in BDF1 mice. J. Toxicol. Pathol. 11: 21-25.

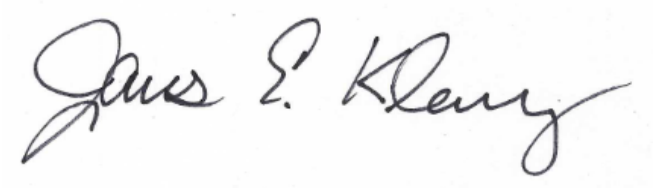
Nagano, K., Sasaki, T., Umeda, Y., Nishizawa, T., Ikawa, N., Ohbayashi, H., Arito, H., Yamamoto, S., and Fukushima, S. (2007). Inhalation carcinogenicity and chronic toxicity of carbon tetrachloride in rats and mice. Inhal. Toxicol. 19: 1089-1103.

Nagano, K., Umeda, Y., Saito, M., Nishizawa, T., Ikawa, N., Arito, H., Yamamoto, S., and Fukushima, S. (2007b). Thirteen-week inhalation toxicity of carbon tetrachloride in rats and mice. J. Occup. Health 49: 249-259.

OECD (2012). OECD Guidance Document 116 on the conduct and design of chronic toxicity and carcinogenicity studies, supporting test guidelines 451, 452, and 453, 2nd Edition. https://www.oecd-ilibrary.org/docserver/9789264221475-en.pdf?expires=1663207771&id=id&accname=guest&checksum=CF8F7C009CE8F2CCC366CB04F82B72A3.

Quist, E., Boorman, G., Cullen, J., Maronpot, R., Remick, A., Swenberg, J., Freshwater, J., and Hardisty, J. (2019). Reevaluation of hepatocellular neoplasms in CD-1 mice from a 2-year oral carcinogenicity study with permethrin. Toxicol. Pathol. 47: 11-17.

Yamate, J., Tajima, M., Kudow, S., and Sannai, S. (1990). Background pathology in BDF1 mice allowed to live out their life-span. Laboratory Animals 24: 332-340.



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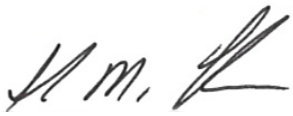

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