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solvents
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July 6, 2020

Environmental Protection Agency
Docket Center
1200 Pennsylvania Avenue, NW
Washington, DC 20460

Re: Docket No. EPA-HQ-OPPT-2019-0502

To whom it may concern:

The Halogenated Solvents Industry Alliance, Inc. (HSIA) represents producers and users of perchloroethylene (PCE). We offer these comments on EPA's draft Risk Evaluation for PCE, 85 Fed. Reg. 26464 (May 4, 2020), developed under § 6(b) of the Toxic Substances Control Act (TSCA), as amended in June 2016 by the Frank R. Lautenberg Chemical Safety for the 21st Century Act ("Lautenberg Act").

I. Non-Compliance with TSCA § 26(h) and (i)

As EPA recognizes, TSCA § 26(h) and (i) require EPA to use scientific information, technical procedures, measures, methods, protocols, methodologies, and models consistent with the best available science and to base its decisions on the weight of the scientific evidence. TSCA § 6(b)(4)(F), as revised by the Lautenberg Act, requires that EPA's risk evaluations must, among other things:

- "integrate and assess available information on hazards and exposures for the conditions of use of the chemical substance, including information that is relevant to specific risks of injury to health or the environment and information on potentially exposed or susceptible subpopulations identified as relevant by the Administrator;"

- "take into account, where relevant, the likely duration, intensity, frequency, and number of exposures under the conditions of use of the chemical substance;" and

- "describe the weight of the scientific evidence for the identified hazard and exposure."

New TSCA § 26(h) requires that, for each risk evaluation (as "a decision based on science") that "the Administrator shall use scientific information, technical procedures, measures, methods, protocols, methodologies, or models, employed in a manner consistent with the best available science, and shall consider as applicable—

(1) the extent to which the scientific information, technical procedures, measures, methods, protocols, methodologies, or models employed to generate the information are reasonable for and consistent with the intended use of the information;

(2) the extent to which the information is relevant for the Administrator's use in making a decision about a chemical substance or mixture;

(3) the degree of clarity and completeness with which the data, assumptions, methods, quality assurance, and analyses employed to generate the information are documented;

(4) the extent to which the variability and uncertainty in the information, or in the procedures, measures, methods, protocols, methodologies, or models, are evaluated and characterized; and

(5) the extent of independent verification or peer review of the information or of the procedures, measures, methods, protocols, methodologies, or models."

TSCA § 26(i), as added by the Lautenberg Act, provides simply that "The Administrator shall make decisions under sections 4, 5, and 6 based on the weight of the scientific evidence." Together, these new provisions (which apply to both cancer and non-cancer assessments) indicate that a risk evaluation that supports a TSCA § 6 rule must be more robust than a screening level assessment. The draft Risk Evaluation, while commendable for its use of systematic review, requires substantial revision to meet these statutory requirements.

With regard specifically to cancer risk assessment, the draft Risk Evaluation continues to rely on the same methodology that EPA has followed without meaningful change for 40 years despite scientific advances, as evidenced *inter alia* by its references to the 2005 Guidelines for Carcinogen Risk Assessment[1] and the 2012 IRIS review of PCE.[2] The following, drawn from a landmark report by the National Academy of Sciences,[3] are among the basic default concepts that underlie EPA's methodology:

- Laboratory animals are a surrogate for humans in assessing cancer risks; positive cancer-bioassay results in laboratory animals are taken as evidence of a chemical's cancer-causing potential in humans.
- Humans are as sensitive as the most sensitive animal species, strain, or sex evaluated in bioassay with appropriate study-design characteristics.

[1] EPA Guidelines for Carcinogen Risk Assessment and Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens, 70 Fed. Reg. 17765 (April 7, 2005) (hereafter the "Cancer Guidelines" or the "Guidelines").

[2] EPA Integrated Risk Information System (IRIS) Review of Toxicological Information on Tetrachloroethylene (Perchloroethylene) (2012) (hereafter the "PCE IRIS Assessment").

[3] National Academy of Sciences, *Science and Judgment in Risk Assessment* (NRC/NAS, 1994).

- Agents that are positive in long-term animal experiments and also show evidence of promoting or carcinogenic activity should be considered as complete carcinogens.
- Benign tumors are surrogates for malignant tumors, so benign and malignant tumors are added in evaluating wither a chemical is carcinogenic and in assessing its potency.
- Chemicals act like radiation at low exposures (doses) in inducing cancer, *i.e.*, intake of even one molecule of a chemical has an associated probability for cancer induction that can be calculated, so the appropriate model for relating exposure-response relationships is the linearized multistage model.
- Important biological parameters, including the rate of metabolism of chemicals, in humans and laboratory animals are related to body surface area. When extrapolating metabolic data from laboratory animals to humans, one may use the relationship of surface area in the test species to that in humans in modifying the laboratory animal data.
- A given unit of intake of a chemical has the same effect, regardless of the time of its intake; chemical intake is integrated over time, irrespective of intake rate and duration.
- Individual chemicals act independently of other chemicals in inducing cancer when multiple chemicals are taken into the body; when assessing the risks associated with exposures to mixtures of chemicals, one treats the risks additively.

EPA's current quantitative risk assessment methodology (QRA) for carcinogens, first used by the Food & Drug Administration (FDA) in the early 1970s, was derived from the precept that mutational responses, specifically X-ray-induced "gene" mutations, are cumulative (*i.e*, that the total dose—and not dose rate—is important), irreversible, and linear with respect to dose. In a comprehensive series of papers over the past two decades, Dr. Edward Calabrese has made the case that the scientific foundations of this linear non-threshold single-hit model were seriously flawed with regard to the effects of radiation and should not have been adopted for cancer risk assessment.[4] EPA's first task in demonstrating that this approach constitutes "best available science" must be a thorough consideration of these criticisms. In this regard, we provide in Appendix 1 a recent collection by Dr. Calabrese and co-authors of scientific papers that document the lack of biological plausibility of the linear no-threshold hypothesis of cancer risk assessment.[5]

As developed by FDA and EPA, the QRA methodology incorporated generic policy choice default assumptions and policy-based choice of analytic procedures adopted in the then state-of-the-science of carcinogenesis.[6] The impact of these generic policy chosen default options can be seen in a chart prepared in 1984 by Elizabeth Anderson, then the Director of EPA's Office

[4] Calabrese, EJ, The road to linearity: why linearity at low doses became the basis for carcinogen risk assessment, *Arch Toxicol* 83(3): 203–225 (2009); Calabrese, EJ, Origin of the linearity no threshold (LNT) dose–response concept, *Arch Toxicol* 87(9): 1621–1633 (2013). Calabrese, EJ, An abuse of risk assessment: how regulatory agencies improperly adopted LNT for cancer risk assessment. *Arch Toxicol.* 89(4):649-50 (2015); Calabrese, EJ, Key studies used to support cancer risk assessment questioned, *Environ Mol Mut* 52(8): 595–606 (2011).

[5] Chemico-Biological Interactions 301 (2019).

[6] Much of this discussion is drawn from Barnard, Scientific Method and Risk Assessment, *Reg. Tox. Pharmacol*. 19, 211-218 (1994).

of Health and Environmental Assessment, illustrating the risk-enhancing impact of default options.[7]

The Anderson chart lists six default options that dated from the 1970s (and are still in the current guidelines) and compared them to alternatives that could result in a *reduction* in risk estimates by a factor of 16 to 10,800:

Factor	Range of possible reduction in estimated cancer risk
A. Weight vs surface area	2-12
B. Maximum or average likelihood vs upper 95% confidence	2-3
C. Malignant tumors vs malignant plus benign tumors	1-2
D. Average animal sensitivity vs most sensitive animal	2-5
E. Pharmacodynamics vs effective dose	1-6
F. Risks at shorter than equilibrium buildup time	2-5
Total	16-10,800

It should be noted that in characterizing the upper confidence limit value generated by the current methodology, EPA did not refer to the impact on the risk estimate of the policy chosen dose-response model, the linearized multistage model (LMS). Alternative models would give risk values several orders of magnitude lower than the LMS model. The best characterization of the plausible upper confidence level estimate generated by the LMS appears in the predecessor to the 2005 Guidelines:

> "Such an estimate, however, does not give a realistic prediction of risk. The true value may be as low as zero. The range of risks, described by the upper limit given by the chosen model and the lower limit which may be as low as zero, should be explicitly stated."[8]

The current risk assessment procedures for carcinogens, although described by EPA as weight-of-the-evidence, involve in fact a mixture of a description of the data which is then used to select those parts of the data for statistical analysis with the analysis limited or constrained by the policy choice of default assumptions and analytic procedures. The data are summarized in the

[7] Anderson, E., Use of Risk Assessment in the Evaluation of Public Health Impacts of Toxic Chemicals, Lecture series on *"Risk Analysis in Environmental Health with Emphasis on Carcinogenesis,"* Harvard School of Public Health, September 18-20, 1984.
[8] 51 Fed. Reg. 33992 (Sept. 24, 1986).

risk assessment document; however, the criteria for interpretation and analysis are policy choices resulting in the regulatory use of an upper confidence limit value calculated using only a selected part of the data. This is not in accordance with TSCA § 26(h) and (i).

EPA's proposed rule to strengthen transparency in regulatory science would require cancer risk assessments to evaluate the appropriateness of assuming a linear non-threshold dose-response model on a case-by-case basis.[9] This is a long-needed corrective. As EPA points out in the current Cancer Guidelines:

> "When risk assessments are performed using only one set of procedures, it may be difficult for risk managers to determine how much health protectiveness is built into a particular hazard determination or risk characterization. When there are alternative procedures having significant biological support, the Agency encourages assessments to be performed using these alternative procedures, if feasible, in order to shed light on the uncertainties in the assessment, recognizing that the Agency may decide to give greater weight to one set of procedures than another in a specific assessment or management decision."

As noted above, overreliance on the linear non-threshold dose-response model by EPA as the default approach to assessing cancer risk without also considering alternative non-linear models obscures a cascade of underlying conservative assumptions in the linear dose-response model. There have been considerable advances in scientific understanding of the MOAs and mechanisms for a particular carcinogenic response, with some MOAs supporting a non-linear (threshold) approach to dose response. Thus, determining the appropriateness of a model for extrapolating the dose-response of a carcinogenic effect of a chemical also entails an evaluation of the hypothesized carcinogenic MOAs. A systematic approach, such as the procedure developed by Becker *et al.* (2017)[10] which enables side-by side comparison of numerical weight of evidence confidence scores for different hypothesized MOAs, would provide the kind of scientific rigor in the selection of dose-response models that the amended TSCA requires in assessing potential cancer risk of PCE.

In sum, the Guidelines recognize that there may be scientific advances not consistent with the policy-based assumptions and the Guidelines accordingly authorize departure in certain cases from the policy default options. In practice the strength of the policy choices has been so strong that departure has rarely occurred. For the reasons described below, a departure is necessary if the PCE Risk Evaluation is to meet the requirements of TSCA as amended by the Lautenberg Act.

[9] 83 Fed. Reg. 18768 (April 30, 2018).

[10] Becker, RA, Dellarco, V, Seed, J, Kronenberg, JM, Meek, B, Foreman, J, Palermo, C, Kirman, C, Linkov, I, Schoeny, R, Dourson, M, Pottenger, LH, and Manibusan, MK, Quantitative weight of evidence to assess confidence in potential modes of action, *Regul. Toxicol. Pharmacol.* 86: 205-220 (2017).

II. Limitations of PCE Cancer Risk Assessment

A. Human Evidence

EPA reviewed for the draft Risk Evaluation any new cancer epidemiology study published since the 2012 IRIS Assessment; this review included an evaluation for study quality using predetermined Data Quality Criteria. However, for any of the studies reviewed previously in the 2012 IRIS Assessment EPA only "evaluated the confidence of the key and supporting data sources, which included evaluation for study quality." EPA did not document why only some of the studies in the 2012 IRIS Assessment were included in the Data Quality Evaluation or what criteria were used to determine which studies would be included and excluded.

Moreover, EPA's continued reliance on carcinogenicity classifications under the EPA Cancer Guidelines and by the International Agency for Research on Cancer (IARC) is inappropriate. Neither of those systems is based on the "weight of the scientific evidence," as required by TSCA § 26(i) following the Lautenberg Act.[11]

Overall, the methodology used to evaluate the cancer epidemiology studies in the draft Risk Evaluation is not scientifically robust and does not constitute a systematic review. The conclusions of the cancer epidemiology studies on PCE would be strengthened if robust, transparent systematic reviews of all relevant studies were conducted for each tumor type.

EPA's objectivity regarding the systematic review of the epidemiology studies is questionable, using the treatment of the data quality of the Vlaanderen *et al.* (2013) study as an example.[12] The goal of using data quality criteria in a systematic review is to ensure that the overall quality of each study is evaluated objectively and in a consistent manner. Vlaanderen *et*

[11] "The International Agency for Research on Cancer (IARC) claims its Monograph working groups evaluate the 'weight of the evidence' when making their classifications on carcinogenicity. 'Weight of the evidence' is defined as 'the measure of credible proof on one side of a dispute as compared with the credible proof on the other.' When scientists take a 'weight of the evidence' approach they give the greatest weight to studies of the highest quality and credibility. IARC claims to use the 'weight of evidence,' but it does not.

- IARC has developed a reputation for cherry picking studies when evaluating a potential cancer hazard. According to IARC Senior Toxicologist Kathryn Z. Guyton, 'As few as two are needed to establish carcinogenicity.'
- Moreover, IARC openly refuses to consider many of the studies relied upon by leading regulatory bodies because they are considered business confidential and thus are not publicly available.
- Finally, IARC frequently ignores the professional conclusions of well-regarded scientists, reinterpreting some studies and coming to their own, sometimes contradictory conclusions.

Simply stated, relying on a handful of isolated findings is not how scientists consider the 'weight of the evidence.'" https://campaignforaccuracyinpublichealthresearch.com/iarc/weight-of-the-evidence/

[12] Vlaanderen, J, Straif, K, Pukkala, E, Kauppinen, T, Kyyrönen, P, Martinsen, JI, Kjaerheim, K, Tryggvadottir, L, Hansen, J, Sparén, P, Weiderpass, E, Occupational exposure to trichloroethylene and perchloroethylene and the risk of lymphoma, liver, and kidney cancer in four Nordic countries, *Occup. Environ. Med.* 70: 393-401 (2013).

al. (2013) was initially rated as a "High" quality study based on the data quality criteria but was then re-rated as a "Medium" quality study. EPA's explanation, which is identical to the explanation in the draft Risk Evaluation for trichloroethylene (TCE),[13] is that:

> "Although this was a large, well-conducted study based on complete ascertainment of cancer cases using national cancer registries and a country-specific JEM, the sensitivity of the study to detect any associations that may exist was limited, but improved by restricting the analysis to the high exposure group where prevalence was likely greater compared to the entire study population, due to exposure misclassification inherent in the generic JEM and resulting bias toward the null."

As pointed out in the Gradient report (Appendix 2), the job exposure matrix (JEM) is indeed subject to misclassification. This should have been accounted for by the initial rating of Metric 4 (Measurement of Exposure) as "Low" quality for the study. It seems unjustified to use the same issue twice in the rating. Moreover, it seems unreasonable to re-rate the entire study for specific issues that should have been accounted for by simply re-rating individual aspects or metrics that contribute to the overall rating of the study. Mathematically, the overall rating change from "High" to "Medium" is equivalent to a rating change specifically for Measurement of Exposure (Metric 4) from "Low" to worse than "Unacceptable," which would be unadjusted given the quality of exposure measurement in the study. It also does not appear that the strict assessment of the potential for exposure misclassification for Vlaanderen *et al.* (2013) was consistently conducted for all the studies under review.

Similarly, Mandel *et al*. (1995) and Travier *et al*. (2002) were re-rated from "High" to "Medium" study quality because a "medium rating [was] assigned due to use of occupation in dry cleaning industry as a surrogate of Perc exposure."[14] Again, this issue with exposure measurement should have been already accounted for in the initial rating of Metric 4 (Measurement of Exposure).

While an extensive quality evaluation was performed for a number of studies, it was not done for every relevant study, and the reasons for the exclusion of studies are not apparent. Individual study quality ratings are discussed in the draft Risk Evaluation and on occasion study uncertainties, but EPA falls short on the data integration step. Specific uncertainties discussed are not consistent across studies (*i.e.*, specific uncertainty will be emphasized for one study but not another), and the impact of these uncertainties on the interpretation of results is not discussed. The draft Risk Evaluation also does not consider that a study with an overall high rating may still have major issues with study interpretation as a result of one or a few study metrics, most notably to exposure. EPA has available several published tools and protocols to integrate scientific

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[13] EPA, Risk Evaluation for Trichloroethylene CASRN: 79-01-6. Office of Chemical Safety and Pollution and Prevention, EPA Document #740R18008 (2020).

[14] Mandel, JS, McLauglin, JK, Schlehofer, B, Mellemgaard, A, Helmut, U, Lindblad, P, McCredie, M, Adami, HO, International renal cell cancer study. IV. Occupation*., Int. J. Cancer* 61: 601-605 (1995); Travier, N, Gridley, G, De Roos, AJ, Plato, N, Moradi, T, Boffetta, P, Cancer incidence of dry cleaning, laundry and ironing workers in Sweden, *Scand. J. Work Environ. Health* 38: 341-348 (2002).

evidence beyond simple data quality scores.[15] The draft PCE Risk Evaluation does not incorporate these tools in a way that allows all evidence for each endpoint to be examined, compared, and contrasted.

1. Bladder Cancer

The draft Risk Evaluation does not discuss how EPA evaluated and integrated the evidence for bladder cancer before and after the 2012 IRIS Assessment or how study quality was considered and whether the evidence was examined in a systematic manner. Neither does EPA elaborate on what it means by there being "little support for an association between bladder cancer and PCE exposure." Does EPA conclude that the evidence supports a modest elevated risk or that the evidence no longer supports a risk?

The 2012 IRIS Assessment reviewed 32 epidemiology studies and one meta-analysis of PCE and bladder cancer. EPA concluded that "The pattern of results from this collection of [32] studies is consistent with an elevated risk for tetrachloroethylene of a relatively modest magnitude. The effect estimates from four of the five studies with the relatively high quality exposure-assessment methodologies provide evidence of an association, with relative risks of 1.44 to 4.03 (Calvert et al., 2011; Lynge et al., 2006; Blair et al., 2003; Pesch et al., 2000b; Aschengrau et al., 1993)." Yet, when EPA conducted a more rigorous data quality evaluation for the draft Risk Evaluation the exposure metric ratings for these studies were downgraded, in some cases considerably. Table 1 of the Gradient report (Appendix 2) presents a summary of the EPA data quality evaluation of the epidemiology studies in the draft Risk Evaluation from the 2012 IRIS Assessment. An advantage of summary tables, such as the ones in the Gradient report showing the quality of any particular dataset, is that it makes it visually possible to evaluate the distribution of a quality metric across studies. EPA should consider such a table in its Risk Evaluations, or at least discuss how these metrics are distributed across studies and how they impact the interpretation of results. Major weaknesses for the five studies mentioned above as well as the other studies from the 2012 IRIS Assessment are the Metrics for "Measurement for Exposure" and/or "Exposure Levels." In fact, out of the 12 studies from the 2012 IRIS Assessment only two studies achieved a rating of "Medium" for Metric 4 (Measurement of Exposure); the rest were rated "Low," except for Sung *et al.* (2007),[16] which was rated "Unacceptable" and even "Blank" for Metric 5 (Exposure Levels). EPA also placed more weight on some studies because they had a relatively large number of observed events (*i.e.*, $\geq$50 cases); however, the Data Quality Evaluations of these studies for the draft Risk Evaluation showed that all these studies had serious limitations with respect to exposure assessment and potential confounding control. Of the five new studies identified by EPA for the draft Risk Evaluation, exposure assessments continue to be a major limitation.

[15] EPA, Application of Systematic Review in TSCA Risk Evaluations (Final), Office of Chemical Safety and Pollution Prevention, Office of Pollution Prevention and Toxics., EPA Document #740-P1- 8001 (2018).

[16] Sung, TI, Chen, PC, Jyuhn-Hsiarn Lee, L, Lin, YP, Hsieg, GY, Wang, JD, Increased standardized incidence ratio of breast cancer in female electronic workers, *BMC Public Health* 7: 102 (2007).

While EPA evaluated the quality of most of the identified studies, it did not fully consider how these study quality issues (*i.e.*, exposure measurement error and confounding) may have impacted the interpretation of the results. Without the Data Integration step, EPA cannot demonstrate that there is a risk of bladder cancer from PCE exposure.

2. Kidney Cancer

The draft Risk Evaluation concluded there was "no association or weak positive association between the occurrence of kidney cancer and exposure to PCE, but [this conclusion] should be interpreted with caution due to the small number of informative studies." As with bladder cancer, there are issues related to study selection, data quality evaluation and consideration, and heterogeneity across individual studies that limit the reliability of the conclusions drawn in the draft Risk Evaluation.

The 2012 IRIS Assessment identified and evaluated 27 "core" epidemiology studies reporting data on kidney cancer and PCE exposure. Six of these studies were given more weight in EPA's analysis because these studies reported Relative Risks (RRs) based on a large number of observed events.[17] As presented in Table 2 of the Gradient report (Appendix 2), the Data Quality Evaluation for the draft Risk Evaluation showed that exposure assessment (Metrics 4 and 5) is a major limitation of most of the studies from the 2012 IRIS Assessment and, indeed, the six studies that carried more weight had similar exposure assessment and confounding limitations as the studies from which effect estimates were based on few observed effects. Thus, any reported small increases in kidney cancer risk associated with PCE exposure from the studies in the 2012 IRIS Assessment should not be interpreted as even suggestive of evidence for a causal association.

For the draft Risk Evaluation, EPA conducted a meta-analysis of five selected epidemiologic studies on kidney cancer risk. EPA considered these studies to be "reliable and informative" but there is no information on how studies were selected. Neither does EPA provide any information on whether any sensitivity analyses were performed. In addition to the issues with data quality of the five studies included in the meta-analysis, the study designs among them are different: three occupational case-control studies, one cohort study, and one study measuring residential exposure through contaminated drinking water. The risk metrics reported in these studies included Odds Ratios (ORs), Hazard Ratios (HRs), Standardized Mortality Ratios (SMRs), and Risk Ratios (RRs), which make the studies less comparable among each other. In addition, the studies likely varied in terms of study population, exposure measurements and contrasts, and confounder adjustments. Two of the studies in the kidney cancer meta-analysis were reviewed in the 2012 IRIS Assessment. As shown in Table 2 (Appendix 2), all of these

[17] Mandel, JS *et al.*, International renal cell cancer study. IV. Occupation*., Int. J. Cancer* 61: 601-605 (1995); Ji, J, Occupational risk factors for kidney cancer: A cohort study in Sweden, *World J. Urol.* 23: 271-278; Pukkala, E *et al.*, Occupation and cancer – follow-up of 15 million people in five Nordic countries, *Acta Oncol.* 48: 646-790 (2009); Travier *et al.*, Cancer incidence of dry cleaning, laundry and ironing workers in Sweden, *Scand. J. Work Environ. Health* 38: 341-348 (2002); Dosemeci, M *et al.*, Gender differences in risk of renal cell carcinoma and occupational exposures to chlorinated aliphatic hydrocarbons, Am. J. Ind. Med. 36: 54-59 (1999); Pesch, B *et al.*, Occupational risk factors for renal cell carcinoma: Agent-specific results from a case-control study in Germany, *Int. J. Epidemiol.* 29: 1014-1024 (2000).

studies have similar overall quality ratings when evaluated using EPA's Data Quality Criteria in the systematic review for the draft Risk Evaluation. More importantly, the data quality ratings of exposure characterization (Metrics 4 and 5) and potential confounding/variable control (Metrics 9-11) of the studies included in the kidney cancer meta-analysis are no better than those not included in the meta-analysis. Overall, an examination of both overall study quality and specific aspects of study quality show that most of the studies, including several rated as having "High" quality overall, may have had serious limitations (particularly with regard to exposure measurement error and confounding) that impacted the interpretation of the study results and the results of the meta-analyses that included them.

In conclusion, similar to the bladder cancer risk evaluation, while EPA evaluated the quality of most of the identified studies, it did not fully consider how study quality issues (*i.e.*, exposure measurement error and confounding) may have impacted the interpretation of the results.

B. Use of Animal Data/Mode of Action

In the 2012 IRIS Assessment, EPA concluded that PCE was "likely to be carcinogenic in humans" based predominantly on evidence of carcinogenicity in two strains of mice (liver tumors) and F344 rats (mononuclear cell leukemia) by inhalation or oral gavage. The draft Risk Evaluation continues to support this conclusion. EPA's reliance on these two tumor types that are of questionable relevance to humans seems incongruent with EPA's cancer classification of PCE. Indeed, EPA must justify its continued reliance on two-year bioassay results in light of the "best available science" mandate of the Lautenberg Act.[18]

The calculation of the Inhalation Unit Risk (IUR) for PCE in the draft Risk Evaluation has not fundamentally changed from the derivation in the IRIS assessment. PCE was tested for carcinogenicity in two mouse inhalation bioassays, and EPA used a linear non-threshold dose-response model on the male mouse liver tumors from the JISA (1993) two-year carcinogenicity study to derive the IUR.[19] EPA justifies both the choice of the tumor type and the linear extrapolation approach because, according to the EPA Cancer Guidelines, "a linear extrapolation approach is used when the mode of action information is supportive of linearity or mode of action

[18] "It is time to say goodbye to the standard two-year rodent bioassay. While a few, primarily genotoxic, compounds which are clearly associated with human cancer test positive in the bioassay, there is no science-based, sound foundation for presuming it provides either a valid broad (across different chemicals) capability for discerning potential human carcinogens or a valid starting point for making human risk assessment decisions. The two basic assumptions underlying the bioassays are; (1) rodent carcinogens are human carcinogens; and (2) results obtained at high doses are indicative of results that will occur at lower, environmentally relevant, doses. Both of these assumptions are not current." Goodman, JI, Goodbye to the Bioassay, *Toxicol. Res.* 7: 558-564 (2018).

[19] National Toxicology Program [NTP], Toxicology and Carcinogenesis Studies of Tetrachloroethylene (Perchloroethylene) (CAS No. 127-18-4) in F344 Rats and B6C3F$_1$ Mice (Inhalation Studies). (NTP TR 311). Research Triangle Park, NC: U.S. Department of Health and Human Services (1986); Japan Industrial Safety Association [JISA], Carcinogenicity Study of Tetrachloroethylene by Inhalation in Rats and Mice, Hadano, Japan (1993).

is not understood." EPA concludes in the draft Risk Evaluation that "the evidence for at least a significant contribution of a genotoxic mode of action (MOA) supports use of the low-dose linear assumption, while other mechanisms are not well-enough supported to suggest a potential threshold approach." However, EPA did not critically evaluate the genotoxicity data on PCE and its metabolites, including conducting a systematic review of the studies for data quality, or provide a scientifically sound rationale for the relevancy of the cited genotoxicity studies to the MOA for the three tumor types discussed in the draft Risk Evaluation. It is particularly egregious that EPA discusses three human genotoxicity studies published since the 2012 IRIS Assessment; does not conduct a systematic review on these studies as well as the other human genotoxicity studies from the 2012 IRIS Assessment; and, similar to the cancer epidemiology studies, fails at the data integration step. Overall, there are significant deficiencies and misstatements in EPA's discussion of the MOA of the animal carcinogenicity data, which is further discussed below.

1. Mouse Liver Tumors

There is sufficient evidence on the MOA for liver tumors in PCE-exposed mice to reasonably support a non-linear (threshold) dose response for risk characterization.

a. *Genotoxicity*

EPA's draft Risk Evaluation concludes that "PCE appears to induce liver tumors through multiple, potentially interdependent modes of action mediated largely by metabolites, including mutagenicity." However, EPA did not present sufficient evidence for a mutagenic MOA in the etiology of mouse liver tumor following PCE exposure. While EPA relied on several reviews including the 2012 IRIS Assessment, a formal International Program on Chemical Safety (IPCS) framework was not presented in support of a mutagenic MOA. There was no discussion in the draft Risk Evaluation on the dose and temporality of the key events in a mutagenic MOA. The available data are not supportive of the initial two key events in a mutagenic MOA, *i.e.*, DNA reactivity and DNA damage in the tumor target tissue. While some of the liver metabolites of PCE are mutagenic in bacteria, there is no evidence that these metabolites are generated at adequate levels in the livers of mice to reach and damage nuclear DNA. Thus, the case for a mutagenic MOA is relatively weak and, as discussed below, a compelling case can be made for an alternate MOA that does not involve mutagenesis as an early key event. A more detailed evaluation from Dr. Bhaskar Gollapudi can be found in Appendix 3.

b. *Peroxisome Proliferation Activation Receptor α (PPARα) MOA*

There is compelling evidence that PPARα is a plausible MOA for the formation of mouse liver tumors from PCE exposure via its oxidative metabolite trichloroacetic acid (TCA). A detailed evaluation of a proposed MOA through activation of PPARα can be found in Appendix 4. PCE and/or TCA have been shown to bind and activate PPARα, induce genes associated with peroxisomal fatty acid β-oxidation, and increase peroxisome proliferation, cell proliferation and oxidative stress, resulting in selective clonal expansion. EPA discredits this MOA in the draft Risk Evaluation in a manner that omits key information that supports the PPARα MOA. For example, EPA fails to mention that palmitoyl CoA oxidase (PCO) activity, a marker of peroxisome proliferation, centrilobular lipid accumulation, and peroxisome proliferation were

increased in B6C3F$_1$ mice (the same mouse strain that had increased liver tumors in the 1986 NTP bioassay) exposed to 200 or 400 ppm PCE vapor for up to 28 days, the end of the study.[20] Increased PCO activity was noted in the livers of male B6C3F$_1$ mice, but not in Sprague-Dawley rats, given oral gavage doses of 1,000 mg/kg PCE for 10 days.[21] The draft Risk Evaluation also refers to Philip *et al.* (2007)[22] [actual citation not provided] as the "original study;" can EPA clarify what it means by "original study?" In what appears to be another significant omission, EPA does not mention its own evaluation of Philip *et al.* (2007) in the 2012 IRIS Assessment on pages 4-166 and 4-167:

> "[Philip *et al.* 2007] concluded that their findings suggest peroxisome proliferation is not a sustained response in spite of continued tetrachloroethylene exposure and, therefore, are not supportive of a close mechanistic relationship of carcinogenicity and PPARα induction for tetrachloroethylene-derived TCA. This interpretation is limited by the possible lack of sensitivity of CYP4A protein expression as a marker of peroxisome proliferation, and the lack of other supporting data for the observed absence of sustained peroxisome proliferation in the context of a robust regenerative proliferative response. Additionally, the sensitivity of the SW mouse to tetrachloroethylene hepatocarcinogenicity is unknown, somewhat limiting the significance of these findings for the interpretation of hepatocellular tumor findings in other mouse strains."

EPA should also distinguish between gene expression and protein expression in the statement "increased expression of CYP4A peroxisomal marker enzymes," as well as palmitoyl coenzyme A oxidase enzyme activity versus gene and/or protein expression of the acyl CoA oxidase gene. EPA also does not include in its summary of the PPARα MOA that, although Buben and O'Flaherty (1985) did not specifically include investigate for peroxisome proliferation in their 6-week oral gavage study with male Swiss-Cox mice, they did report liver effects in the PCE-dosed mice that are consistent with a role for PPARα (*i.e.*, marked dose-related accumulation of triglycerides in the liver at ≥100 mg/kg-day).[23]

Two TCE studies involving PPAR knock-out mice and mice expressing humanized PPARα are included in the draft Risk Evaluation "to provide insight into the role of PPARα activation in PCE-induced liver effects in mice." It seems pointless to insert these studies into the PCE MOA discussion, particularly since EPA's only justification for doing so is that "PCE and trichloroethylene share the common metabolite TCA, which is believed to play a role in the hepatic toxicity and carcinogenicity of both compounds." In that case, the PPAR knock-out

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[20] Odum, J, Green, T, Foster, JR, Hext, PM, The role of trichloroacetic acid and peroxisome proliferation in the differences in carcinogenicity of perchloroethylene in the mouse and rat, *Toxicol. Appl. Pharmacol.* 92: 103-112 (1988).

[21] Goldworthy, TL, Popp, JA, Chlorinated hydrocarbon-induced peroxisomal enzyme activity in relation to species and organ carcinogenicity, *Toxicol. Appl. Pharmacol.* 88: 225-233 (1987).

[22] Philip, BK, Mumtaz, MM, Latendresse, JR, Mehendale, HM, Impact of repeated exposure on toxicity of perchloroethylene in Swiss Webster mice, *Toxicol.* 232: 1-14 (2007).

[23] Buben, JA, O'Flaherty, Delineation of the role of metabolism in the hepatotoxicity of trichloroethylene and perchloroethylene: a dose-effect study, Toxicol. Appl. Pharmacol. 78: 105-122 (1985).

studies by Laughter *et al.* (2004)[24] provide specific information on the role of PPARα activation in gene expression in the livers of TCA-treated mice without the potential complications of differences in toxicokinetics and metabolism between the two compounds.

The draft Risk Evaluation concludes that "PPARα activation is probably not a necessary event for PCE-induced liver tumors but may influence both the metabolism and the nature of the hepatic effects induced." This conclusion is contradicted by the Zhou *et al.* (2017) study, which showed a dose-related induction of peroxisome proliferation-responsive genes in the livers of PCE-dosed $B6C3F_1$/J mice (30 to 1,000 mg/kg PCE, single dose).[25] The transcriptional changes were highly correlated with PCE administered dose and with TCA levels in the liver, implicating TCA as cause of the observed liver responses. Importantly, the $B6C3F_1$ mouse is one of only two strains of mice that have been tested in cancer bioassays on PCE (the $B6C3F_1$ mouse has also been used in TCA cancer bioassays). Thus, PPARα studies using the $B6C3F_1$ mouse provide importance mechanistic information linking early molecular events in liver cells from PCE exposure and known cancer outcome.

EPA has devoted a considerable amount of text describing the findings of Cichocki *et al.* (2017), which used "a genetically diverse mouse population of 45 CC [Collaborative Cross] mouse strains to quantify the extent of interstrain variability in response to a single high [1,000 mg/kg] dose of [PCE]."[26] Endpoints, including PCE and TCA levels in the liver, liver histopathology, PPARα responsive genes, and Cyp2e1 protein in the liver were assessed at time points up to only 24 hours post-dosing and in only one mouse per strain. It would be very helpful to the reader if EPA provided some background information on the CC mouse strains.

While this study provides some interesting insight into interstrain or interindividual differences on PCE kinetics and toxicity with regards to the liver, it is difficult to figure out how the overall findings from Cichocki *et al.* (2017) are relevant to this MOA section, except that PCE-induced liver toxicity and liver tumors could possibly be mouse strain-specific. Since Cichocki *et al.* (2017) only investigated liver endpoints at a single high dose of PCE and at a short time point following dosing, it cannot be determined that the biological outcome (*i.e.*, liver pathology and liver tumors) is likely to occur from the observed liver endpoints in these CC mouse strains. EPA notes "The reason why dose-related gene expression changes were correlated with hepatic TCA levels in male B6C3F1 mice [a mouse strain that develops liver toxicity/tumors from PCE exposure] (Zhou et al. 2017), but not correlated across the strains tested by Cichocki et al. 2017) is unclear…" Yet, in what appears to be a contradiction to EPA's conclusion on the CC

[24] Laughter, AR, Dunn, CS, Swanson, CL, Howroyd, P, Cattley, RC, Corton, Role of the peroxisome proliferator-activated receptor α (PPARα) in responses to trichloroethylene and metabolites, trichloroacetate and dichloroacetate in mouse liver, Toxicol. 203: 83-98 (2004).

[25] Zhou, Y-H, Cichocki, JA, Soldatow, VY, Scholl, EH, Gallins, PJ, Jima, D, Yoo, H-S, Chiu, WA, Wright, FA, Rusyn, I, Comparative dose-response analysis of liver and kidney transcriptomic effects of trichloroethylene and tetrachloroethylene in B6C3F1 mouse, *Toxicol. Sci.* 160: 95-110 (2017).

[26] Cichocki, JA, Furuya, S, Venkatratnam, A, McDonald, TJ, Knap, AH, Wade, T, Sweet, S, Chiu, WA, Threadgill, DW, Rusyn, I, Characterization of variability in toxicokinetics and toxicodynamics of tetrachloroethylene using the collaborative cross mouse population, *Environ. Health Perspect.* 125: 057006 (2017).

mouse strain data, Luo *et al.* (2019)[27] state "In our previous study [Cichocki *et al.*, *Environ. Health Perspect.* 125: 57006 (2017)], we found that PERC induced liver expression of PPARα-responsive genes, which positively correlated with the internal dose of TCA."

In the summary section, EPA concludes "TCA appears to be an important hepatic metabolite but is probably not the only metabolite involved in hepatic effects of PCE." Given the weakly-supported attempt by EPA to use a weight of the scientific evidence approach for the mouse liver tumor MOA, this conclusion is not justified. Does EPA base this conclusion on Cichocki *et al.* (2017)? If so, EPA has failed to consider the caution issued in Cichocki *et al.* (2017) that single animal and single high-dose CC-findings at best represent only a "prerequisite step" to prioritize selection of preferred mouse strains to better inform the MOA implications of a particular phenotype such as hepatic TCA levels (*i.e.*, metabolite formation) and toxicity/tumorigenicity outcomes. EPA also ignored the alternative explanation given in the conclusion of Cichocki *et al.* (2017) "that other *genetic determinants* contribute to interindividual susceptibility to PERC-associated hepatotoxicity" [emphasis added].

2. Male Rat Kidney Tumors

a. *Metabolism*

It is inappropriate for the draft Risk Evaluation to characterize the short communication research paper by Irving and Elfarra (2013)[28] as a review of the available literature on the role of metabolism of PCE in the MOA for kidney toxicity and kidney cancer. It is particularly problematic when EPA uses the conclusions of authors, who have a vested interest in the results of their study, as a substitute for "best available science" in a draft Risk Evaluation. Irving and Elfarra (2013) is not a review paper but a short communication on a limited number of *in vitro* mutagenicity studies conducted on the cysteine S-conjugate sulfoxides of TCE and PCE. Furthermore, the paper does not provide sufficient detail on the role of PCE metabolism in the proposed MOAs for kidney toxicity and kidney cancer; nor is it up to date with the literature. The draft Risk Evaluation states "TCVG is processed into the cysteine conjugate (TCVC) in the kidney, bile duct epithelium, intestinal lumen, or bile canalicular membrane of hepatocytes; TCVC enters the circulatory system and is translocated to the kidney." However, this is an incomplete and oversimplified description, and serum levels of both S-(1,2,2-trichlorovinyl)-*L*-glutathione (TCVG) and S-(1,2,2-trichlorovinyl)-*L*-cysteine (TCVC) have been quantified in male C57Bl/6J mice following a single oral dose of 300 or 1,000 mg/kg PCE, with only TCVC measurable at 100 mg/kg PCE.[29] TCVG is cleared from plasma by the kidney either by

[27] Luo, Y-S, Hsieh, N-H, Soldatow, VY, Chiu, WA, Rusyn, I, Comparative analysis of metabolism of trichloroethylene and tetrachloroethylene among mouse strains, *Toxicol.* 409: 33-43 (2018a).

[28] Irving, RM, Elfarra, AA, Mutagenicity of the cysteine S-conjugate sulfoxides of trichloroethylene and tetrachloroethylene in the Ames test, *Toxicol.* 306: 157-161 (2013).

[29] Luo, Y-S, Cichocki, JA, McDonald, TJ, Rusyn, I, Simultaneous detection Simultaneous detection of the tetrachloroethylene metabolites S-(1,2,2-trichlorovinyl) glutathione, S-(1,2,2-trichlorovinyl)-L-cysteine, and N-acetyl-S-(1,22-trichlorovinyl)-L-cysteine in multiple mouse tissues via ultra-high performance liquid chromatography electrospray ionization tandem mass spectrometry. *J. Toxicol. Environ. Health, Part A* 80: 513-524 (2017).

peritubular handling or by glomerular filtration and uptake by proximal tubulular cells. Either pathway can involve degradation of TCVG by γ-glutamyltransferase (GGT) and dipeptidase enzymes with subsequent uptake of TCVC, or by uptake of TCVG via a membrane transport system in the case of the peritubular mechanism. A more complete picture of the GSH conjugation pathway and the interorgan involvement (liver, bile duct, small intestine, kidney) for PCE is needed for the Risk Evaluation. Also, for the MOA discussion, EPA should include information on the critical enzymes involved in the GSH conjugation pathway, such as GGT and β-lyase, which is important for understanding the results of the toxicity and mutagenicity studies on the glutathione conjugate metabolites. The information on mutagenicity studies should be removed and discussed in the following section on genotoxicity.

There is no mention in the draft Risk Evaluation of the findings from Luo *et al.* (2018) showing the comparative metabolism of TCE and PCE in three strains of mice following a single oral equimolar dose of either TCE (800 mg/kg) or PCE (1,000 mg/kg).[30] An importance aspect of this study is that both the oxidative and glutathione (GSH) conjugates of PCE and TCE were measured simultaneously using a sensitive LC-MS/MS analytical method. Total TCE metabolism was higher in mice than PCE metabolism (15.7-38.3% vs. 6.6-9.7%, respectively); yet the flux through the GSH pathway, although very low for both compounds (<0.3% of administered dose), was 20-fold higher in mice treated with PCE compared to the TCE-treated mice (0.19-0.30% vs. 0.010-0.013%, respectively). Furthermore, the model estimated fraction of the reactive species formation from the cysteine conjugated metabolites was considerably higher for PCE compared to TCE (46.7-52.6% vs. 2.1-2.4%). Overall, the reactive metabolites from a comparable amount of PCE *vs*. TCE were estimated to be about 300-fold higher (on a percentage basis) for PCE (~ 0.095% of administered dose) compared to TCE (~ 0.0003% of administered dose).

In addition, there is some indication that PCE is more acutely toxic to the kidney, based on KIM-1 expression in the proximal tubule compared to an equimolar dose of TCE (Luo *et al.*, 2018b; Yoo *et al.*, 2015).[31] TCVC has also been shown to be more nephrotoxic than S-(1,2-dichlorovinyl)-*L*-cysteine (DCVC) following a single intravenous injection into the tail vein of rats (Birner *et al.*, 1997).[32] These results are difficult to reconcile with the difference in carcinogenic response between PCE and TCE if the glutathione conjugate metabolites of these two compounds are responsible for kidney cancer.

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[30] Luo, Y-S, Hsieh, N-H, Soldatow, VY, Chiu, WA, Rusyn, I, Comparative analysis of metabolism of trichloroethylene and tetrachloroethylene among mouse strains, *Toxicol.* 409: 33-43 (2018a).

[31] Luo, Y-S, Furuya, S, Soldatow, VY, Kosyk, O, Yoo, HS, Fukushima, H, Lewis, L, Iwata, Y, Rusyn, I, Metabolism and toxicity of trichloroethylene and tetrachloroethylene in cytochrome P450 2E1 knockout and humanized transgenic mice, *Toxicol. Sci.* 164: 489-500 (2018b); Yoo, HS, Bradford, BU, Kosyk, O, Uehara, T, Shymonyak, S, Collins, LB, Bodnar, WM, Ball, LM, Gold, A, Rusyn, I, Comparative analysis of the relationship between trichloroethylene metabolism and tissue-specific toxicity among inbred mouse strains: kidney effects, *J. Toxicol. Environ. Health, Part A* 78: 32-49 (2015).

[32] Birner, G, Bernauer, U, Werner, M, Dekant, W, Biotransformation, excretion and nephrotoxicity of haloalkene-derived cysteine S-conjugates, *Arch. Toxicol.* 72: 1-8 (1997).

EPA concludes in the draft Risk Evaluation that "Tissue concentrations of metabolites of the GSH pathway (liver TCVG, serum TCVG, liver NAcTCVC, and kidney NAcTCVC) were found to be significantly correlated with increased kidney levels of K[IM]-1…supporting a link between this metabolic pathway and kidney toxicity." What EPA fails to discern from the correlation heatmap presented as Figure 5 in the Luo *et al. (*2019) publication is that there appears to be *little to no* correlation in the kidney (the target organ) between KIM-1 expression and TCVG, TCVC, or even TCA levels; even serum TCVC does not appear to correlate with KIM-1 expression.[33] It is unclear why serum and liver TCVG levels show some correlation with kidney toxicity, but the inconsistency with kidney TCVG and TCVC levels suggest that there is no link or that there are other determinants that contribute to interstrain susceptibility to PCE-induced kidney toxicity. Interestingly, kidney PCE levels appear to show a positive correlation with KIM-1 expression.

b. *Mutagenicity*

There is insufficient evidence for a mutagenic MOA for kidney tumors in male rats exposed to PCE. As with the mouse liver tumors, EPA did not use a formal IPCS framework to support its position that "available data provide evidence for mutagenicity as a likely mode of action for renal carcinogenicity induced by PCE." The available data are not supportive of the initial two key events in a mutagenic MOA, *i.e.*, DNA reactivity and DNA damage in the tumor target tissues. While some of the kidney metabolites of PCE are mutagenic in bacteria, it is uncertain whether these metabolites are generated at adequate levels in the kidney to reach and damage nuclear DNA. Thus, the case for a mutagenic MOA is relatively weak.

c. *Human Studies*

The summary information in the draft Risk Evaluation on the epidemiological literature on kidney changes seems to have originated from the most recent IARC Monograph on PCE,[34] rather than an independent review by EPA. In any event, the review is superficial, selective, and uncritical and the draft Risk Evaluation includes no systematic review of the studies. It also makes no mention of the study by Solet and Robins (1991),[35] which is among the largest and most methodologically rigorous investigations on this topic. Solet and Robins (1991) examined kidney parameters for 192 Detroit-area dry cleaners exposed to an average of 14 ppm PCE for 12 years. Note that this study was part of a larger investigation of Detroit-area dry cleaners that includes the study by Escheverria *et al.* (1995),[36] which was used by EPA to derive the Reference

[33] Luo, Y-S, Cichocki, JA, Hsieh, N-H, Lewis, L, Wright, FA, Threadgill, DW, Chiu, WA, Rusyn, I, Using collaborative cross mouse population to fill data gaps in risk assessment: a case study of population-based analysis of toxicokinetics and kidney toxicodynamics of tetrachloroethylene, *Environ. Health Perspect.* 127: 067011 (2019).

[34] IARC, Trichloroethylene, Tetrachloroethylene, and Some Other Chlorinated Agents, IARC Monographs on the Evaluation of Carcinogenic Risks to Humans Volume 106, World Health Organization, Lyon, France (2014).

[35] Solet, D, Robins, TG, Renal function in dry cleaning workers exposed to perchloroethylene, *Am. J. Ind. Med.* 20: 601-614 (1991).

[36] Echeverria, D, White, RF, Sampaio, C, A behavioral evaluation of PCE exposure in patients and dry cleaners: a possible relationship between clinical and preclinical effects, *J. Occup. Environ. Med.* 37: 667-680 (1995).

Concentration (RfC) in the 2012 IRIS assessment. Solet and Robins (1991) described participation, which was good (87%) among businesses that chose to participate (although 77% of businesses declined). Solet and Robins (1991) also used multivariate regression models to compare several markers of exposure to several urinary parameters, while appropriately adjusting for potentially important confounding factors. Regression diagnostics were performed to account for influential outlying observations. This study was unlikely to be influenced by baseline differences between groups, because dry cleaners with less exposure were compared to those with more. It is notable that no renal parameters were significantly associated with exposure, and that most models explained ≤ 10% of the variation in urinary markers. There was a marginally significant (p=0.08) adjusted association between breath PCE level and log N-acetyl-D-glucosaminidase, but this was in the opposite direction to expectation (*i.e.*, this urinary marker decreased with increasing exposure). This study did not find any significant associations between kidney parameters and exposure metrics.

Significant changes in retinol binding protein (RBP) have been reported in two studies of workers exposed to PCE (Mutti *et al.*, 1992; Verplanke *et al.*, 1999).[37] However, these studies were not evaluated critically by EPA, limitations were not explored, and author conclusions were accepted as fact. Both studies had potential for selection bias that is not discussed by EPA. Mutti *et al.* (1992) provide no information on selection (sample frame, percent participation, etc.), and their referents appear to represent a convenience sample of blood donors. Verplanke *et al.* (1999) compared dry cleaners to unexposed workers from either laundry or dry-cleaning establishments, which represents a more reasonable reference group, but all were "volunteers" with no information provided on participation rates, refusal etc. Furthermore, the exposed and referent populations in Verplanke *et al.* (1999) had substantive differences on demographic and lifestyle factors that suggest baseline differences between the groups. For example, dry cleaners smoked (64%) and drank alcohol (14 g/d) more than referents (42% and 10 g/d, respectively). Dry cleaners were also significantly taller and had a higher prevalence of men (61%) than did unexposed workers (42%). Most of these differences were not statistically significant, driven largely by the small number of workers (19) in the reference sample. However, such substantive but non-significant differences can still represent important sources of bias that influence results. EPA ignores the fact that neither study adjusted for potentially confounding factors such as alcohol intake, smoking, diet, or socio-economic status (SES) (which is an important limitation of these studies). This is a notable omission because EPA frequently cites adjustment for confounding as a strength of the studies in which it places more confidence. As both Mutti *et al.* (1992) and Verplanke *et al.* (1999) reported a lack of correlation of kidney damage with objective measures of PCE exposure (*i.e.*, intensity or duration of exposure), the differences between groups may be due to chance or group differences other than exposure (e.g., SES) may explain the results.

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[37] Mutti, A, Alinovi, R, Bergamaschi, E, Biagini, C, Cavazzini, S, Franchini, I, Lauwerys, RR, Bernard, AM, Roels, H, Gelpi, E, Rosello, J, Ramis, I, Price, RG, Taylor, SA, DeBroe, M, Nuyts, GD, Stolte, H, Fels, LM, Herbort, C, Nephropathies and exposure to perchloroethylene in dry-cleaners, *The Lancet*, 340: 1890193 (1992); Verplanke, AJW, Leummens, MHL, Herber, RFM, Occupational exposure to tetrachloroethene and its effects on kidneys, *J. Occup. Environ. Med.* 41: 11-16 (1999).

Neither Franchini *et al.* (1983) nor Vyskocil *et al.* (1990) found any significant correlations between kidney parameters and objective markers of exposure.[38] Trevisan *et al.* (2000) reported some significant correlation coefficients of 0.3-0.6 between urinary parameters and measures of PCE exposure, but these correlations were of similar magnitude for both exposed dry cleaners and ironers with very little exposure.[39] The results reported by Trevisan *et al.* were also confounded somewhat by co-exposure to TCE, which was present in low levels in some shops. However, the limitations cited above appear to be endemic to this literature, most likely because the authors have clinical experience but less familiarity with epidemiological methods. For example, Franchini *et al.* (1983), Vyskocil *et al.* (1990), and Trevisan *et al.* (2000) did not provide information on selection procedures. Furthermore, Vyskocil *et al.* (1990) compared dry cleaners to clerical workers, which is a reference group that is likely to have different baseline characteristics. Indeed, dry cleaners were older (42 years) and contained more regular drinkers (23%) compared to clerical workers (36 yrs and 12.5%, respectively). Trevisan *et al.* (2000) also reported that dry cleaners were significantly older (41 yrs) and drank significantly more alcohol (8 g/d) compared to ironers (29 yrs and 3 g/d, respectively), suggesting substantive differences between these two groups. Of the three studies, two performed no statistical adjustment for confounders. Trevisan *et al.* (2000) ostensibly controlled for age and alcohol, because of statistically significant differences between groups, but did not control for other potentially important factors such as diet, smoking, or SES. Furthermore, it is not clear that Trevisan *et al.* (2000) actually adjusted for age and alcohol use, because they ascribe liver changes among the exposed to age, suggesting that age was not adjusted in this comparison.

In summary, all studies represented cross-sectional (*i.e.*, snapshot) evaluations, so one cannot establish firm temporal relationships between exposure and outcome. Most studies appeared to use convenience samples without any description of selection processes, so that selection bias is a potential problem. This is especially a concern where dry cleaners were compared to clerical staff, students, or other workers with different sociodemographic characteristics. Differential selection is supported by the fact that many studies showed substantive differences between groups on major characteristics (*e.g.*, age and alcohol intake), suggesting that the exposed and referent groups came from different base populations. Only three studies adjusted for confounding factors in the analysis. Of these, Solet and Robins (1991) describe the most thorough and statistically rigorous approach, which includes regression diagnostics. It is interesting to note that this study did not find any significant associations between kidney parameters and exposure metrics. Results are inconsistent both within and between studies. Some studies reported statistically significant associations between dry cleaning and certain urinary markers, whereas other studies found no substantive association for the same or related parameters. Trevisan *et al.* (2000) reported a significant correlation between glutamine synthetase activity and PCE air levels, but very similar mean glutamine synthetase levels between groups (1.05 vs. 1.08), even though dry cleaners had up to two orders of magnitude higher PCE

[38] Franchini, I, Cavatorta, A, Falzoi, M, Lucertini, S, Mutti, A, Early indicators of renal damage in workers exposed to organic solvents, *Int. Arch. Occup. Environ. Health* 52: 1-9 (1983); Vyskocil, A, Emminger, S, Tejral, J, Fiola, Z, Ettlerova, E, Cermanová, A, Study on kidney function in female workers exposed to perchloroethylene, *Human Exp. Toxicol.* 9: 377-380 (1990).

[39] Trevisan, A, Maccà, I, Rui, F, Carrieri, M, Bartolucci, GB, and Manno, M, Kidney and liver biomarkers in female dry-cleaning workers exposed to perchloroethylene, *Biomarkers* 5: 399-409 (2000).

exposure than ironers. These authors also reported good correlation between urinary proteins and urinary PCE level only among ironing workers, who represent the ostensibly unexposed group. With rare exceptions, studies did not find a correlation between urinary markers and objective measures of PCE exposure. Most notably, the study with the largest numbers, most rigorous selection process, and best control for confounding factors (Solet and Robins, 1991) found no association between markers of exposure and kidney outcomes.

All studies were exploratory, performing dozens of statistical associations. Therefore, some significant associations are likely to be due to chance. This could easily explain those studies that found one or two significant positive associations. The organ changes reported in the studies are not in and of themselves indicative of early or future disease, thereby complicating interpretation.

3. Rat Mononuclear Cell Leukemia (MNCL)

The MOA section on the rat MNCL contains references to studies that have reported immune system and blood changes from PCE exposure, but EPA provides no rationale for including these studies in this section; in fact, there does not seem to be any apparent link. What is highly problematic about this section is EPA's failure to include any of the literature on rat MNCL and its significance, of which there are several reviews, the most recent being Maronpot *et al.* (2016).[40]

MNCL has a high and variable spontaneous incidence in the F344 strain of rat. The high spontaneous incidence is confined to the F344 strain of rat (with the historical exception of an inbred line of Wistar Furth rats) and it occurs in both sexes. The incidence has increased over the course of the NTP bioassay program, and it is highly variable from laboratory to laboratory and study to study. Maronpot *et al.* (2016) even point out that this rise was one of the reasons for NTP deciding to halt the use of the F344 rat in 2006. Thomas *et al.* (2007) tabulated the changes in the historical control incidence rates of F344 rat MNCL from two-year NTP studies. The incidence of MNCL in male F344 rats increased from 7.9% in 1971 to 52.5% in 1995-1998; in female F344 rats, the increase was 2.1% in 1971 to 24.2% in 1995-1998. The incidence in F344 rats is modulated by a variety of factors not clearly related to carcinogenicity. Corn oil gavage, for example, has been shown consistently to reduce the incidence of MNCL in male, but not female, controls. It is clear that the F344 rat is uniquely susceptible to developing MNCL, although the reason for this susceptibility is unknown.

F344 rat MNCL cells have variable natural killer (NK) cell activity and have characteristics of normal rat large granular lymphocytes (LGLs). In the F344 rat, MNCL is an aggressive, often fatal disease in older animals. The closest analogues in humans with LGL features similar to the F344 rat MNCL are the LGL leukemias derived either from $CD3^+$ T cells

[40] Ismael, J, and Dugard, PH, A review of perchloroethylene and rat mononuclear cell leukemia, *Regul. Toxicol. Pharmacol.* 45: 178-184 (2006); Thomas, J, Haseman, JK, Goodman, JI, Ward, JM, Loughran, YP, Jr, Spencer, PJ, A review of large granular lymphocytic leukemia in Fischer 344 rats as an initial step toward evaluating the implication of the endpoint to human cancer risk assessment, *Toxicol. Sci.* 99: 3-19, (2007); Maronpot, RR, Nyska, A, Foreman, JE, and Ramot, Y, The legacy of the F344 rat as a cancer bioassay model (a retrospective summary of three common F344 rat neoplasms), *Crit. Rev. Toxicol.* 46: 641-675 (2016).

or $CD3^-$ natural killer (NK) cells.[41] The clinical picture and pathogenesis of the non-aggressive form of the $CD3^+$ LGL leukemia show that it is clearly unrelated to the rat F344 MNCL; the aggressive form does appear to have clinical resemblance to the rat F344 MNCL but it is so rare that it is not included in the 2008 World Health Organization (WHO) Classification of Hematologic Malignancies. Regarding the $CD3^-$ LGL leukemias, one of the disorders of this disease is aggressive NK cell leukemia (ANKCL), which has clinical and pathological features very similar to F344 rat MNCL. ANKCL is also extremely rare with only 98 cases reported worldwide as of 2016 and mostly in Asia or Central/South America; it is also acutely fatal with a median survival time from diagnosis of about 58 days. An absolute requirement for the pathogenesis of ANKCL is an infection with Epstein-Barr virus, which does not occur with F344 rat MNCL. Given its unique viral etiology and extremely rare incidence rate, ANKCL cannot be considered to be the human equivalent of the commonly occurring strain-specific F344 rat MNCL.

Thomas *et al.* (2007) reviewed the possible application of the Food and Drug Administration (FDA) criteria for statistical significance for common and variable tumors such as MNCL. These criteria are $p< 0.01$ for pairwise comparisons and $p< 0.005$ for trend tests. For PCE, if these criteria are applied to the results of the two PCE two-year inhalation carcinogenicity studies using F344 rats,[42] only the trend test in the males in the JISA study achieves statistical significance (Cochran-Armitage trend and Fisher's exact tests). Maronpot *et al*. (2016) also reviewed the MNCL data from the NTP (1986) study and noted "The frequency distribution of MNCL stages 1, 2, and 3 was similar and not statistically significant among the controls and exposed rats. Comments during the NTP peer review regarding concerns about the high laboratory control rates of MNCL in this study were made suggesting conclusions regarding MNCL are questionable for both sexes."

EPA does not give due consideration to the absence of PCE effects on MNCL in other strains of rats. Thus, in terms of weight of evidence, it is important to recognize that MCL was not induced by PCE in long term studies in Sprague-Dawley rats (NTP, 1986) or Osborne-Mendel rats (NCI, 1977),[43] although the NCI study is weakened in that respect by poor survival. Overall, there were no indications in rat or mouse long-term studies that PCE can induce any other forms of lymphohematopoietic disease. In general, increases in the F344 rat MNCL do not appear to be tied to genotoxicity based on the list of NTP studies showing MNCL responses (*see* Maronpot *et al.*, 2016). Thus, the moderate MCL response limited to the highly susceptible F344 rat strain provides no indication that PCE will be leukemogenic in humans.

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[41] Steinway, SN, LeBlanc, F, Loughran Jr, TP, The pathogenesis and treatment of large granular lymphocyte leukemia, *Blood Reviews* 28: 87-94.

[42] NTP, Toxicology and carcinogenesis studies of tetrachloroethylene (perchloroethylene) (CAS No. 127-18-4) in F344 rats and B6C3F1 mice (inhalation studies). (NTP TR 311). Research Triangle Park, NC: U.S. Department of Health and Human Services (1986); Japan Bioassay Research Center [JISA], Carcinogenicity study of tetrachloroethylene by inhalation in rats and mice, Hadano, Japan (1993).

[43] National Cancer Institute [NCI], Bioassay of tetrachloroethylene for possible carcinogenicity, NCI-CGTR-13; DHEW Publication No. (NIH) 77-813, National Institutes of Health, Bethesda, MD (1977).

III. Limitations of Neurotoxicity Assessment

A. Altmann *et al.* (1990) is a Poor Choice for Derivation of the Acute Toxicity Risk Value.

The acute effects of PCE in humans and animals have been well reviewed, with the central nervous system (CNS), characterized by CNS depression, being the target of concern.[44] Humans are expected to exhibit CNS effects following acute inhalation exposures of about 100 ppm PCE and higher. The Altmann *et al.* (1990) study measured changes in visual evoked potentials (VEP) in human volunteers (22 total) exposed to 10 or 50 ppm PCE 4 hours/day for up to four consecutive days.[45] Brainstem auditory-evoked potentials (BAEP) were also measured, as well as visual contrast sensitivity (VCS) in some subjects. The VEP latency values were reported to be statistically significantly higher at 50 ppm compared to 10 ppm on each of the four exposure days. However, the BAEP peak latencies were not significantly different between the two exposure groups and the limited number of VCS tests indicated a non-statistically significant contrast sensitivity loss following exposure to 50 ppm PCE only. Blood PCE concentration was significantly correlated with the VEP peak N150 *only*, and not to all three VEP peak latencies as implied in the draft Risk Evaluation.

While the results seem to suggest that exposure to 50 ppm, but not 10 ppm, PCE affects the visual system, there are difficulties when interpreting the data. First, it is unclear why the VEP peak latencies showed an increase (perceived as a deficit) at 50 ppm, but a decrease (perceived as an improvement) at 10 ppm, when compared to pre-exposure values. The reason for this lack of dose-dependency is unknown. It is unfortunate that the study investigators did not include three exposure concentrations in their study, which would have provided a more convincing case for a biological effect of PCE on the visual system (a bi-phasic response is certainly possible, but needs a biologically sound explanation). Second, the statistical analysis is not described in detail, as pointed out in the data quality review. It is unknown whether the statistical significance indicated by the authors is reliable (*i.e.*, false positive rate) given the large number of multiple comparisons. Factorial analysis of variance was not performed and only a multitude of unadjusted group comparisons were reported. Without specific hypotheses for the various VEP tests there should be some sort of ANOVA analysis to determine an overall p-value before making individual comparisons, or else an appropriate adjustment of α level. Finally, the size of the observed effect of PCE exposure on VEP peak latencies is in the range of 1.0 to 2.5 ms, which is a very small change. Moreover, only 3 of the 6 patterns used to elicit VEPs were affected, the amplitudes of all VEP latencies were not changed, and the BAEP was similar in both exposure groups and with the pre-exposure values. In conclusion, the changes in VEP latencies reported by Altmann *et al.* (1990) from acute to short-term PCE inhalation exposures appear to be highly selective results and of questionable toxicological significance.

[44] AEGL, Tetrachloroethylene, Interim Acute Exposure Guideline levels (AEGLs), for NAS/COT Subcommittee for AEGLs (2009).

[45] Altmann, L, Böttger, A, Wiegand, H, Neurophysiological and psychophysical measurements reveal effects of acute low-level organic solvent exposure in humans, *Int. Arch. Occup. Environ. Health* 62: 493-499 (1990).

B. EPA's Interpretation of Cavelleri *et al.* (1990) is Inaccurate and Misleading.

EPA misinterprets the data from Cavelleri *et al.* (1994),[46] one of two principal studies used in the draft Risk Evaluation to derive a chronic non-cancer toxicity value. Among color vision studies, Cavalleri *et al.* (1994) provided the best information on participation, reporting complete participation from all 35 workers at dry cleaning shops in Modena, Italy. There was no mention of selection procedures for referents, but matching on age, sex, alcohol consumption, and smoking probably limited potential for biased selection. Using the Lanthony 15 Hue desaturated panel or D15 d test, Cavalleri *et al.* (1994) reported significantly higher color confusion index (CCI) for dry cleaners exposed to average PCE levels of 7.3 ppm (mean CCI 1.19) vs. matched referents (mean CCI 1.09), but not for ironers exposed to mean PCE levels of 4.8 ppm (CCI 1.06). *Exposure was significantly associated with CCI in regression models, but this was driven by exposures above 10-12 ppm (especially two values above 20 ppm), with no evidence of a linear association below 10 ppm* [emphasis added]. Such findings suggest a threshold at 10-20 ppm (rather than an exposure-response relationship), with no effect from lower exposures. Furthermore, neither duration of exposure nor cumulative exposure (ppm-year) was associated with CCI, suggesting a temporary or at least non-cumulative effect.

In the 2012 IRIS Assessment, EPA considered the mean PCE exposure for the full study sample of workers at dry cleaning facilities as the Lowest-Observed-Adverse-Effect-Level (LOAEL) from the Cavelleri *et al.* (1994) study:

> "Although no apparent CCI deficit was observed in ironers, their reported exposure range (0.52-11.28 ppm, or 3.5-76 mg/m^3) was completely contained within the range of exposures for dry cleaners (0.38-31.19 ppm, or 2.6-210 mg/m^3). Yet elevated CCI scores were observed at exposures lower than the mean exposure of the ironers (4.8 ppm, or 33 mg/m^3), indicating that the mean exposure of the ironers cannot be considered a NOAEL [No-Observed-Adverse-Effect-Level]."

EPA's rationale is severely flawed and is based on an incomplete understanding of the data in Cavelleri *et al.* (1994). First, EPA's premise for combining the two groups of workers in dry cleaning facilities is based on the assumption that there is a positive linear correlation between CCI scores and PCE exposures. However, Cavelleri *et al.* (1994) pointed out that "Only 3 environmental values of PCE exceeded 12.5 ppm, i.e. 50% of ACGIH occupational limit; *excluding these data the significance of the correlation between exposure and effect disappeared"* [emphasis added]. Interestingly, EPA did not include this information in its review of Cavelleri *et al.* (1994) in the 2012 IRIS Assessment. These "high" exposures of PCE are only associated with the workers defined as "dry-cleaners" (0.38 to 31.19 ppm) and not with the ironers (0.52 to 11.28 ppm). So, as noted in the previous paragraph, PCE exposure below 12 ppm (which includes all of the ironers) are not significantly correlated with a deficit in color vision (increased CCI scores). This lack of linear correlation is supported by the lack of statistical significance in the comparison of the mean CCI scores between the ironers and the controls. Thus, the mean exposure of 4.8

[46] Cavalleri, A, Gobba, F, Paltrinieri, M, Fantuzzi, G, Righi, E, and Aggazzotti, G, Perchloroethylene exposure can induce colour vision loss, *Neurosci. Lett.* 179: 162-166.

ppm PCE for the ironers can be considered the NOAEL for the study. This is the conclusion of the authors themselves: "the mean exposure and the range of TWA levels of PCE in *ironers* and *dry-cleaners* (Table 2) suggest a mean threshold for colour vision effect of the solvent ranging approximately between 5 and 11 ppm."

Second, EPA has ignored the task differences between the dry-cleaners and ironers in the dry-cleaning facilities of those selected for the study in Cavelleri *et al.* (1994); these task differences have a significant impact on the estimation of PCE exposures (more on this in Section V for current dry-cleaning facilities). As noted by the authors, "the exposures of *dry-cleaners* is not constant throughout the working day, but sudden increases are expected during specific tasks such as the retrieval of just washed garments or maintenance. As an example, our spot samples documented a tenfold increase (from 2 to 29 ppm nearly) during retrieval of garments. We cannot exclude that such peak exposures, not documented by TWA levels, could exert some effects on colour vision. *In ironers similar variations of exposure are unlikely*" [emphasis added]. EPA did not factor task-specific PCE peak exposures as being an important consideration of workplace exposures, but it does indeed justify the separation of the two groups of workers in determining a LOAEL/NOAEL for the study, particularly since PCE exposures could be significantly underestimated in the "dry-cleaners" when only the TWA data are considered in the analysis. Finally, it is a faulty argument to state "elevated CCI scores were observed at exposures lower than the mean exposure of the ironers (4.8 ppm, or 33 mg/m^3), indicating that the mean exposure of the ironers cannot be considered a NOAEL." Remarkably, EPA fails to note that similar elevated CCI scores are also seen in the matched (non PCE-exposed) controls and the statistical analysis used by Cavelleri *et al.* (1994) showed no significance difference between the mean and standard deviation (SD) of CCI values of ironers compared to the non-PCE exposed controls (1.061 ± 0.058 for ironers versus 1.073 ± 0.079 for controls). Thus, EPA cannot properly infer that the elevated CCI scores in the ironers are due to PCE exposure.

In conclusion, while the Cavelleri *et al.* (1994) study provides qualitative evidence of color vision deficit from PCE exposure, the data are not sufficiently robust for quantitative risk assessment purposes, although there is evidence of a NOAEL at 4.8 ppm. Instead, EPA should rely on the Echeverria *et al.* (1995) study to derive a POD for the chronic, non-cancer endpoint.

IV. Limitations of Hazard Assessments for Other Non-Cancer Endpoints

A. Reproductive and Developmental Toxicity

1. Spontaneous Abortions

The summary of the PCE spontaneous abortion studies in the draft Risk Evaluation is incomplete and biased and represents an approach that is incompatible with TSCA § 26(h) as added by the Lautenberg Act. The draft Risk Evaluation states "The epidemiological evidence for developmental effects associated with PCE exposure is suggestive based on several studies of maternal occupational exposure to PCE that suggest an increased risk of spontaneous abortion at high concentrations (Olsen et al. 1990; Kyyronen et al. 1989)." Inexcusably, EPA fails to mention that other studies reviewed in the 2012 IRIS assessment did not find an association of

spontaneous abortion with PCE exposure. Ahlborg (1990) performed a case-control study of Swedish dry-cleaning workers using two complimentary approaches, one identifying workers through businesses and the other identifying workers via occupation listed on the census.[47] The second approach was instituted because almost half of the businesses failed to participate in the first study. Response to questionnaires was slightly worse for cases in the first study (75%), but similar for other cases and referents (87%-88%). There was no suggestion of a statistically increased association with PCE exposure. The combined relative risk (RR) for the two studies were 1.0 (0.4-2.2) for low exposure and 0.9 (0.4-2.1) for high exposure, after adjustment for smoking, drinking, medical conditions, and history of adverse pregnancy. Lindbohm *et al.* (1990)[48] performed a study very similar to that of Kyyronen *et al.* (1989),[49] collecting questionnaire information for spontaneous abortion cases identified through hospital-discharge data during 1973-1983. Response rates were very similar between cases and controls (85%), but again >20% of cases did not report the pregnancy of interest. A similar percentage of cases (5%) and controls (6%) worked in "laundry and dry cleaning," but those with PCE exposure had an adjusted RR of 1.4 (0.5-4.2), which increased to 2.5 (0.6-10.5) for high PCE exposure. Statistical models were adjusted for previous spontaneous abortion, drinking, smoking, parity, and exposure to other solvents. Heavy lifting was not associated with spontaneous abortion in this analysis. The 2012 IRIS Assessment also identified other studies of maternal and paternal PCE exposure and spontaneous abortions.

Nevertheless, EPA provides no explanation for why only two studies were selected for inclusion in the draft Risk Evaluation, while the other studies were excluded. Most importantly, EPA has not conducted a systematic review of the literature; nor has it provided any evidence that the information represents the best available science. EPA's arbitrary and capricious approach to inclusion/exclusion of information on the human studies on spontaneous abortion and on developmental toxicity in general (see next section) is unacceptable. Absent substantial revision, the Risk Evaluation will not fulfill the requirements of TSCA §26(h) and (i) regarding use of the best available science and decisions based on the weight of the science evidence.

2. Developmental Toxicity in Humans

Citing the 2012 IRIS Assessment, the draft Risk Evaluation states "drinking water studies have suggested associations between PCE exposure and pre-term birth, low birth weight, eye and ear anomalies, and oral cleft defects." Unfortunately, the following analysis of these studies from page 4-352 of the 2012 IRIS Assessment was omitted:

> "Studies of tetrachloroethylene in drinking water have reported that exposure during pregnancy is associated with low birth weight, eye/ear anomalies, and oral cleft

[47] Ahlborg, GA, Validity of exposure data obtained by questionnaire. Two examples from occupational studies, Scand. *J. Work Environ. Health* 16: 284-288 (1990).

[48] Lindbohm, ML, Taskinen, H, Sallmenm M, Hemminki, K, Spontaneous abortions among women exposed to organic solvents, Am. J, Ind. Med. 17: 449-463 (1990).

[49] Kyyrönen, P, Taskinen, H, Lindbohm, M-L, Hemminki, Km Heinonen, OP*, J. Epidemiol. Community Health* 4: 346-351 (1989).

> [references omitted]. However, the number of cases with birth anomalies in specific diagnostic groups was very small, and CIs often included one. In addition, imprecise exposure estimates likely resulted in nondifferential misclassification, biasing risk estimates toward the null. Participants in the studies were exposed to multiple contaminants, and it was not possible to disentangle substance-specific risks."

EPA does not acknowledge that Aschengrau *et al.* (2008) found no meaningful associations between PCE exposure in drinking water and birth weight or gestational duration.[50] Aschengrau *et al.* (2008) compared birth weight and gestational duration among women with or without pre-pregnancy exposure to water distribution contaminated with PCE. A total of 1,353 exposed births were compared to 772 unexposed ones. Information on important confounding factors (*e.g.*, smoking, drinking, education, medical complications, etc.) was obtained via self-administered questionnaire, with analyses adjusted as appropriate. Exposure was determined using a water- contamination model developed for an earlier cancer study by some of the same authors.[51] Birth weight was generally non-significantly elevated among the exposed, even after adjustment for confounding factors. This population was further followed to see if prenatal or early postnatal exposure to contaminated drinking was associated with greater learning or behavioral disorders.[52] The authors found only modest (RR 0.8-1.5) and non-significant associations, there was no evidence of a dose-response, and those with high exposure generally had OR $\leq$ 1.0.

TSCA § 26(h) and (i) require risk assessments that "rel[y] on the best available science and [are] based on the weight of the scientific evidence." In defining "best available science," EPA's risk evaluation rule considers as applicable "the extent to which the variability and uncertainty in the information, or in the procedures, measures, methods, protocols, methodologies, or models, are evaluated and characterized." Clearly, in the example above on the human developmental studies of PCE in drinking water, EPA has not used the best available science.[53] Furthermore, EPA has not conducted a systematic review of the literature that includes studies published since the 2012 IRIS Assessment in order to meet the requirement of "weight of the scientific evidence." These deficiencies need to be corrected in the final Risk Evaluation.

3. Animal Developmental Toxicity Studies

For the animal developmental toxicity studies, a systematic review was conducted on only a few studies, and the draft Risk Evaluation provides no justification as to why these studies were

[50] Aschengrau, A, Weinberg, J, Rogers, S, Gallagher, L, Winter, M, Vieira, V, Webster, T, Ozonoff, D, Prenatal exposure to tetrachloroethylene-contaminated drinking water and the risk of adverse birth outcomes, *Environ. Health Perspect.* 116: 814-820 (2008).

[51] Aschengrau, A, Ozonoff, D, Paulu, C, Coogan, P, Vezina, R, Heeren, T, Zhang, Y, Cancer risk and tetrachloroethylene-contaminated drinking water in Massachusetts, *Arch. Environ. Health* 48: 284-292 (2003).

[52] Janulewicz, PA, White, RF, Winter, MR, Weinberg, JM, Gallagher, LE, Vieira, V, Webster, TF, Aschengrau, A, *Neurotoxicol. Teratol.* 30: 175-185 (2008).

[53] 40 CFR Section 8702.33

considered more reliable and informative than other studies. These deficiencies need to be corrected in the final Risk Evaluation.

B. Immunotoxicity

The study by Seo *et al.* (2012) is included in the draft Risk Evaluation even though it was given an overall data quality rating of "Unacceptable" in the systematic review.[54] In doing so, EPA disregards its own procedure for systematic review. The Seo *et al.* (2012) study received an "Unacceptable" score for the Metric "# per group," which is an important concern when evaluating the robustness of the data. If EPA overrides its systematic review procedure and includes a study that is rated "Unacceptable," the Risk Evaluation should provide the rationale for this decision.

Moreover, EPA overlooked a potentially serious methodological flaw in Seo *et al.* (2012) that introduces considerable uncertainty in the interpretation of the study. Based on the physico-chemical properties of both PCE and TCE (both were tested in Seo *et al.*, 2012), there will be a high propensity for both chemicals to volatilize into air from water. The challenges of keeping TCE in drinking water solutions and achieving target concentrations of TCE in drinking water are well known (EPA docket number EPA-HQ-OPPT-2019-0500-0094). A comparison of the Henry's Law constant of PCE (0.0177 atm-m^3mole) to TCE (0.00985 atm-m^3-mole) suggests that volatilization from drinking water solutions in laboratory animal studies is likely to be even more problematic for PCE than for TCE. Thus, it is absolutely necessary that a methodology be developed to minimize PCE and TCE volatilization from the drinking water solutions and that analytical measurements be done to confirm whether the target concentrations were met at the beginning as well as at the end of the water bottle exposure period. Seo *et al.* (2012) state that "[t]he water was changed every other day to ensure dose maintenance"; no analytical data are provided in the publication, however, on whether the target concentrations were achieved, loss of PCE or TCE from the water bottles over the two-day exposure period, and the variability of concentrations over the entire two-week exposure period. In fact, the study authors do not indicate whether any analytical measurements were conducted or what methods were used, if any, to minimize volatilization loss of either chemical. Thus, Seo *et al.* (2012) cannot be considered sufficiently reliable to be included in the Risk Evaluation.

V. Limitations of the Exposure Assessment

A. Aerosol Brake Cleaner Exposure Estimation

Using an alternative modeling approach, Cardno ChemRisk evaluated EPA's modeled PCE worker exposures from the use of PCE-containing aerosol brake cleaner (see Appendix 5). The sensitivity of the estimates to specific modeling inputs were also examined. A well-accepted

[54] Seo, M, Kobayashi, R, Okamura, T, Ikeda, K, Satoh, M, Inagaki, N, Nagai, H, and Nagase, H, Enhancing effects of trichloroethylene and tetrachloroethylene on type I allergic responses in mice, *J. Toxicol. Sci.* 37: 439-445 (2012).

model (IH Mod 2.0) was parameterized based on empirical observations and subsequently validated against measurement data collected under "reasonable worst-case conditions." The measurement data were from Fries *et al.* (2018),[55] in which typical exposures were measured with the use of an aerosol brake cleaner containing toluene and other non-chlorinated solvents in a vehicle repair shop. PCE specific assumptions (*e.g.*, percent PCE of the product) were then substituted into the model to develop lower and upper bound estimates of short-term near-field exposure concentrations for auto mechanics using brake cleaner while performing brake work under "reasonable worst-case" conditions. Lower and upper bound and mid-point (for two different PCE product content and brake work scenarios) 8-hour TWA concentrations were estimated using this modeling approach with assumptions about number of brake jobs performed per day.

The estimated lower bound and upper bound concentrations (e.g. using lower and upper bound assumptions, respectively, for number of brake jobs per day, number of brakes repaired per job, and PCE content) encompass the EPA's modeled 8-hour TWA exposure concentrations of 5.5 ppm as a 50th percentile and 17 ppm as a 95th percentile. Additionally, the estimated mid-point concentrations (assuming 20% PCE content and four brakes repaired per job or 99% PCE content and two brakes repaired per job) are similar to EPA's modeled 50th percentile or between the 50th and 95th percentile. It is important to note that the estimated mid-point 8-hour TWAs are modeled using a "reasonable worst-case" approach and are not an actual estimation of the average 8-hour TWA across all usage scenarios.

Overall, the estimated 8-hour TWA exposures by Cardno ChemRisk based on 15-min TWA concentrations modeled using a "reasonable worst-case" approach developed using the empirical data from Fries et al. (2018) indicate that EPA's modeling approach is representative of "reasonable worst-case" conditions, but not all usage scenarios (*e.g.*, typical or low-use scenarios). However, EPA's use of survey derived brake cleaner usage data rather than measured data of brake cleaner use resulted in an approximately 2- to 4- fold overestimate of exposure concentrations from their model application. EPA used data from a 2000 report from the California Air Resources Board (CARB), which included 1998 survey data from the state of California as well as site visits presumably conducted sometime in the 1990s. In contrast, direct observation and measurement of mass used from the Fries *et al.* (2018) study indicate that the upper bound estimate of product use per brake estimated by EPA is excessive for "reasonable worst-case" use conditions. EPA should consider using a range of product use volumes in their analysis in order to represent "reasonable worst-case" use conditions as well as typical and low use conditions. Inclusion of the use of local ventilation and higher than minimal air changes per hour could also yield a more representative estimate of typical central tendency values.

A survey was conducted in 1993 of automotive repair facilities on chemical brake cleaner usage by John Norton (George Mason University) for HSIA (Appendix 6). This study provides information regarding the use of brake cleaners and the context of that use relevant to the inputs in the previously used model and 8-hour TWA concentration estimates. Specifically, information regarding facility size, brake cleaner use, and number of brake jobs performed per week were

[55] Fries, M, Williams, PRD, Ovesen, J, Maier, A, Airborne exposures associated with the typical use of an aerosol brake cleaner during vehicle repair work, *J. Occup. Environ. Hyg.* 15: 531-540 (2018).

reported by Norton (1993), all of which are relevant either to the model inputs or 8-hour TWA concentration estimate inputs. However, a limitation of much of the information reported by Norton (1993) is that it was collected on a categorical basis which makes it difficult to estimate averages and maximum and minimum values. Also, similar to the CARB 2000 data, the data reported by Norton (1993) is over 20 years old. Nevertheless, the study by Norton (1993) are supportive of the empirical observations of Fries *et al*. (2018), specifically the number of brake jobs per day and the volume of brake cleaner used. With regards to aerosol brake cleaner use, Norton (1993) reported that the majority of respondents indicated they used less than one can of aerosol brake cleaner, supporting the use of 50 g as a reasonable high end estimate of the amount of brake cleaner applied per brake based on the empirical data from Fries et al. (2018). Use of 50 g of brake cleaner per brake equates to 100 g to 200 g used per brake job (on two or four brakes) or 3.5 to 7 ounces. By comparison, EPA assumed in the draft Risk Evaluation that aerosol brake cleaner usage was 14.4 ounces per brake job or 2- to 4-fold higher.

B. Exposures at Dry Cleaning Facilities

The magnitude of potential worker exposures to PCE in the dry cleaning industry had been reduced significantly over the last several decades. This decrease has been due to changes in dry cleaning technology, which is summarized in Appendix 7. While EPA's efforts to assess exposure to dry cleaners based on data using only newer machines, there are additional occupational datasets that EPA has missed that can enhance the empirical basis for the risk determination. For the Risk Evaluation, EPA has used an OSHA dataset for "post 2006" dry cleaning machines. The OSHA datasets were collected during compliance inspections at nine different facilities between 2012 and 2016; these inspections may have been complaint-triggered and would thus tend to be high-end of the true distribution of exposures in industrial settings (as noted in the draft Risk Evaluation). *The OSHA data also did not specify the dry cleaner types (machine generation)*; EPA assume they were representative, but it is unknown what the impact is on the exposure estimates from any misclassification.

The New York Department of Environmental Conservation (NYSDEC) has been collecting data under 6 NYCCRR Part 232, which regulates dry cleaning. Under this regulation, New York requires yearly compliance inspections with trained inspectors registered with the state (*e.g.*, an engineer or Certified Industrial Hygienist) (6 NYCRR 232-2.11). The inspector must collect badge monitoring data, which they provide to NYSDEC. It is our understanding that the NYSDEC monitoring data are available to EPA for use in the risk evaluation and that the dataset is very robust, covering a large number of facilities collected under normal operating conditions. While personal breathing zone samples are typically preferred as a source of worker exposure data, area samples from this data set can also provide reliable estimates of TWA exposures appropriate for assessing 8-hour and longer-term daily dose estimates.

EPA should also consider a weight-of-evidence approach to test the reasonableness of the central tendency estimate (CTE) and upper bound estimates based on maximum drum concentration of PCE and considering current emission controls and work activity patterns. High-end exposure estimates are likely to represent an equipment failure or instance of misuse, which would not represent a routine exposure in a dry cleaning facility. As noted in the Cardno

ChemRisk report, equipment design specifications only allow for 300 ppm residual vapor in the drum of the machine post drying. Finally, for ONUs, EPA should rely on a weighted average of the NYSDEC data and work activity patterns that would include combinations of time spent in the production and non-production areas.

Attached as Appendix 8 is a report titled "A Report on Drycleaning Plant Emissions based on Test Data from Plants in the New York State" prepared by Tatch Technical Services in 2002 for HSIA. The report provides a review of 300+ dry cleaning plant inspections in New York State and an independent analysis of PCE emissions.

Attached as Appendix 9 [Attachment 5] is an Excel spreadsheet file that contains critical data from New York State Part 232 Dry Cleaning Compliance Inspection Reports for the years 2013 to 2105. The Excel file contains a separate record (excel row) for every machine tested by compliance inspectors during this period. As a result, some of the badge sampling information is duplicated in separate entries. The duplicate badge sampling data can be identified by sorting the data by DEC ID and inspection date. A key, describing the data in each column heading, is provided at the bottom of the spreadsheet. The Excel file also contains a folder named "EDITED SHEET" and a folder named "duplicate badge data removed". All the duplicate badge sampling data was removed in the "duplicate badge data removed" spreadsheet whereas the "EDITED SHEET" folder is only a temporary transitional spreadsheet.

C. Dermal Exposure

In an accompanying report (Appendix 10), Cardno ChemRisk review the dermal exposure characterizations in the draft Risk Evaluation and the impact of assumptions on model estimates for PCE use in industrial systems that generally occur in closed systems, such as manufacturing, repackaging, and processing as a reactant. In addition, dermal modeling was also conducted using realistic workplace scenarios to show that appropriate modeling is valuable for predicting exposures from common industry tasks.

For PCE manufacturing and other processing using closed systems, it is imperative to understand the exposure scenarios, after accounting for industrial hygiene practices (a description is provided in the Cardno ChemRisk report submitted to the EPA docket: EPA-HQ-OPPT-2019-0502-0027). For the majority of the operational time, PCE is present only in closed vessels or process equipment with no dermal contact. Small magnitude exposures during short-term tasks can occur in unit operations and maintenance activities. Liquid material present on equipment during maintenance or repair is usually a mixture of residuals from the process and the solutions used to clean and purge the equipment (often water from steam or other process aids) and not neat PCE. The duration of active liquid contact is also typically short (*e.g.*, minutes) and diminishes once the equipment has been drained.

PCE dose estimates in the draft Risk Evaluation may have been substantially overestimated based on assumptions applied for the occupational exposure scenarios (OES) and used in the Dermal Exposure to Volatile Liquids (DEVL) model for closed industrial systems. As with the draft TCE Risk Evaluation, the DEVL model and the assumptions used by EPA for

dermal exposure do not reflect exposure scenarios that are likely under normal operational scenarios (particularly in chemical manufacturing facilities) following typical industrial hygiene practices.

Appendix 10 includes several modeling examples where the draft Risk Evaluation may have considerably overestimated dermal exposures. For instance, in the non-occluded (ungloved hand) exposure scenarios, EPA did not account for exposure duration of industrial scenarios nor the saturation of the skin by PCE. Cardno ChemRisk used the IHSkinPerm model to estimate dermal exposures. IHSkinPerm is a peer-reviewed exposure assessment tool published by the American Industrial Hygiene Association's Exposure Assessment Strategies Committee. It is a common tool to produce reliable estimates of dermal exposure by practitioners of industrial hygiene and exposure assessment. Revised analyses using the IHSkinPerm model, in which duration and saturation factors were appropriately considered, show that exposure scenarios without PPE in the draft Risk Evaluation may have overestimated the absorption fraction of PCE by 40- to 80-fold for exposure to an ungloved hand, and the total dermal dose of PCE by approximately 2.5- to 10-fold for exposure to an ungloved hand assuming eight one-hour exposure events per day.

For the draft Risk Evaluation overall, Cardno ChemRisk concluded that both occluded and non-occluded dermal PCE exposure estimates were likely to be considerably overestimated based on numerous factors, including (but not limited to):

- The absorption factor used (13-19%), which is higher than expected for PCE under realistic scenarios assuming evaporation and saturation kinetics;
- The assumption that the skin surface area that comes in contact with PCE is one to two full hands, rather than the more likely interior hand surfaces;
- The assumption that PCE exposure occurs continuously for 8 hours rather than intermittently; and
- The assumption that the worker does not change gloves or wash hands at all during the work shift.

In the case of the occluded scenarios, additional overestimation likely occurred based on the assumption that the whole hand (or hands) were coated with PCE in-glove, and the lack of consideration for possible permeation back out of the glove and evaporative losses.

The PCE Risk Evaluation would be strengthened by refinements to the methodology of the exposure characterization. EPA should first consider whether grouping OES into six categories of general exposure are truly representative, or whether EPA should consider more specific groupings. EPA should then consider the incorporation of additional exposure modeling in the revised risk evaluation that reflects well-characterized industrial handling practices. Moreover, at a minimum, the Risk Evaluation should include discussion of the impacts of these assumptions on the level of confidence in the overall estimates, and the degree to which the assumptions are more than adequately protective. Given the many uncertainties inherent in the

PCE dermal assessment, EPA should also investigate whether an empirical study of dermal exposure to PCE can be conducted, and the findings incorporated into the final assessment. Another data-gathering approach could include conducting or soliciting surveys that characterize the current tasks at facilities manufacturing and utilizing PCE, including information on task duration, contact volumes and frequencies, and PPE practices.

D. Assumptions Regarding Glove Protection

The Protection Factors (PFs) utilized by EPA in the dermal exposure assessment were developed for the ECETOC targeted risk assessment (TRA) model. There is, however, very little information on how these protection factors were derived. EPA cites Marquart *et al.* (2017)[56] in the draft Risk Evaluation as support for the ECETOC PFs; but, in fact, the conclusion of the authors was that "the effect of gloves is *underestimated* if the reasonable worst case defaults used in regulatory risk assessment practice are used" [emphasis added]. What Marquart *et al.* (2017) found was "the [dermal ECETOC] model was shown to have clear bias towards (severe) overestimation of dermal exposure at low measured exposure values." Across the dataset, the effect of gloves yielded an average protective factor of 34, relative to PFs of 5 to 10 in the model estimations. In addition, standard IH practices also support little, if any penetration, of PCE through the glove in typical work conditions. In the industry, a glove is tested and selected to ensure suitability for the specific chemical being used and the use duration to ensure no chemical breakthrough for the duration of specific tasks. Further, general industrial hygiene practice in place at facilities would likely incorporate PPE change out schedules designed to limit breakthrough time. Any detectable breakthrough or glove degradation would indicate the need for new gloves. It also noted that situations in chemical manufacturing with full glove coverage of liquid material would be rare, and if considered probable would involve specific job hazard analyses that would include specific controls (*e.g.*, use of an inner glove) to limit dermal contact.

EPA should incorporate empirically-derived protection factors using literature on solvent permeation through gloves, considering critical factors such as the extent and length of contact with the chemical, the amount of hand/glove flexion, and worker behavior.[57] While "in-use" empirical studies of permeation through gloves under a company's specific working conditions would be ideal, there are also methods to calculate/model glove protection using chemical-specific inputs. For example, Cherrie *et al.* (2004) presented a technique for estimating chemical-specific glove protection factors using toluene as a case study.

[56] Marquart, H, Franken, R, Goede, H, Fransman, W, Schinkel, J, Validation of the dermal exposure model in ECETOC TRA, *Annals Work Exposure Health* 61: 854-871 (2017).

[57] Cherrie, JW, Semple, S, Brouwer, D, Gloves and dermal exposure to chemicals: proposals for evaluating workplace effectiveness, *Ann. Occup. Hyg.* 48: 607-615 (2004); Chao, K.-P., Wang, V.-S, Lee, P.-H, Modeling organic solvents permeation through protective gloves, *J. Occup. Environ. Hyg.* 1: 57-61 (2004).

E. Distribution Analysis of PCE Manufacturing Data

EPA utilized the worker monitoring data provided by HSIA in its draft Risk Evaluation to characterize exposures to workers and occupational non-users (ONUs) for manufacturing use scenarios. These exposure data contained a considerable number of values below the limit of detection; thus, the calculated exposure estimates are highly influenced by the high-end outliers in this dataset. EPA relied on the guidance provided in the *Guidelines for Statistical Analysis of Occupational Exposure Data* to address values reported as below the LOD. However, there are alternative approaches that are conducted with resources utilized by occupational health and safety professionals and reflect best practices (see Appendix 11).

It is important to consider that workers may have different exposures based on the nature of their tasks, including the frequency and duration of each task, specific materials used, and the manner in which the tasks are performed.[58] The American Industrial Hygiene Association (AIHA) recommends that occupational data be categorized by similar exposure groups (SEG) in order to accurately represent the exposure profiles for workers conducting similar tasks. Failure to distinguish between SEGs in exposure data by combining data for workers or tasks with different exposure profiles may lead to misrepresentation of exposures and misguided risk management decisions.

As demonstrated in the Cardno ChemRisk report (Appendix 11), alternative analyses of occupational exposure data for PCE manufacturing by task length and task frequency reveal important differences in exposure potential based on the nature of specific tasks. Comparing these results to the occupational exposure estimates for PCE manufacturing presented in the draft Risk Evaluation, which group all HSIA data points together, indicate that EPA's exposure estimates do not represent average routine exposures in the industry.

Specifically, infrequent, non-routine tasks may present a substantially greater potential for worker exposure, a distinction that is not made in EPA's current approach to its draft Risk Evaluation for PCE. Grouping data for infrequent tasks with high exposure potential with data for routine tasks based solely on task length overestimates both the central tendency and 95th percentile PCE exposures. Thus, it would be prudent for EPA to adopt a more refined approach in the revised risk evaluation for PCE. It is recommended that EPA re-analyze the HSIA data to not only consider task length, but also task frequency, in estimating exposures. Estimates for non-routine, infrequent exposures should be compared with acute health benchmarks, and estimates of routine exposures should be compared with chronic benchmarks. Such an approach will allow EPA to distinguish the SEGs present within the HSIA dataset and develop a more robust characterization of potential risks to PCE manufacturing workers in the final risk evaluation. Finally, EPA should consider conducting near-field/far-field modeling of ONU exposures rather than relying on a single empirical data point.

[58] American Industrial Hygiene Association (AIHA) Exposure Assessment Strategies Committee (EASC), A strategy for assessing and managing occupational exposures, 4th Edition, Ed. By Jahn, SD, Bullock, WH, Ignacio, JS (2015).

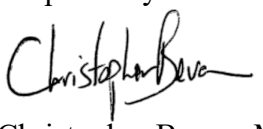
VI. Conclusion

In sum, the "applicable requirements of TSCA § 6," with which the Lautenberg Act mandates that a completed risk assessment must comply before it can support § 6 rulemaking, include taking into account exposure under the conditions of use, describing the weight of the scientific evidence for the identified hazard and exposure, the use of scientific information employed in a manner consistent with the best available science, the consideration of variability and uncertainty in the information, and consideration of the extent of independent verification or peer review of the information.

Regrettably, the draft Risk Evaluation does not fulfill the requirements of the Lautenberg Act. Its hazard assessment is not based on the best available science; there are inconsistent, inaccurate, and apparently subjective alterations of the data quality assessments in the systematic review; and the exposure assessments are not realistic and do not reflect current industrial hygiene practices at facilities that manufacture and use PCE.

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 assessment before proceeding with rulemaking.

Respectfully submitted,



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Director, Scientific Programs

Appendices

Comments on the Bladder Cancer and Liver Cancer Systematic Reviews in US EPA's Draft Risk Evaluation for Perchloroethylene (Ethene, 1,1,2,2-Tethrachloro) CASRN: 127-18-4

Julie E. Goodman, Ph.D., DABT, FACE, ATS

Overview

In the draft "Risk Evaluation for Perchloroethylene (Ethene, 1,1,2,2-Tethrachloro) CASRN: 127-18-4," (Draft Risk Evaluation; US EPA, 2020a), the United States Environmental Protection Agency (US EPA) stated that it conducted systematic reviews of perchloroethylene (PCE) and bladder cancer and kidney cancer, and that these analyses build on analyses conducted in the US EPA 2012 Integrated Risk Information System (IRIS) "Toxicological Review of Tetrachloroethylene" (US EPA, 2012). US EPA (2020a) stated it "evaluated the confidence of the key and supporting data sources [published in the 2012 PCE IRIS Assessment] as well as newer information instead of evaluating the confidence of all the underlying [epidemiology] evidence ever published."

The methodology used in the Draft Risk Evaluation to evaluate epidemiology studies of PCE and bladder and kidney cancer is not scientifically robust and does not constitute a systematic review. With respect to bladder cancer, the Draft Risk Evaluation did not provide any information on how it evaluated and integrated the evidence available before and after the 2012 review or how study quality was considered and whether it was done so in a systematic manner. The evaluation was also not clear regarding whether it concludes the evidence supports a modest elevated risk or no risk for bladder cancer. In terms of kidney cancer, although the Draft Risk Evaluation concluded there was "no association or [a] weak positive association" (US EPA, 2020a), as with bladder cancer, there are issues related to study selection, data quality evaluation and consideration, and heterogeneity across individual studies that limit the reliability of the conclusions drawn in the Draft Risk Evaluation.

Although it appears that the epidemiology studies identified in the Draft Risk Evaluation do not support an association between PCE and either bladder or kidney cancer, US EPA should conduct a robust, transparent systematic review of all relevant studies.

1 Systematic Review

US EPA discusses its approach to systematic review in Section 1.5 and indicates it relies predominantly on the 2018 guidance, "Application of Systematic Review in TSCA Risk Evaluations." While some of the key elements of the Toxic Substances Control Act (TSCA) systematic review process are performed in the PCE risk evaluation (*e.g.*, data collection and evaluation), the critical step of Data Integration has not been fully completed. US EPA (2018) describes data integration as follows:

> Data integration is the stage where the analysis, synthesis and integration of data/information takes place by considering quality, consistency, relevancy, coherence and biological plausibility. It is in this stage where the weight of the scientific evidence

> approach is applied to evaluate and synthetize multiple evidence streams in order to support the chemical risk evaluation.
>
> EPA/OPPT is required by TSCA to use the weight of the scientific evidence in TSCA risk evaluations. Application of weight of evidence analysis is an integrative and interpretive process that considers both data/information in favor (e.g., positive study) or against (e.g., negative study) a given hypothesis within the context of the assessment question(s) being evaluated in the risk evaluation...
>
> Within the TSCA context, the weight of the scientific evidence is defined as "a systematic review method, applied in a manner suited to the nature of the evidence or decision, that uses a preestablished protocol to comprehensively, objectively, transparently, and consistently identify and evaluate each stream of evidence, including strengths, limitations, and relevance of each study and to integrate evidence as necessary and appropriate based upon strengths, limitations, and relevance". 40 C.F.R. 702.33. In other words, it will involve assembling the relevant data and evaluating the data for quality and relevance, followed by synthesis and integration of the evidence to support conclusions (U.S. EPA, 2016). The significant issues, strengths, and limitations of the data and the uncertainties that require consideration will be presented, and the major points of interpretation will be highlighted. Professional judgment will be used at every step of the process and will be applied transparently, clearly documented, and to the extent possible, follow principles and procedures that are articulated prior to conducting the assessment (U.S. EPA, 2016).
>
> The last step of the systematic review process is the summary of findings in which the evidence is summarized, the approaches or methods used to weigh the evidence are discussed, and the basis for the conclusion(s), recommendation(s), and any uncertainties are fully described. This step occurs in each of the components of the risk assessment (i.e., exposure assessment and hazard assessment) and is summarized in the risk characterization section of the TSCA risk evaluation.

An important aspect of data integration is study quality. US EPA conducted an extensive evaluation of study quality using predetermined Data Quality Criteria (US EPA, 2020b), which included six general domains and a total of 22 metrics that each captured a specific aspect of study quality. As summarized in the Data Quality Evaluation (US EPA, 2020c), individual studies were first evaluated and rated against each individual study quality metric (*i.e.*, "High," "Medium," "Low," or "Unacceptable"), with a score assigned to each rating (*i.e.*, 1, 2, 3, or 4, respectively). Then, a summary score was calculated for each study as the weighted average across individual metric quality scores. The weight carried by each metric towards the summary score was determined *a priori* to reflect what US EPA concluded was its relative importance towards the overall study quality. Finally, the summary score for each study was categorized into ranges that were defined to indicate "High," "Medium," "Low," or "Unacceptable" study quality overall.

However, while the Data Quality Evaluation included all of the new studies that estimated bladder or kidney cancer risk in the 2020 Draft Risk Evaluation, only 12 studies for bladder cancer and 23 studies for kidney cancer in the 2012 IRIS Assessment were evaluated. It is unclear why only some of the studies included in the 2012 IRIS Assessment were included in the Data Quality Evaluation or what criteria were used to determine which studies would be included and excluded. This should be addressed for transparency.

In addition, while US EPA included extensive summaries for individual studies in the Data Quality Evaluation (US EPA, 2020c), there are no succinct tables showing the quality of any particular dataset, such as the ones shown here in Tables 1 and 2 for bladder and kidney cancer epidemiology studies,

respectively. These tables make it possible to evaluate the distribution of a quality metric across studies. At the very least, US EPA should have a discussion of how these metrics are distributed across studies and how they impact the interpretation of results.

US EPA conducted an extensive quality evaluation for a number of studies, but as discussed below in Sections 2 and 3, it was not conducted for every relevant study, and reasons for the exclusion of studies are not apparent. Importantly, while US EPA discussed toxicity and epidemiology studies in the Hazard Identification Section 3.2.3 and Appendix F of the Draft Risk Evaluation and noted where certain studies have low, medium, or high quality and, on occasion, study uncertainties, the specific uncertainties discussed are not consistent across studies (*i.e.*, a specific uncertainty will be emphasized for one study but not another), and the impact of these uncertainties on the interpretation of results are not discussed. The Draft Risk Assessment also does not consider that a study with an overall high rating may still have major issues with study interpretation as a result of one or a few study metrics, most notably related to exposure.

Data integration should include comparative analyses of positive and negative results, discussions of risk of bias, meta-analyses combining results across studies if appropriate, and visual displays of all relevant evidence. US EPA (2018) points to several published tools and protocols to integrate scientific evidence beyond simple data quality scores. The PCE risk evaluation does not fully incorporate these tools such that all evidence for each endpoint can be examined, compared, and contrasted. Additional specific examples of the lack of data integration are provided in the next sections for bladder and kidney cancer.

2 Bladder Cancer

The US EPA 2012 IRIS Assessment reviewed 32 epidemiology studies and one meta-analysis of PCE and bladder cancer (US EPA, 2012). In the Draft Risk Evaluation (US EPA, 2020a), five additional studies were identified and evaluated by US EPA. Of the 37 epidemiology studies identified, 15 studies were cohort studies, 21 studies were case-control studies, and 1 was an ecological study.

Among all cohort studies identified and included in the analyses, none reported significant associations between PCE and bladder cancer. A few case-control studies reported elevated risk of bladder cancer; while some reported an exposure-response trend, others did not.

2.1 US EPA 2012 IRIS Assessment

Based on 32 studies, the US EPA 2012 IRIS Assessment concluded:

> [T]he pattern of results from this collection of studies is consistent with an elevated risk for tetrachloroethylene of a relatively modest magnitude. The effect estimates from four of the five studies with the relatively high quality exposure-assessment methodologies provide evidence of an association, with relative risks of 1.44 to 4.03 (Calvert et al., 2011; Lynge et al., 2006; Blair et al., 2003; Pesch et al., 2000b; Aschengrau et al., 1993). (US EPA, 2012)

As indicated in this quote, the 2012 IRIS Assessment considered studies from Calvert *et al*. (2011), Lynge *et al*. (2006), Blair *et al*. (2003), Pesch *et al*. (2000b), and Aschengrau *et al*. (1993) as having "relatively high quality exposure-assessment methodologies" (US EPA, 2012). However, the 2020 Data Quality Evaluation (US EPA, 2020c) does not support the statement. Almost all five studies were rated as having "Low" quality with regard to Measurement of Exposure (Metric 4) and Exposure levels (Metric 5), except for a "Medium" rating of Measurement of Exposure (Metric 4) for Lynge *et al*. (2006) and a "Medium"

rating of Exposure levels (Metric 5) for Aschengrau *et al*. (1993). Among these five studies, three (Calvert *et al*., 2011; Lynge *et al*., 2006; and Blair *et al*., 2003) used occupation in dry-cleaning and laundry industries as proxies for PCE exposure, which are prone to misclassification bias. As acknowledged in the 2012 IRIS Assessment:

> The exposure surrogate in studies of dry-cleaners and laundry workers is a broad category containing jobs of differing potential for tetrachloroethylene exposure. Thus, these studies have a greater potential for exposure misclassification bias compared to studies with exposure potential to tetrachloroethylene assigned by exposure matrix approaches. (US EPA, 2012)

With respect to Pesch *et al*. (2000b), these investigators reported odds ratios (ORs) among those with medium, high, and substantial exposures to PCE, or 1.0 (95% CI: 0.7-1.5), 1.2 (95% CI: 0.8-1.7), and 1.8 (95% CI: 1.1-3.1), respectively, with a significant trend. However, as noted in the 2020 Data Quality Evaluation (US EPA, 2020c), "Exposure categories estimated by JEM and JETM were based on job titles and job tasks from questionnaires and interviews (not employment records). Specified chemical agent exposures were estimated based on probability and intensity of exposure associated with the job titles and task." It was thus given a "Low" quality rating with respect to Measurement of Exposures (Metric 4). In addition, this study was rated "Low" for Co-exposure Confounding Quality (Metric 11) because "[o]ther chemical agent worker exposures were not [appropriately] adjusted for which could result in biased exposure-outcome association" (US EPA, 2020c). Finally, although the Covariate Adjustment (Metric 9) was rated as being "High" in the study, the study only adjusted for age, study center, and smoking. Other potential confounders such as body mass index (BMI), gender, underlying diseases, and socioeconomic status (SES) were not adjusted for in the study.

As another example, Lynge *et al*. (2006) reported an increased risk of bladder cancer among dry-cleaners based on 93 exposed cases (relative risk [RR]=1.44, 95% CI: 1.07-1.93). However, the study used length of employment in laundry and dry-cleaning shops as a proxy for exposure to PCE, resulting in Measurement of Exposure (Metric 4) and Exposure levels (Metric 5) ratings as "Medium" and "Low," respectively. Setting aside this issue with quality, risk did not increase with length of employment.. There are also issues with potential confounders. Although the study adjusted for smoking and alcohol consumption, this was only done in a subset of the study participants. Also, other risk factors such as BMI, chronic infections, and SES were not adjusted for in the study. Neither Pesch *et al*. (2000b) or Lynge *et al*. (2006) should be considered to have "relatively high quality exposure-assessment methodologies."

The 2012 IRIS Assessment (US EPA, 2012) also noted that it placed more weight on seven studies because they had a relatively large number of observed events (*i.e*., ≥50 cases) (Pukkala *et al*., 2009; Travier *et al*., 2002; Wilson *et al*., 2008; Ji *et al*., 2005a; Pesch *et al*., 2000b; Andersen *et al*., 1999; Lynge *et al*., 2006) . However, the quality of these studies were reviewed in 2020, and the Data Quality Evaluation indicated all of these studies had serious limitations with respect to exposure assessment and potential confounding control (US EPA, 2020c).

In addition, it is worth noting that Sung *et al*. (2007) was classified as "Unacceptable" in the Data Quality Evaluation (US EPA, 2020c) due to "Unacceptable" Measurement of Exposure (Metric 4). In terms of Measurement of Exposure (Metric 4), US EPA (2020c) stated:

> Employees were considered exposed if they had worked in the factory anytime during 1973-1992. The authors do not report any actual exposure data. "No data on solvent exposure had been kept by the factory, and although we attempted to produce a reconstruction of such exposure, our dataset was too limited and crude to permit any possible linkage to individual workers."

In addition, Metric 5 (Exposure Levels) was left in blank in the Data Quality Evaluation. The reason given by US EPA (2020c) was:

> No description is provided on the levels or range of exposure for any of the solvents the workers were exposed to. Workers were categorized as exposed and compared to the general population.

The remainder of the studies that were evaluated in the 2012 IRIS Assessment and later rated in the Data Quality Evaluation were mostly rated as "Low" for both Measurement of Exposure (Metric 4) and Exposure Levels (Metric 5). Many of these studies also used job titles such as working in the dry-cleaning and laundry industry as a proxy for PCE exposure. Therefore, with respect to Co-exposure Confounding (Metric 11), most of these studies were rated as having "Low" quality.

Finally, the 2012 IRIS Assessment indicated a meta-analysis of 14 studies that examined the association between dry-cleaners and laundry workers with bladder cancer (Reulen *et al*., 2008) came to similar conclusions as US EPA (*i.e*., a small increased risk), "[d]espite the differences in the specific studies in this analysis." The pooled RR estimate reported in the study was 1.27 (95% CI: 0.95-1.71). When stratified by study design, a significantly increased risk was observed in case-control studies (OR=1.66, 95% CI: 1.23-2.24) but not in cohort studies. However, as acknowledged by the authors, "occupations are, in effect, proxies for potential occupational exposures, and as such exposures may differ between subjects with the same job title in terms of exposure type, duration and intensity" (Reulen *et al*., 2008). In addition, the exposure metrics and contrasts used in individual studies were different, which may have introduced heterogeneity across the meta-analyzed studies and hinders the interpretability of the meta-analyses results. Also, different studies adjusted for different sets of covariates, and even the same covariates were often defined and measured differently across studies. These serve as another source of heterogeneity among the individual effect estimates. Finally, the analysis did not assess if publication bias was present. All these limitations hinder the interpretability of the meta-analysis results.

Overall, the limitations of the studies reviewed in the 2012 IRIS Assessment, particularly with respect to exposure measurements and confounding, indicate that reported small increases in bladder cancer risk associated with PCE exposure should not be interpreted as evidence for a causal association.

2.2 US EPA 2020 Draft Risk Evaluation

The 2020 Draft Risk Evaluation stated:

> (U.S. EPA 2012c) concluded that, with respect to bladder cancer, the pattern of results from the studies available at that time was consistent with an elevated risk for PCE of a relatively modest magnitude (i.e., a 10−40% increased risk)….More recent studies provide little support for an association between bladder cancer and PCE exposure. (US EPA, 2020a)

The Draft Risk Evaluation did not provide any information on how the evidence available before and after that 2012 review were evaluated and integrated. There is no information on what constitutes "little support." It is also not clear whether US EPA (2020a) concludes the evidence supports a modest elevated risk or whether the evidence no longer supports a risk.

Like many of the studies included in the 2012 IRIS Assessment, the five newly identified studies in the Draft Risk Evaluation have major limitations with respect to exposure measurements. For example, in a case-control study, Hadkhale *et al*. (2017) used a standardized job exposure matrix (JEM) to estimate

cumulative occupational exposure to PCE and reported a slight increase in bladder cancer in the medium PCE exposure group (hazard ratio [HR]=1.12, 95% CI: 1.02-1.23), but not in the low exposure and high exposure groups, and no significant dose-related trend was reported (p=0.10). US EPA (2020a) concluded that the results suggest "a cause other than PCE exposure for the slight association observed in the medium-exposure group." The Measurement of Exposure (Metric 4) and Exposure Levels (Metric 5) of this study were both rated as "Medium." In addition, the authors themselves acknowledged the limitation of the exposure assessment, as stated:

> Only small proportions of the populations of Norway, Finland, Sweden and Iceland had considerable exposure to solvents. This limited our choice of cumulative exposure categorization in our study. Therefore, the threshold of the highest exposure level had to be set to a modest exposure level. Variation in exposure levels within occupational categories means the use of average exposure estimates for everyone in the occupational category, and that may under- or overestimate the true exposure for some individuals. (Hadkhale *et al*., 2017)

In addition, although the study analysis adjusted for age, sex, country, and solvents that may potentially relate to bladder cancer, the authors were not able to adjust for smoking, SES, and other non-occupational risk factors as they were not available.

As another example, the Measurement of Exposure (Metric 4) for Christensen *et al*. (2013) was rated as having "Low" quality because "[e]xposure was assessed based on self-reported job history translated into exposure by chemists and industrial hygienists. Authors reported that there was no indication that completeness or validity of job histories differed between cases and controls" (US EPA, 2020c). This study is also subject to co-exposure to other solvents, as indicated in the Data Quality Evaluation: "[co]-exposures to other chlorinated solvents were likely, given the overlapping job-exposure combinations; the study did not control for co-exposures or even report the distributions of co-exposures" (US EPA, 2020c). Therefore, the Co-exposure Confounding (Metric 11) was rated as "Low" for this study. Similar limitations are also seen in Silver *et al*. (2014). The Exposure Levels (Metric 5) and Co-exposure Confounding (Metric 11) metrics were both rated as "Low" because the exposure to PCE was very low (*i.e*., 15.1%) in the study, and there were inadequate adjustment for potential co-exposures to other solvents.

The other three studies had similar limitations. Overall, while US EPA evaluated the quality of most of the identified studies, it did not fully consider how these study quality issues (*i.e*., exposure measurement error and confounding) may have impacted the interpretation of the results. Therefore, US EPA has not demonstrated there is a risk of bladder cancer from PCE exposure.

3 Kidney Cancer

The US EPA 2012 IRIS Assessment identified and evaluated 27 "core" epidemiology studies reporting data on kidney cancer and PCE exposure. In the Draft Risk Evaluation, 6 additional studies were identified, for a total of 33. Of the 33 studies, 16 were cohort studies, 16 were case-control studies, and 1 was an ecological study.

Among all cohort studies identified and included in the analyses, none reported significant associations between PCE and kidney cancer. Three case-control studies reported PCE was associated with increased kidney cancer risks. The only ecological study reported that an increased prevalence rate of kidney cancer was associated with a greater density of dry-cleaners at the zip code level (Ma *et al*., 2009).

In the Draft Risk Evaluation, US EPA conducted a meta-analysis of five studies (two of which were reviewed in the 2012 Assessment) and concluded that there was "no association or weak positive association between the occurrence of kidney cancer and exposure to PCE, but [this conclusion] should be interpreted with caution due to the small number of informative studies" (US EPA, 2020a).

3.1 US EPA 2012 IRIS Assessment

Based on 27 studies, the US EPA 2012 IRIS Assessment concluded:

> [T]he epidemiologic data provide limited evidence pertaining to tetrachloroethylene exposure and kidney cancer risk. The studies that support this finding include the largest international case-control study (245 exposed cases from Australia, Denmark, Germany, Sweden, and the United States), which reported a relative risk of 1.4 (95% CI: 1.1, 1.7) for any exposure to dry-cleaning solvents (Mandel et al., 1995). This study was able to adjust for smoking history, BMI, and other risk factors for kidney cancer. The large cohort studies, using a more general exposure classification based on national census occupation data, present more variable results, with relative risks of 0.94, 1.11, and 1.15 in Pukkula et al. (2009), Travier et al. (2002), and Ji et al. (2005b), respectively. (US EPA, 2012)

The 2012 IRIS Assessment stated that six studies carried more weight in its analysis because these studies reported RRs based on a large number of observed events (*i.e.*, ≥50 cases); these studies include Mandel *et al*. (1995), Ji *et al*. (2005b), Pukkala *et al*. (2009), Travier *et al*. (2002), Dosemeci *et al*. (1999), and Pesch *et al*. (2000a). The quality of these six studies was evaluated in the 2020 Draft Risk Assessment, and the rating for each metric and the overall rating for each study are summarized in Table 2 below. It can be seen in this table that the studies that carried more weight in the assessment had similar limitations as the studies from which effect estimates were based on fewer observed events.

For example, Mandel *et al*. (1995) reported a significant increased risk of renal cell carcinoma for any exposure to dry-cleaning solvents. However, in the 2020 Data Quality Evaluation (US EPA, 2020c), this study was rated as having "Low" quality with regard to both Measurement of Exposure (Metric 4) and Exposure Levels (Metric 5). The study used occupation in the dry-cleaning industry as a proxy for PCE exposure, and presented risk estimates by employment duration. This limitation was also noted in the 2012 IRIS Assessment:

> Because employment duration does not account for variation in exposure levels, it is a weaker exposure measurement (*i.e*., more subject to misclassification) compared with one defined as a semiquantitative measure. (US EPA, 2012)

In addition, Mandel *et al*. (1995) was originally given a "High" overall rating, although this was updated to "Medium," "due to use of occupation in dry cleaning industry as a surrogate of perc exposure" (US EPA, 2020c).

The other five studies that carried more weight in the analysis have similar limitations (Ji *et al*., 2005b; Pukkala *et al*., 2009; Travier *et al*., 2002; Dosemeci *et al*., 1999; and Pesch *et al*., 2000a). Almost all studies were rated as having "Low" quality with regard to Measurement of Exposure (Metric 4) and Exposure Levels (Metric 5), except Dosemeci *et al*. (1999), which received a "Medium" rating of Measurement of Exposure (Metric 4), and Pesch *et al*. (2000a), which received a "Medium" rating of Exposure levels (Metric 5). In addition, three studies (Ji *et al*., 2005b; Pukkala *et al*., 2009; and Pesch *et al*., 2000a) were rated as having "Low" quality with regard to Co-exposure Confounding (Metric 11). It is likely that the cases in these studies were exposed to other solvents.

Among the studies for which effect estimates were based on fewer observed events, two case-control studies (McCredie and Stewart, 1993 and Schlehofer *et al*., 1995) reported significant positive associations of renal cell carcinoma or renal pelvis cancer from PCE exposure. McCredie and Stewart (1993) studied renal pelvis cancer and renal cell carcinoma in dry-cleaner and laundry jobs, and US EPA reported ORs in this study were 6.09 (95% CI: 1.95, 8.9) for renal pelvis cancer and 2.70 (1.08-6.72) for renal cancer carcinoma, after adjusting for age, sex, and method of interview for both types of cancers, and education for renal pelvic cancer only. It is worth noting that US EPA did not report the mostly fully adjusted model from the paper. When both models further adjusted for smoking, BMI (for renal cell carcinoma), and phenacetin containing analgesics (for renal pelvis cancer), the associations were attenuated and became nonsignificant for renal cell carcinoma (OR=2.49, 95% CI: 0.97-6.35). Although the risk estimate for renal pelvis cancer remained significant (OR=4.68, 95% CI: 1.32-16.56), it was based on only eight cases, and the confidence became wider. In terms of exposure characterization, both Measurement of Exposure (Metric 4) and Exposure Levels (Metric 5) were rated as having "Low" quality. In terms of Measurement of Exposure (Metric 4), the Data Quality Evaluation (US EPA, 2020c) commented:

> Exposure was characterized by self-reported occupational exposure to general categories of chemicals, such as solvents. Elsewhere, exposure was categorized by occupational field, such as dry-cleaning industry. Subjects had at least 10 years of exposure before interview (date of interview 1989-1992). There is no mention of perchloroethylene as the primary solvent; however dry-cleaning industry was acknowledged as source of exposure to hydrocarbons and serves as a surrogate for perchloroethylene exposure for this evaluation.

Finally, for each exposure characterization, the study participants were classified as exposed or unexposed, which did not take into consideration of exposure duration, intensity, or frequency. As the authors acknowledged: "[d]rawback of the present investigation include small numbers of exposed subjects, no validation of the self-reported exposures, and no possibility of categorizing exposures by intensity" (McCredie and Stewart, 1993). These limitations hinder the interpretation of the findings.

Another case-control study that reported significant positive finding was by Schlehofer *et al*. (1995). An elevated risk was observed for renal cell carcinoma with exposure to PCE and tetrachlorocarbonate (OR=2.52, 95% CI: 1.23-5.16). However, the authors reported that no time trend was observed. The Comparison Group (Metric 3) was rated as being "Low" for the study. Although the controls in the study were randomly chosen from the population register of the study area and frequency matched for age and gender to the cases, it is unclear how controls were confirmed to be disease free. More importantly, the overall study quality was classified as "Unacceptable" in the Data Quality Evaluation (US EPA, 2020c) due to "Unacceptable" Measurement of Exposure (Metric 4) and Exposure Levels (Metric 5). In terms of Measurement of Exposure (Metric 4), the US EPA (2020c) stated:

> No specific exposure to perchloroethylene was evaluated in this study. The study focused on occupational exposure, specific industry, or substance. Occupational exposure assessment was requested at 4 levels: 1st- all industries in which subject ever been employed; 2nd- occupations in which the subject had been trained; 3rd- precise activities the subject carried out during employment; 4th- exposure to specific substances. A subject was considered exposed to a specific industry, occupation, or substance when the duration of the exposure lasted at least 5 years. Occupation included 10 categories, and 22 substances. Broad "textile" occupational group in not an appropriate proxy for Perc exposure; no dry cleaning occupation specified; exposure to solvents included "perchloroethylene, dyes, cadmium and mercury."

Regarding Exposure Levels (Metric 5), US EPA (2020c) commented:

> Qualitative (nominal) levels of occupational exposure assessment (industry, occupation, specific activity and substances) were included in the analysis as binary variables. Specific ranges of exposure to perchloroethylene not provided.

In addition to Schlehofer *et al*. (1995), three other studies (Auperin *et al*., 1994; Chang *et al*., 2003; Sung *et al*., 2007) received an overall rating of "Unacceptable" in the 2020 Data Quality Evaluation, due to an "Unacceptable" Measurement of Exposure (Metric 4). In addition, the rest of the studies that were evaluated in the 2012 IRIS Assessment and later rated in the Data Quality Evaluation were mostly rated as "Low" for both Measurement of Exposure (Metric 4) and Exposure Levels (Metric 5). Many of these studies also used job titles such as working in the dry-cleaning and laundry industry as a proxies for PCE exposure. Therefore, with respect to Co-exposure Confounding (Metric 11), most of these studies were rated as having "Low" quality.

Overall, the limitations of the studies reviewed in the 2012 IRIS Assessment, particularly with respect to exposure measurements and confounding, indicate that any reported small increases in kidney cancer risk associated with PCE exposure should not be interpreted as even suggestive of evidence for a causal association.

3.2 US EPA 2020 Draft Risk Evaluation

The 2020 Draft Risk Evaluation stated:

> (U.S. EPA 2012c) acknowledged mixed results in studies of kidney cancer available at that time, concluding that overall the evidence was suggestive but limited….Mixed results were obtained in newer studies as well. (US EPA, 2020a)

As mentioned above, US EPA conducted a review of 33 studies and a meta-analysis of 5 studies selected from the 2012 IRIS Assessment and 2020 Draft Risk Evaluation. While a brief review of the epidemiology evidence does not support an association between PCE and kidney cancer, there are several issues related to the methods by which US EPA (2020a) reached this conclusion, discussed below.

3.2.1 Study Selection

The Draft Risk Evaluation stated:

> A meta-analysis of five selected epidemiologic studies (Purdue et al. 2017; Silver et al. 2014; Vlaanderen et al. 2013; Dosemeci et al. 1999; Aschengrau et al. 1993) considered to be reliable and informative for the association of kidney cancer and exposure to PCE was performed as part of the current assessment. (US EPA, 2020a)

There is no justification provided regarding why these five studies are reliable and informative and other studies are not. Inclusion and exclusion criteria set boundaries for systematic reviews and meta-analyses. They are determined based on the research question and influence the literature search strategy. All studies that meet inclusion criteria should be included in the analyses.

3.2.2 Data Quality Evaluation

Two of the studies (Aschengrau *et al*., 1993; Dosemeci *et al*., 1999) in the kidney cancer meta-analysis were reviewed in the 2012 IRIS Assessment. US EPA's Data Quality Evaluation for these two studies and all of the studies that evaluated kidney cancer reviewed in the 2020 Draft Risk Evaluation are included in Table 2. As shown in Table 2, all of these studies have similar overall quality ratings. More importantly, the data quality ratings of exposure characterization (Metrics 4 and 5) and potential confounding/variable control (Metrics 9-11) of the studies included in the kidney cancer meta-analysis are no better than those not included in the meta-analysis. For instance, the Measurement of Exposure (Metric 4) and Covariate Characterization (Metric 10) of Aschengrau *et al*. (1993) were both rated as "Low," while for Lipworth *et al*. (2011), the metrics were rated as "Medium" and "High," respectively. It is also notable that the study conducted by Aschengrau *et al*. (1993) is subject to reporting bias, as Metric 8 was rated "Low" *vs*. a "High" rating for Lipworth *et al*. (2011). The rest of the metrics were comparable between the two studies.

Overall, our examination of both overall study quality and specific aspects of study quality show that most of the studies, including several rated as having "High" quality overall, may have had serious limitations (particularly with regard to exposure measurement error and confounding) that impacted the interpretation of the study results and the results of the meta-analyses that included them.

3.2.3 Data Quality Rating Adjustment

The goal of using Data Quality Criteria in a systematic review is to ensure the overall quality of each study is evaluated objectively and in a consistent manner. However, in this review, US EPA changed the study quality rating for Vlaanderen *et al*. (2013) after completing an evaluation based on the predetermined Data Quality Criteria (US EPA, 2020b). Vlaanderen *et al*. (2013) was initially rated as a "High" quality study based on the Data Quality Criteria (US EPA, 2020b), but then re-rated as a "Medium" quality study in the current Draft Risk Assessment. The explanation given by the US EPA is identical to the explanation in the "Risk Evaluation for Trichloroethylene" (CASRN: 79-01-6) (US EPA, 2020a). Both documents state:

> Although this was a large, well-conducted study based on complete ascertainment of cancer cases using national cancer registries and a country-specific JEM, the sensitivity of the study to detect any associations that may exist was limited, but improved by restricting the analysis to the high exposure group where prevalence was likely greater compared to the entire study population, due to exposure misclassification inherent in the generic JEM and resulting bias toward the null.

Although a JEM is indeed subject to exposure misclassification, this should have been accounted for by the initial rating of Metric 4 (Measurement of Exposure) as "Low" quality for the study (as shown in Table 1), where it was noted that:

> Exposure during each period was assigned based on generic JEM constructed using expertise and data specific to the Nordic countries.…Although there was no specific evidence in the paper, exposure misclassification may be "considerable" because the prevalence of TCE or perchloroethylene exposure in most job categories was low ("as low as 5%") resulting in a wide variation in exposure frequency and intensity in the exposed resulting in a bias toward the null. The census occupational information does not include job task data or information about changes between each census increasing the potential for exposure misclassification. (US EPA, 2020c)

It is unclear why the same issue was double-counted in the rating. It is also unreasonable to re-rate the entire study (from "High" to "Medium" quality) for specific issues that should have been accounted for by simply re-rating individual aspects/metrics that contribute to the overall rating of the study. Finally, it is unclear whether the considerations for re-rating this study were consistently evaluated in all of the included studies.

Similarly, Mandel *et al*. (1995) and Travier *et al*. (2002) were re-rated from "High" to "Medium" study quality, for which US EPA's explanation was that a "[m]edium rating [was] assigned due to use of occupation in dry cleaning industry as a surrogate of Perc exposure" (US EPA, 2020c). Again, this issue with exposure measurement should have been already accounted for in the initial rating of Metric 4 (Measurement of Exposure).

3.2.4 Meta-analysis Methodology

The Draft Risk Evaluation provides little information regarding how the meta-analysis was conducted. As discussed above, there is no information on how studies were selected. There is also no information on whether any sensitivity analyses were conducted.

In addition to the issues with data quality of the five studies included in the meta-analysis, the study designs among them are different. There are three occupational case-control studies (Purdue *et al*., 2017; Vlaanderen *et al*., 2013; Dosemeci *et al*., 1999), one cohort study (Silver *et al*., 2014), and one study measuring residential exposure through contaminated drinking water (Aschengrau *et al.*, 1993). The risk metrics reported in these studies included ORs, an HR, a standardized mortality ratio, and a risk ratio, which make the studies less comparable among each other. In addition, the studies likely varied in terms of study population, exposure measurements and contrasts, and confounder adjustments.

In conclusion, similar to the bladder cancer risk evaluation, while US EPA evaluated the quality of most of the identified studies, it did not fully consider how study quality issues (*i.e*., exposure measurement error and confounding) may have impacted the interpretation of the results.

US EPA has not demonstrated even weak positive association of kidney cancer from and PCE exposure.

4 Conclusions

The methodology used to evaluate epidemiology studies of PCE and bladder and kidney cancer in the Draft Risk Evaluation was not scientifically robust and does not constitute a systematic review. Although it appears that the epidemiology studies identified do not support an association between PCE and either bladder or kidney cancer, US EPA's conclusion would be strengthened if robust, transparent systematic reviews of all relevant studies are conducted for each endpoint.

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Tables

Table 1 Summary of US EPA Data Quality Evaluation of PCE Bladder Cancer Epidemiology Studies Included in the 2012 IRIS Assessment and the 2020 Draft Risk Evaluation

Study	Metric															Overall	Score
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15		
	Participant Selection	Attrition	Comparison Group	Measurement of Exposure	Exposure Levels	Temporality	Outcome Measurement/ Characterization	Reporting Bias	Covariate Adjustment	Covariate Characterization	Co-exposure Confounding	Study Design and Methods	Statistical Power	Reproducibility of Analyses	Statistical Models		
Studies reviewed in the 2012 IRIS Assessment																	
Anderson *et al*., 1999	H	H	M	L	L	H	H	H	M	M	L	M	M	M	M	M	1.7
Aschengrau *et al*., 1993	H	M	H	L	M	M	H	L	H	L	M	M	M	M	M	M	1.8
Blair *et al*., 2003	H	M	H	L	L	H	M	M	M	M	L	M	M	M	M	M	2.0
Calvert *et al*., 2011	M	H	H	L	L	M	H	H	M	M	L	M	M	M	M	M	1.8
Lynge and Thygesen, 1990	M	M	M	L	L	L	M	M	M	L	L	M	M	L	M	L	2.3
Lynge *et al*., 2006	H	M	H	M	L	M	H	H	M	M	M	M	M	M	M	M	1.7
Pukkala *et al*., 2009	H	H	H	L	L	M	H	H	M	H	L	M	M	M	M	M	1.7
Siemiatycki, 1991	H	H	H	L	M	L	H	H	H	M	M	M	M	M	M	M	1.7
Selden and Ahlborg, 2011	H	H	H	M	L	M	H	M	M	M	L	M	M	M	M	M	1.8
Sung *et al*., 2007	H	H	H	U	B	H	H	H	H	H	L	M	M	M	M	U	0.0
Travier *et al*., 2002	H	H	H	L	L	H	H	H	M	H	L	M	M	M	M	M	1.6
Wilson *et al*., 2008	H	H	H	L	L	M	H	M	M	M	L	M	M	M	M	M	1.8
Additional Studies Reviewed in the 2020 Draft Risk Evaluation																	
Bove *et al.*, 2014	H	H	H	L	M	H	H	H	M	M	M	M	M	M	M	H	1.6
Christensen *et al.*, 2013	M	M	M	L	M	M	M	H	H	M	L	M	M	M	L	M	2.0
Hadkhale *et al*., 2017	H	H	H	M	M	M	M	H	M	M	M	M	M	M	M	M	1.7
Lipworth *et al.*, 2011	H	H	H	M	M	M	M	H	H	H	M	M	M	M	M	H	1.6
Silver *et al.*, 2014	M	H	H	M	L	M	H	H	M	M	L	M	M	M	M	M	1.8

Notes:
B = Blank; H = High (light grey shaded); L = Low (darkest grey shaded); M = Medium (second darkest grey shaded); PCE = Perchloroethylene; U = Unacceptable (pink shaded); US EPA = US Environmental Protection Agency.
Metrics 16-22 are not shown because none of the studies were rated for those metrics.

For those studies with an overall "U" rating, US EPA noted: "Consistent with our *Application of Systematic Review in TSCA Risk Evaluations* document, if a metric for a data source receives a score of Unacceptable (score = 4), EPA will determine the study to be unacceptable. In this case, one or more of the metrics were rated as unacceptable. As such, the study is considered unacceptable and the score is presented solely to increase transparency" (US EPA, 2020c).

Table 2 Summary of US EPA Data Quality Evaluation of PCE Kidney Cancer Epidemiology Studies Included in the 2012 IRIS Assessment and the 2020 Draft Risk Evaluation

Study	Metric															Overall	Score
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15		
	Participant Selection	Attrition	Comparison Group	Measurement of Exposure	Exposure Levels	Temporality	Outcome Measurement/ Characterization	Reporting Bias	Covariate Adjustment	Covariate Characterization	Co-exposure Confounding	Study Design and Methods	Statistical Power	Reproducibility of Analyses	Statistical Models		
Studies reviewed in the 2012 IRIS Assessment																	
Anderson *et al.*, 1999	H	H	M	L	L	H	H	H	M	M	L	M	M	M	M	M	1.7
Asal *et al.*, 1988	M	M	H	L	L	M	H	M	H	M	M	M	M	M	M	M	1.8
Aschengrau *et al.*, 1993*	H	M	H	L	M	M	H	L	H	L	M	M	M	M	M	M	1.8
Auperin *et al.*, 1994	H	H	H	U	U	L	M	H	H	L	L	M	M	M	M	U	2.1
Blair *et al.*, 2003	H	M	H	L	L	H	M	M	M	M	L	M	M	M	M	M	2.0
Calvert *et al.*, 2011	M	H	H	L	L	M	H	H	M	M	L	M	M	M	M	M	1.8
Chang *et al.*, 2003	H	H	H	U	L	H	M	H	H	M	NR	M	M	M	M	U	1.7
Delahunt *et al.*, 1995	M	H	M	L	L	L	H	M	L	M	L	M	M	M	M	M	2.1
Dosemeci *et al.*, 1999*	H	M	M	M	L	L	H	M	M	M	M	M	M	M	M	M	1.9
Ji *et al.*, 2005b	H	H	H	L	L	M	H	H	H	M	L	M	M	M	M	M	1.7
Lynge and Thygesen, 1990	M	M	M	L	L	L	M	M	M	L	L	M	M	L	M	L	2.3
Lynge *et al.*, 2006	H	M	H	M	L	M	H	H	M	M	M	M	M	M	M	M	1.7
Ma *et al.*, 2009	M	M	M	L	M	M	M	L	H	M	L	M	M	M	M	M	2.1
Mandel *et al.*, 1995	H	M	H	L	L	H	H	H	H	M	M	M	M	M	M	M	1.6
McCredie and Stewart, 1993	M	H	M	L	L	M	M	H	H	L	L	M	M	M	M	M	2.0
Mellemgaard *et al.*, 1994	M	H	M	L	L	H	H	H	M	M	L	M	M	M	M	M	1.8
Pesch *et al.*, 2000a	H	M	H	L	M	M	H	H	H	H	L	M	M	M	M	M	1.7
Pukkala *et al.*, 2009	H	H	H	L	L	M	H	H	M	H	L	M	M	M	M	M	1.7
Schlehofer *et al.*, 1995	M	H	L	U	U	M	H	L	H	M	L	M	M	M	M	U	2.1

Study	Metric															Overall	Score
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15		
	Participant Selection	Attrition	Comparison Group	Measurement of Exposure	Exposure Levels	Temporality	Outcome Measurement/ Characterization	Reporting Bias	Covariate Adjustment	Covariate Characterization	Co-exposure Confounding	Study Design and Methods	Statistical Power	Reproducibility of Analyses	Statistical Models		
Selden and Ahlborg, 2011	H	H	H	M	L	M	H	M	M	M	L	M	M	M	M	M	1.8
Sung *et al*., 2007	H	H	H	U	B	H	H	H	H	H	L	M	M	M	M	U	0.0
Travier *et al*., 2002	H	H	H	L	L	H	H	H	M	H	L	M	M	M	M	M	1.6
Wilson *et al*., 2008	H	H	H	L	L	M	H	M	M	M	L	M	M	M	M	M	1.8
Additional Studies Reviewed in the 2020 Draft Risk Evaluation																	
Bove *et al.*, 2014	H	H	H	L	M	H	H	H	M	M	M	M	M	M	M	H	1.6
Christensen *et al.*, 2013	M	M	M	L	M	M	M	H	H	M	L	M	M	M	L	M	2.0
Lipworth *et al.*, 2011	H	H	H	M	M	M	M	H	H	H	M	M	M	M	M	H	1.6
Purdue *et al.*, 2017*	H	M	H	M	M	H	H	H	H	H	M	M	M	M	M	H	1.4
Silver *et al.*, 2014*	M	H	H	M	L	M	H	H	M	M	L	M	M	M	M	M	1.8
Vlaanderen *et al.*, 2013*	H	H	H	L	M	H	H	H	M	M	M	M	M	M	M	M	1.6

Notes:
H = High (light grey shaded); L = Low (darkest grey shaded); M = Medium (second darkest grey shaded); NR = Not Rated; PCE = Perchloroethylene; U = Unacceptable (pink shaded); US EPA = US Environmental Protection Agency.
*Included in the meta-analysis for bladder cancer in the Draft Risk Evaluation.
Metrics 16-22 are not shown because none of the studies were rated for those metrics.
For those studies with an overall "U" rating, US EPA noted: "Consistent with our *Application of Systematic Review in TSCA Risk Evaluations* document, if a metric for a data source receives a score of Unacceptable (score = 4), EPA will determine the study to be unacceptable. In this case, one or more of the metrics were rated as unacceptable. As such, the study is considered unacceptable and the score is presented solely to increase transparency" (US EPA, 2020c).

COMMENTS ON THE SECTIONS DEALING WITH GENOTOXICITY IN THE U.S. EPA DRAFT RISK EVALUATION FOR PERCHLOROETHYLENE

EPA Document # EPA-740-R1-8011

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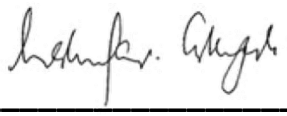

July 1, 2020

COMMENTS ON SECTIONS DEALING WITH GENOTOXICITY IN THE U.S. EPA DRAFT RISK EVALUATION FOR PERCHLOROETHYLENE - EPA Document # EPA-740-R1-8011

The U.S. EPA's draft risk evaluation (DRE) concluded that "PCE appears to induce liver tumors through multiple, potentially interdependent modes of action mediated largely by metabolites, including mutagenicity , epigenetic changes, cytotoxicity and oxidative stress, PPARα activation, and possibly also through other changes in gene expression." Regarding the male rat kidney tumors, the DRE concluded that "… the available data provide evidence for mutagenicity as a likely mode of action for renal carcinogenicity induced by PCE …".

Genotoxicity assessment on PCE in section 3.2.3.2.1 of the DRE was primarily based on prior reviews prepared by the EPA (2012), IARC (2014), and ATSDR (2019). The following comments on the DRE sections dealing with the potential role of mutagenicity in the mouse liver and rat kidney tumor induction are focused on the following aspects: 1) Terminology used in the DRE, 2) Mode of Action Framework, 3) Genotoxicity/Mutagenicity Evaluation in Tumor Target Tissues, 4) Role of Metabolites, 5) New Human Biomonitoring Studies, 6) Miscellaneous Issues, and 6) Concluding Comments.

1. <u>Terminology</u>:

Prior to commenting on the role (or lack thereof) of mutagenicity in PCE induced liver and kidney tumors, it is important to distinguish the terms "mutagenicity" and "genotoxicity" especially when these data are used for risk assessment purposes. These two terms are often mistakenly used synonymously, including in the DRE. For example, on Page 292, the DRE refers to genotoxicity of PCE and/or its metabolite as contributing to liver and kidney tumors and further refers to the mode of action (MoA) as genotoxic MoA. In other instances, the DRE identifies mutagenicity as contributing to the MoA (e.g., page 288). Genotoxicity describes a continuum of events affecting DNA that may or may not lead to mutations. Mutagenicity, on the other hand, refers to heritable changes in the DNA sequence that are transmitted from one cell to the next or from parent to the offspring. Mutations, by definition, are apical effects and are not repairable. Mutations in certain genes (e.g., oncogenes, tumor suppressor genes, etc.) are thought to play a critical role along the pathway to tumorigenesis. On the other hand, a vast majority of the genotoxicity assays are merely indicator assays and do not necessarily inform mutagenicity *per se*. Examples of such assays include DNA binding, DNA strand breaks, unscheduled DNA synthesis (UDS), etc. Similarly, routine assays for chromosomal aberrations (including the micronucleus test) do not evaluate the transmissibility of the aberration(s) to the daughter cell. Unlike mutations, the endpoints measured in the above assays are repairable by cellular defense mechanisms and as such they may or may not lead to an adverse outcome, such as mutations in genes critical to carcinogenesis. For the purpose of cancer MoA, mutagenicity should be the endpoint of interest, rather than any genotoxicity endpoint.

As stated earlier, the DRE depended heavily on prior reviews of genotoxicity data including the one conducted by the EPA (2012). Of the nearly 40 studies listed in Table 4-39 of this EPA review under the header "Genotoxicity of tetrachloroethylene – mammalian systems (in vitro and in vivo)", only one in vitro study examined mutagenicity as an endpoint. Similarly, of the nearly 20 studies evaluating genotoxicity of the trichloroacetic acid. a metabolite of PCE, in mammalian in vitro and in vivo systems (Table 4-41), only one in vitro study evaluated mutation as an endpoint. Thus, the preponderance of data from mammalian test systems for PCE and its metabolites comes from genotoxicity endpoints that may or may not lead to the manifestation of mutations in the tumor target tissue. It is acknowledged that considerable database exists for PCE and several of its metabolites where mutagenicity was evaluated in non-mammalian in vitro test systems, primarily in bacteria. However, these in vitro results should be contextualized regarding their value to predict effects in the tumor target tissue. For example, a positive finding in a bacterial mutagenicity assay for a substance would have more weight if a follow-up in vivo study is conducted in the tissue of interest, preferably using a mutagenicity endpoint.

2. Mode of Action Framework:

A glaring deficiency of the DRE is its failure to follow the International Program on Chemical Safety (IPCS) framework for the analysis of available data, as recommended in the EPA's Guidelines for Carcinogen Risk Assessment (EPA, 2005), to determine whether a mutagenic MoA is plausible for the induction of liver and kidney tumors by PCE. It is noteworthy that just because a substance is positive in mutagenicity assays and the same substance induces tumors in a rodent bioassay, it does not necessarily mean that the substance is operating through a mutagenic MoA for tumor induction. Per the IPCS framework, among other things, the dose-response and temporality of the key events in the proposed MoA should be systematically examined to determine whether the MoA is biologically plausible. For a mutagenic MoA, the generally accepted key events include a) DNA reactivity, b) mutation induction, and c) cell proliferation to enable clonal expansion of mutations, eventually leading to the adverse outcome (i.e., tumor induction). The dose-response and temporality for these key events should be examined, ideally in the tumor target tissue. No such attempt was made in the DRE for this MoA either for the liver or kidney tumors.

3. Genotoxicity Evaluation in Tumor Target Tissue:

a. *Mouse Liver Tumors*: There are only 4 studies that examined the effects of PCE on the mouse liver DNA - two investigated DNA binding (Schuman et al., 1980; Mazullo et al., 1987), one studied DNA strand breaks using the comet assay (Cederberg et al., 2010) and one study examined micronucleus induction (Murakami and Horikawa, 1995). No DNA binding was observed in the study by Schuman et al. (1980) following 6 h inhalation exposure up to 600 ppm PCE (3X the tumorigenic concentration) or a single oral gavage dose of 500 mg/kg (tumorigenic dose). Although Mazullo et al. (1987) reported DNA binding in the mouse liver following i.p. injection of 1.4 mg/kg PCE, these results were attributed to the likely contamination of the DNA samples by RNA (EPA, 2012).

In the Cederberg et al. (2010) publication, a marginal increase in DNA strand breakage was reported following oral dosing of mice with 1000 or 2000 mg/kg PCE (2 doses, 24 h apart). However, as discussed by the EPA (2012), the interpretation of these results were questioned in a number of publications based on statistical and biological considerations. Murakami and Horikawa (1995) identified a small (<2-fold), but significant, increase in micronucleated hepatocytes following i.p. dosing of mice with 1000 or 2000 mg/kg PCE. However, the authors did not provide any information on their laboratory's historical negative control data in order to determine whether the values observed among their treated groups wee within or outside of the historical range. This information is critical given the small increase in the micronucleus frequencies observed in the treated groups.

In summary, the above studies do not provide convincing evidence for the genotoxicity of PCE or its in vivo metabolites in the livers of mice.

b. *Rat Kidney Tumors*: There is paucity of data on the genotoxicity of PCE in male rat kidneys, with the DRE listing only two studies. In one study, PCE did not induce DNA strand breaks in male Fischer 344 rat kidney following oral dosing with 1000 mg/kg/day for 7 days (Potter et al., 1996). In the study by Mazullo et al. (1987), a weak DNA binding activity was reported in male Wistar rat kidneys at 22 h following i.p. injection with 8.70 µM/kg PCE. However, as mentioned earlier, the validity of these results was questioned based on the likely contamination of DNA by RNA (EPA, 2012). Thus, the available data do not provide convincing evidence for PCE-induced effects on the DNA of this tumor target tissue.

4. <u>Role of Metabolites</u>:

a. *Mouse Liver*: The DRE lists the following liver metabolites of PCE resulting from glutathione conjugation: S-(1,2,2-trichlorovinyl) glutathione (TCVG), N-acetyl-S-(1,2,2-trichlorovinyl)-L-cysteine (NAcTCVC), S-(1,2,2-trichlorovinyl)-L-cysteine (TCVC) and TCVC sulfoxide (TCVCS). All these metabolites, plus the oxidative metabolites (PCE-oxide and trichloroacetyl chloride), were stated to induce mutagenicity in the Ames bacterial reverse mutation assay. Based in part on these results, the DRE came to the conclusion for mutagenicity playing a role in the MoA for PCE-induced mouse liver tumors.

It is worth pointing that TCVG was mutagenic only in the presence of subcellular fractions from rat kidney, but not rat liver, due to the very low or non-detecable levels of γ-glutamyltransferase (GGT) in the liver fractions (Vamvakas et al., 1989). Without GGT present in liver cells, TCVG cannot be metabolized to TCVC, which is necessary for the formation of the reactive (and potentially mutagenic) metabolites. No data exists on the ability of mouse liver microsomes to activate TCVG to a bacterial mutagen.

The primary issue with the extrapolation of this in vitro data on the metabolites is that it is not known whether PCE treated mice do indeed generate adequate quantities of the above metabolites to elicit a mutagenic response in this tissue. In addition, as

discussed previously, assays for DNA binding in the livers of mice treated with PCE did not provide definitive evidence for this initial key event in the proposed MoA, raising the possibility that the concentrations of these metabolites might not be high enough to reach the nuclear DNA and elicit a mutagenic response in the liver.

b. Rat Kidney: The renal metabolites TCVG, TCVC, TCVCS, and NAcTCVC have been listed by the DRE as showing mutagenic activity in vitro in bacteria. PCE itself is not mutagenic in TA100 either on its own or in the presence of rat kidney microsomes. Furthermore, no mutagenic activity of PCE was observed In the presence of rat kidney microsomes supplemented with GSH. This is most likely due to insufficient levels of TCVG formation (Vamvakas et al., 1989a). However, these authors observed a clear mutagenic response following supplementation of the above pre-incubation mixture with GSH-transferase, suggesting the generation of higher concentrations of TCVG by the enzyme. Inhibition of the β-lyase activity in the above pre-incubation mixture by aminooxyacetic acid (AOAA; a β-lyase inhibitor) or serine-borate; a GGT inhibitor) significantly reduced the mutagenic activity, indicating a role for these enzymes in the mutagenicity of TCVG.

   TCVC was mutagenic in TA100 without any external metabolic activation and addition of rat kidney microsomes or cytosol did not enhance the mutagenic response (Dekant et al., 1986; Irving and Elfarra, 2013). Addition of AOAA, the β-lyase inhibitor, to the preincubation mixture significantly reduced/abrogated the mutagenic response of TCVC, suggesting a role for bacterial β-lyase in the biotranformation of TCVC into a DNA reactive intermediate (Dekant et al., 1986). These authors also demonstrated approximately 4-fold higher levels of β-lyase activity in Salmonella TA100 compared to rat kidney cytosol or microsomes. Vamvakas et al. (1989b) demonstrated induction of unscheduled DNA synthesis by TCVC in a porcine cell line (LLC-PK1) exhibiting the characteristics of proximal tubular cells, providing further support to the DNA reactivity of this cysteine conjugate in cultured cells.

   The above studies provided interesting insights into the bioactivation of the glutathione conjugate of PCE in the in vitro test systems. However, the relevance of these findings to the manifestation of mutagenicity in the rat kidney following PCE treatment requires further elucidation. For example, assays for DNA binding and DNA strand breakage in kidneys of rats treated with PCE have been negative (Mazullo et al., 1987; Potter et al., 1986). Thus, it is possible that the above bacterial mutagenic metabolites might not be generated at high enough concentrations in PCE treated rat kidneys to interact and damage the nuclear DNA .

5. New Human Biomonitoring Studies:

Three new human biomonitoring studies that investigated the genotoxic potential of PCE exposure in peripheral blood lymphocytes were reviewed in the DRE.

Everatt et al (2013) reported increases in micronucleus frequency and DNA strand breakage (via comet assay) in PCE exposed dry-cleaning workers (mean PCE concentration of approximately 4.63 ppm) compared to controls (supermarket workers). Although chromosomal aberration frequency was not increased in PCE exposed workers, multiple regression analyses showed a significant association between duration and frequency of exposure to PCE vs. chromosomal aberration frequency. The reported increase in the micronucleus frequency (<2-fold over the control value) is rather surprising given the lack of an effect on chromosomal aberration frequency in the same study. Typically, such discordant results signify mitotic spindle disturbances since micronuclei can result either from lagging acentric fragments resulting from chromosomal breakage or lagging whole chromosomes from spindle malfunction. Speit et al. (2011) and Speit (2013) presented persuasive arguments against the validity of human biomonitoring studies that use the type of cytokinesis-block micronucleus assay used by Everatt et al. for hazard evaluation. These authors argue that the protocol used for the detection of micronuclei in the above assay do not actually assess the in vivo effect of the occupational exposure. Even if the micronuclei scored by Everett et al. resulted from an effect on the mitotic spindle, there is no evidence linking induced aneuploidy with carcinogenic effect (Tweats et al., 2019). Finally, Everatt et al. used mean of individual values of the comet tail lengths for statistical comparison, which is not a recommended method for such comparisons. For example, the OECD guideline for the in vivo comet assay (OECD 2016) recommends the comparison of the mean of the individual median values. Given these uncertainties, the results reported by Everatt et al. should be interpreted with caution for their relevance, if any, in the PCE risk assessment.

In the second study, Tucker et al. (2011) assessed chromosomal aberrations in peripheral blood lymphocytes of dry-cleaning workers exposed to PCE (TWA 3.8 ppm) as compared to control laundry workers (PCE TWA <0.02 ppm). These authors concluded that there was no significant effect of PCE exposure on chromosome damage, even for translocations which measured accumulated exposure. The statement in the DRE that the dry-cleaning workers had significant increase in the frequencies of acentric fragments is not consistent with the Tucker et al. who only stated that "…PCE levels were significantly correlated with acentric fragments…" and who further stated in their conclusions that the increases in fragments were non-significant. Thus, these results reinforce the lack of a significant effect on chromosomal aberrations in the study by Everatt et al. at comparable exposure concentration of PCE.

In the third study, DNA strand breakage using the comet assay was performed on the peripheral blood lymphocytes of dry-cleaning workers (N=33) and healthy control subjects from general population (N= 26; Azmi et al., 2017). The authors reported a significant increase in DNA damage in the exposed group as compared to the controls for all parameters evaluated (% DNA in tail, Tail length, Tail Moment, and Olive Tail Moment). The primary weakness of this study was lack of information on PCE exposure levels as appropriately identified by the DRE. In addition, the authors did not provide any information on the length of time (days, weeks, or months) during which the samples from these 59 subjects were collected and analyzed and how they controlled for the temporal

variability (e.g., balancing the samples for analysis, batch to batch variation in reagents, any seasonal effects, etc.).

There are other human biomonitoring studies that investigated sister chromatid exchanges and chromosomal aberrations in lymphocytes in PCE exposed workers and there is no evidence for a genotoxic effect in these studies (EPA, 2012). Overall, the evidence for genotoxicity from human biomonitoring studies is not conclusive given some of the uncertainties as indicated above.

6. Miscellaneous Issues:

The DRE included results of studies that investigated morphological cell transformation (Page 272, line 7014) under genotoxicity studies. This test is not usually considered to be a genotoxicity assay and as such should not be included under this section.

The DRE also reviewed several studies assessing the induction of sister chromatid exchanges (SCE). SCE induction is no longer considered to represent a *bona fide* genotoxicity outcome as reflected in the deletion of a guideline for this assay by the OECD.

7. Concluding Comments:

The DRE did not present sufficient evidence for a mutagenic MoA in the etiology of PCE-induced mouse liver tumor or male rat kidney tumors. A formal IPCS framework was not presented to support of a mutagenic MoA. There was no discussion in the DRE on the dose and temporality of the key events in a mutagenic MoA. The available data are not supportive of the initial two key events in a mutagenic MoA, i.e., DNA reactivity and DNA damage in the tumor target tissues. While some of the liver and kidney metabolites of PCE are in vitro mutagens/genotoxicants, it is uncertain whether these metabolites are generated at adequate levels in these tumor target tissues to reach and damage nuclear DNA. Thus, the case for a mutagenic MoA is relatively weak and a compelling case can be made for an alternate MoA that does not involve mutagenesis as an early key event for both the mouse liver tumors and male rat kidney tumors.

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PPARα MOA for Liver Tumors in Tetrachloroethylene (PCE)-exposed Mice

The key events for the PPARα MOA following exposure and systemic absorption of PCE are assumed as follows:

1. Activation of PPARα by trichloroacetic acid (TCA)
2. PPARα-dependent regulation of genes of proliferation and apoptosis.
3. PPARα-dependent regulation of fatty acid metabolism genes.
4. Peroxisome proliferation.
5. Hepatocyte oxidative stress.
6. Perturbation of cell proliferation and/or apoptosis.
7. Selective clonal expansion.

A summary of the evidence in animals and humans for the key events are presented in Table 1 and 2 for PCE and TCA, respectively.

Strength, Consistency and Specificity of Association

Trichloroacetic acid (TCA), but not PCE, activate mouse and human PPARα in a COS-1 cell transfection assay *in vitro*, with no difference between species in terms of receptor sensitivity or maximal responsiveness (Zhou and Waxman, 1998; Maloney and Waxman, 1999). TCA produced little response with PPARγ. Cultured human hepatocytes transiently transfected with mouse PPARα and mouse RXRα displayed increased expression of PPARα, and increased PPRE-reporter activity when treated with 4mM TCA (Walgren *et al.*, 2000b). A single oral dose of PCE (30 to 1,000 mg/kg) to male $B6C3F_1$/J mice resulted in a dose-dependent induction of peroxisomal fatty acid β-oxidation gene expression in the liver 24 hours later. The transcriptional changes were strongly correlated with PCE administered dose and with TCA levels in the liver (Zhou *et al.*, 2017).

Following exposure to TCA in drinking water for seven days, induction of CYP4A and acyl-CoA oxidase (ACO) protein expression and increased palmitoyl CoA oxidase (PCO) enzyme activity was observed in male SV129 wild-type mice but not in the PPARα-null mice (Laughter *et al.*, 2004). In a 14-day drinking water study, increased PP-A protein was seen in the livers of male $B6C3F_1$ mice treated with TCA (DeAngelo *et al.*, 1989). CYP4A protein expression was increased in liver microsomes from Swiss-Webster mice dosed orally with 1,000 mg/kg PCE for seven days (Philip *et al.*, 2007).

Peroxisome proliferation occurs in the livers of mice, but not in rats, exposed to PCE. Increased PCO activity was noted in the livers of male $B6C3F_1$ mice, but not in Sprague-Dawley rats, given oral gavage doses of 1,000 mg/kg PCE for 10 days (Goldsworthy and Popp, 1987). In the study by Odum *et al.* (1988), the number of peroxisomes, PCO activity (up to 3.7-fold), and centrilobular lipid accumulation were observed in the livers of male and female $B6C3F_1$ mice exposed by inhalation to 200 or

400 ppm PCE for 28 days. In contrast, PCO activity was only slightly increased (1.3-fold) in the livers of similarly exposed male and female Sprague-Dawley rats.

TCA has also been shown to increase peroxisome proliferation in the livers of mice. In a 14-day drinking water study, increased PCO activity was seen in male $B6C3F_1$ mice treated with TCA (statistically significant at 31 mM or 442 mg/kg), with an induction of 959% above controls (DeAngelo *et al.*, 1989). TCA also increased the peroxisome number and volume and induced the PP-A protein in the liver. Three other strains of mice (Swiss-Webster, C3H, and C57BL/6) also showed increased PCO activity when given 12 or 31 mM TCA for 14 days (DeAngelo *et al.*, 1989). Increased liver weights and peroxisomal β-oxidation was reported in mice given oral doses of 500 mg/kg TCA for 10 days, but not after a single dose (Nelson *et al.*, 1989). Parrish *et al.* (1996) showed a dose-related increase in ACO activity in male $B6C3F_1$ mice given 0, 0.1, 0.5 or 2.0 g/L g/L TCA in drinking water for 3 or 10 weeks, which was statistically significant in all dose groups at both 3 and 10 weeks of treatment. Peroxisome volume densities and PCO activity were increased dose-dependently in the livers of male Swiss mice given oral doses of 50 to 200 mg/kg TCA (in corn oil) for up to 10 days (Elcombe, 1985). The increase in PCO activity was 4.8-fold after 10 days dosing with 200 mg/kg TCA. Increased PCO activity was also seen in isolated hepatocytes from male Swiss mice treated with TCA *in vitro* (Elcombe, 1985). PCO activity was increased 285% in $B6C3F_1$ mice (both sexes) dosed orally with 500 mg/kg TCA; relative liver weights were also increased (Goldsworthy and Popp, 1987).

PCO activity was consistently elevated in the livers of $B6C3F_1$ mice administered 0.5 g/L (68 mg/kg-day) and 5 g/L or (602 mg/kg-day) TCA in drinking water at 4, 15, 30, 45, and 60-weeks of exposure. The range of PCO activity was 129 to 260% and 326 to 575% for the 0.5 and 5 g/L dose groups, respectively, compared to controls (DeAngelo et al., 2008). In a separate study, PCO activity was also increased (352 to 1,890%) in the liver of $B6C3F_1$ mice administered 4.5 g/L TCA at 15, 30, 45, and 104 weeks of exposure (DeAngelo *et al.*, 2008). Cell proliferation (labeling index of nuclei) was not consistently observed in the livers at the various time point throughout the study. There was significant increase in the 5 g/L TCA mice at 30 and 45 weeks, and the 0.5 g/L group was significantly increased at 60 weeks; and the 4.5 g/L group was significantly increased at 45 weeks only.

Rat TCA studies have shown mixed results on peroxisome proliferation in the liver. There was no increased PCO activity in male Sprague-Dawley rats, and only a modest increase in the F344 rat (163%) and Osborne-Mendel rat (238%) when given 31 mM TCA in the drinking water (DeAngelo *et al.*, 1989). However, peroxisome volume densities and PCO activity were increased dose-dependently in the livers of male Wistar rats given oral doses of 50 to 200 mg/kg TCA (in corn oil) for up to 10 days (Elcombe, 1985). The increase in PCO activity was 6.5-fold after 10 days dosing with 200 mg/kg TCA. Increased PCO activity was also seen in isolated hepatocytes from male Wistar rats treated with TCA *in vitro* (Elcombe, 1985). PCO activity was increased 280% in F344 rats (both sexes) dosed orally with 500 mg/kg TCA; relative liver weights were also increased (Goldsworthy and Popp, 1987). Zanelli *et al.* (1996) showed increased PCO

and P-450 4A-dependent activities in the livers of male Sprague-Dawley rats given intraperitoneal injections of 400 mg/kg TCA for three days (Zanelli *et al.*, 1996).

Hepatomegaly has been consistently observed in mice exposed to PCE and TCA. This effect can occur from increases in cell number or cell size. In the case of PCE, some of the hepatomegaly can be attributable to increased cell size. Schumann *et al.* (1980) reported that DNA content in $B6C3F_1$ mice was significantly decreased at doses as low as 100 mg/kg tetrachloroethylene for 11 days. This effect was not seen in Sprague-Dawley rats exposed to doses as high as 1,000 mg/kg. A dose-dependent decrease in DNA content (mg/g liver) was also seen in Swiss-Webster in mice dosed up to 1,000 mg/kg PCE for six weeks (Buben and O'Flaherty, 1985). In $B6C3F_1$ mice given 0.3, 1.0 or 2.0 g/L TCA in their drinking water for 14 days, liver weights were increased in a dose-dependent manner and was generally accompanied by decreases in DNA content (Sanchez and Bull, 1990). Evidence that the hepatomegaly from PCE (and thus TCA) exposure comes from the PPARα-null mice study by Laughter *et al.* (2004). Centrilobular hepatocyte hypertrophy was observed in wild-type, but not PPARα-null mice, exposed to 2.0 g/L TCA in their drinking water for seven days.

A dose-related increase in DNA synthesis was observed in $B6C3F_1$ mice, but not in Sprague-Dawley rats, given oral doses of 100, 250, 500 or 1,000 mg/kg PCE for 11 days (Schumann *et al.*, 1980). Increased DNA synthesis was observed in $B6C3F_1$ mice, but not in Sprague-Dawley rats, given 12 doses of 500 mg/kg PCE for 16 days (Schumann *et al.*, 1980). A dose-dependent elevation in [^{3}H] thymidine incorporation in liver cells was observed in Swiss-Webster mice dosed with 150, 500 or 1,000 mg/kg PCE for seven days and remained significantly elevated in the 500 and 1,000 mg/kg groups after 14 days of dosing (Philip *et al.*, 2007). After 30 days of dosing, incorporation of [^{3}H]thymidine in liver cells from the treated groups was reduced to near control levels. The 500 and 1,000 mg/kg mice exhibited significantly greater number of hepatocytes in the S-phase after 7 and 14 days of dosing compared to controls; the number of cells in S-phase was also reduced to near control levels by day 30.

Cell proliferation in the liver has been shown to occur in mice given TCA in drinking water. Male $B6C3F_1$ mice and male and female Swiss-Webster mice were given 0, 0.3, 1 or 2 g/L TCA in their drinking water for up to 14 days (Sanchez and Bull, 1990). Incorporation of [^{3}H]thymidine into hepatic DNA was significantly increased at 2 g/L TCA on day 5 and 14. A dose-related increase in the incorporation of [^{3}H]thymidine into hepatocytes was also seen in male and female $B6C3F_1$ given oral doses of 0, 100, 250, 500 or 1000 mg/kg TCA for 11 days (Dees and Travis, 1994).

Stauber and Bull (1998) conducted a study in which male $B6C3F_1$ mice were given in their drinking water 2 g/L TCA for 38 and 50 weeks, respectively. The pretreated mice were then given water containing up to 2.0 g/L TCA for two additional weeks to determine whether cell proliferation in the normal liver or tumors induced by TCA were dependent on continued treatment. TCA caused a small but significant increase in hepatocyte division rates early in treatment. However, this increase was sustained for only 28 days with TCA. At 52 weeks of treatment, rates of cell division in

the normal hepatocytes of mice treated with TCA were significantly decreased relative to those observed in control mice at 52 weeks. In contrast, rates of cell division within TCA-induced altered hepatic foci and tumors were very high and appeared to be independent of continued treatment. TCA seemed to produce little, if any, direct stimulation of the replication of initiated cell populations. Cells within altered hepatic foci and tumors appear to be resistant to the inhibition of cell division that chronic treatment with TCA appears to produce in normal hepatocytes, providing some selective growth advantage to initiated cells. TCA has been shown to stimulate the growth of hepatocytes from non-exposed $B6C3F_1$ mice *in vitro*, indicating that TCA is acting primarily by increasing the clonal expansion of a specific group of initiated cells within the liver of the $B6C3F_1$ mouse (Stauber *et al.*, 1998). TCA produced a dose-dependent transformation of hepatocytes from anchorage-dependent to anchorage-independent growth. These cells did not display immunoreactivity to either *c-Jun* or *c-Fos* oncogene protein antibodies (as opposed to dichloroacetic acid), which is reflective in the liver tumors induced by TCA (Stauber and Bull, 1997).

Ge *et al.* (2001) found that the promoter region of the protoconcogene *c-myc* gene was hypomethylated 72 and 96 hours (but not earlier) in liver cells from female $B6C3F_1$ mice given a single oral dose of 500 mg/kg TCA. Cell proliferation was also increased at 72 and 96 hours (but not earlier) postdosing, Earlier studies had shown that TCA induced hypomethylation of DNA and of the protooncogene, *c-myc*, in mouse liver (Tao *et al.*, 2000; Tao *et al.*, 1999) and that tumors promoted by TCA contained decreased levels of methylation (Tao *et al.*, 1998). Addition of methionine in the diet prevented the decrease in methylation of the *c-myc* gene induced by TCA (Tao *et al.*, 2000). An overall decrease in the content of 5-methylcytosine (5-MeC) in DNA and hypomethylation of specific genes have been observed as an early event in many human and animal tumors (Counts and Goodman, 1995; Robertson and Jones, 2000; Goodman and Watson, 2002).

Oncogene activation has also been reported in liver hepatic tissue of mice treated with TCA. In $B6C3F_1$ mice given 1 or 2 g/L TCA in drinking water for up to 52 weeks, *c-myc* expression in liver hyperplastic nodules was increased three-fold in TCA-treated animals compared to controls (Nelson *et al.*, 1990). *c-myc* expression was approximately six-fold higher in TCA-induced carcinomas compared to control tissue (controlling for non-specific binding). For the oncogenes *c-H-ras*, TCA treatment increased its expression in the carcinomas but not the hyperplastic nodules compared to the untreated controls. Tumors from mice initiated with MNU and promoted by TCA contained $\geq$ 50% of its hepatocytes essentially negative for the protooncogenes *c-myc* and *c-jun* (Latendresse and Pereira, 1997). Tao *et al.* (2000b) showed that the promoter regions of the *c-jun* and *c-myc* protooncogenes and expression of the mRNA and proteins of the two protooncogenes were increased in the TCA-promoted liver tumors.

TCA inhibited gap junction intercellular communication (GJIC) in mouse hepatocytes but not in rat hepatocytes, parelleling the *in vivo* liver tumor response data (Klaunig *et al.*, 1989). GJIP is highly correlated with tumor induction by PPARα agonists, although GJIC inhibition is not specific for PPARα agonists and may be a common process for other nongenotoxic carcinogens (Klaunig *et al.*, 2003).

A few studies have investigated whether exposure to TCA induces oxidative stress in the livers of mice. Austin *et al.* (1996) reported a slight increase in levels of 8-hydroxydeoxxyguanosine (8-OHdG) in liver nuclear DNA of male $B6C3F_1$ mice eight hours following a single oral dose of 300 mg/kg TCA. After exposure to up to 2 g/L TCA in drinking water for 3 or 10 weeks, there was no change in 8-OHdG levels in the nuclear DNA of the TCA-treated mouse livers at either time point (Parrish *et al.*, 1996). Interestingly, lipofucsin deposits were prominent in the livers of mice chronically treated with TCA, which would be an indication some oxidative stress (Bull *et al.*, 1990).

Increased cell proliferation and apoptosis ultimately leads to selective clonal expansion of altered hepatocytes and tumors. TCA has been shown to promote liver tumors in mice (Herren-Freund *et al.*, 1987; Bull *et al.*, 1990; Pereira *et al.*, 1997). Bull *et al.* (1990) found that if treatment of mice with 2 g/L TCA in drinking water was stopped at 37 weeks, there was a smaller number of total tumors in these mice at 52 weeks than in mice treated continuously for the entire 52-week period based on total dose administered. This would suggest that TCA-induced benign lesions regressed when treatment was stopped at 37 weeks. However, most of the tumors that remained in the stop-exposure group were hepatocellular carcinomas: the relative yield of hepatocellular carcinomas was more than twice that expected from continuous treatment. In an initiation-promotion protocol, 52 weeks of 20 mmol/L TCA in drinking water increased the yield of both hepatocellular adenomas and carcinomas in methylnitrosourea (MNU)-initiated mice (Pereira and Phelps, 1996). If treatment was suspended at 37 weeks, there was a significant reduction in the numbers and incidences of hepatocellular carcinomas at 52 weeks relative to initiated mice receiving continuous treatment for 52 weeks. Interestingly, although hepatocellular adenomas were at a higher incidence and multiplicity in initiated mice treated with TCA than in untreated initiated mice, they appeared to be insensitive to any change in the treatment period for TCA: the incidence of adenomas were essentially the same whether treatment was for 37 or 52 weeks, or in the 37-week stop exposure group.

Tumors promoted by TCA have been shown to be predominantly basophilic, lacked GST-π, and stained variably; usually more than 50% of the tumor hepatocytes were essentially negative for the other biomarkers (Latendresse and Pereira, 1997). In rodents, peroxisome proliferators lead to tumors that are histologically adenomas or carcinomas that are characterized as basophilic and have absence of γ-glutamyl transpeptidase expression and placental GST (Kraupp-Grasl *et al.*, 1990; Marsman and Popp, 1994; Rao *et al.*, 1986). Stauber and Bull (1997) also reported that TCA-induced liver tumors did not display immunoreactivity to c-Jun or c-Fos antibodies. The liver tumors induced by PCE have not been characterized.

Dose Response Concordance

There is inadequate information to assess a dose-response concordance between proposed key events and tumor response for PCE. However, data are available to

evaluate the dose-response concordance for TCA. In a 14-day drinking water study, increased PCO activity was seen in male $B6C3F_1$ mice (and three other strains) administered 1-5 g/L TCA in drinking water (DeAngelo *et al.*, 1989). PCO activity was increased in the livers of $B6C3F_1$ mice administered 0.5 g/L (68 mg/kg-day) or 5 g/L (602 mg/kg-day) of TCA in drinking water at time points up to study termination at 60 weeks. Liver tumors were significantly increased in both dose groups. Peroxisome proliferation and liver tumor induction showed a strong linear association (DeAngelo et al., 2008).

PCO activity was increased in mice treated with 0.5 g/L (68 mg/kg-day) or 5 g/L (602 mg/kg-day) of TCA. The doses that induce hepatocellular proliferation in mice corresponded to tumorigenic doses of TCA in DeAngelo et al. (2008). Thus, the doses of TCE that induce peroxisome proliferation in the livers of mice are also tumorigenic to the liver.

Temporal Relationships

A dose-dependent induction of peroxisomal fatty acid β-oxidation gene expression was observed in the livers of male $B6CeF_1$/J mice 24 hours after an oral gavage dose of PCE. The transcriptional changes strongly correlated with TCA levels in the liver (Zhou et al., 2017). Peroxisomal enzyme activities are increased in the livers of mice as early as 10 days of oral dosing with PCE (Elcombe, 1985; Goldsworthy and Popp, 1987). Increased expression of CYP4A protein was noted in liver microsomes from Swiss-Webster mice after seven days of dosing with 1,000 mg/kg PCE (Philips *et al.*, 2007).

Following 14 days of exposure to TCA in drinking water, $B6C3F_1$ mice exhibited increased peroxisomal enzyme activity, with increased peroxisomal number and size in the liver (DeAngelo *et al.*, 1989). Liver PCO activity was significantly increased above control values in male $B6C3F_1$ given 0.5 and 5 g/L TCA in their drinking water for 60 weeks, and in male $B6C3F_1$ given 4.5 g/L TCA in their drinking water for 104 weeks (DeAngelo *et al.*, 2008). In both studies, the increased PCO activity was sustained throughout the entire exposure period (60 and 104 weeks, respectively). Unlike wild-type mice, livers from PPARα-null mice exposed to 2.0 g/L TCA in drinking did not exhibit centrilobular hepatocyte hypertrophy, increased protein expression of CYP4A, increased ACO protein expression and PCO enzyme activity (Laughter *et al.*, 1994).

The temporal association between cell proliferation and/or apoptosis and tumors has not been well established. There are no data in rodents exposed by inhalation to PCE. In an oral gavage study, increased DNA synthesis was noted in $B6C3F_1$ mice given doses of 100 to 1,000 mg/kg PCE for 11 days (Schumann *et al.*, 1980). A time course study was conducted in Swiss-Webster mice given oral doses of 150, 500 or 1,000 mg/kg PCE. A dose-dependent elevation of cell proliferation in liver cells was observed after 7 and 14 days of dosing, but not at 30 days (Philips *et al.*, 2007). For TCA, increased DNA synthesis was observed in the liver of mice treated with TCA in their drinking water for

11 days (Dees and Travis, 1994), 14 days (Sanchez and Bull, 1990), and 28 days (Stauber and Bull, 1997). In the study by Stauber and Bull (1997), the rates in altered hepatocyte foci and tumors in which TCA administration had been suspended for two weeks following 50 weeks of treatment still had very high replication rates, matching those rates observed in tumors of mice with continuous treatment, indicating that TCA-induced tumors were independent of TCA treatment. In contrast, cell replication rates were significantly depressed in normal hepatocytes in the same TCA-treated mice. Thus, cells within altered hepatic foci and tumors appear to be resistant to the inhibition of cell division that chronic treatment with TCA appears to produce in normal hepatocytes, providing some selective advantage to initiated cells.

Hypomethylation of the promoter region of the *c-myc* gene correlated temporally with increased cell replication in $B6C3F_1$ mice dose with 500 mg/kg TCA (Ge *et al.*, 2001). Hypomethylation of the promoter region of the *c-myc* gene in the liver did not occur until 72 hours after dosing, which was also the time when DNA replication was increased. Methylation of DNA (5-methylcytosine) occurs after the formation of newly synthesized strands of DNA from DNA replication.

In vivo studies have demonstrated that cessation of treatment of TCA may arrest or alter the carcinogenic process. Bull *et al.* (1990) found that if treatment of mice with 2 g/L TCA in drinking water was stopped at 37 weeks, there was a smaller number of total tumors in these mice at 52 weeks than in mice that had been treated continuously for the entire 52 weeks based upon total dose administered. This would suggest that TCA-induced benign lesions regressed when treatment was stopped at 37 weeks. However, most of the tumors that remained in the stop-exposure group were hepatocellular carcinomas. In an initiation-promotion protocol, 52 weeks of TCA in drinking water increased the yield of both hepatocellular adenomas and carcinomas in methylnitrosourea (MNU)-initiated mice (Pereira and Phelps, 1996). If treatment was suspended at 37 weeks, however, there was a significant reduction in the numbers and incidences of hepatocellular carcinomas at 52 weeks relative to initiated mice receiving continuous treatment for 52 weeks. The hepatocellular adenomas appeared to be insensitive to any change in the treatment period for TCA. Cessation of treatment with TCA did not reverse the hypomethylation of hepatocellular adenomas of TCA-treated mice to levels found in control animals (Tao *et al.*,1998).

In summary, the key events PPARα activation, peroxisomal proliferation and cell proliferation show an initial burst of activity following the initiation of exposure to PCE (and TCA). There is sustained activity for these key events, and cessation of exposure shows some reversibility of tumor expression, as expected for tumor promoters.

Biological Plausibility and Coherence

TCA is a PPARα agonist, but there is no direct evidence that either TCA or PCE exposure leads to mouse liver tumors via a PPARα MOA. There are no carcinogencity studies on PCE (or TCA) have been using PPARα-null or PPARα humanized mice.

However, there was a dose-dependent increase in PPARα-responsive gene expression in the livers of PCE-dosed $B6C3F_1$ mice which strongly correlated with TCA levels in the liver (Zhou *et al.*, 2017). PPARα-null mice exposed to TCA in drinking water for seven days did not exhibit several key events that are PPARα-dependent, such as increased peroxisome proliferation, expression of fatty acid metabolism genes, and hypertrophy (Laughter *et al.*, 2004). Peters *et al.* (1997) showed a similar lack of peroxisomal enzyme activity and hepatocyte hypertrophy in PPARα-null mice compared to wild-type mice when dosed with WY 14,643, a more potent peroxisome proliferating agent. In addition, wild-type mice developed liver tumors, whereas PPARα-null mice did not. PPARα-null mice have also been shown to be resistant to liver tumors induced bezafibrate, another peroxisome proliferator (Hays *et al.*, 2005). It is assumed that a long-term study of PCE (and TCA) using PPARα-null mice would also show a lack of liver tumors at doses which produce liver tumors in normal ($B6C3F_1$) or wild-type mice.

Liver tumors are increased $B6C3F_1$ mice, but not Sprague-Dawley rats, exposed to PCE. TCA, the major metabolite of PCE, also produces liver tumors in mice, but not rats in two-year carcinogenicity studies. Mice metabolize PCE at a faster rate than rats (Schumann *et al.*, 1980; Reitz *et al.*, 1996; Mitoma *et al.* 1985), and therefore generate greater tissue levels of TCA in the liver. Peroxisome proliferation and increased cell proliferation is observed in mice, but not rats, exposed to PCE, presumably due to the differences in these two species in TCA tissue levels and thus PPARα activation.

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Table 1
Tetrachloroethylene and PPARα Mode of Action

Event	Evidence in Animals	Evidence in Humans	References
Activation of PPARα	Did not activate mouse PPARα in COS-1 cell transfection reporter assay.	Did not activate human PPARα in COS-1 cell transfection reporter assay.	Zhou and Waxman, 1998; Maloney and Waxman, 1999
PPARα-dependent regulation of proliferation/apoptosis	No data.	No data.	
PPARα-dependent regulation of fatty acid metabolism genes.	Increased PPARα responsive gene expression (mouse liver); CYP4A protein induction (mouse liver microsomes)	No data.	Zhou et al., 2017; Philip *et al.*, 2007
Peroxisome proliferation	Increased peroxisome enzyme activity, peroxisome number and size in mice, but not rats.	No data.	Goldsworthy and Popp, 1987; Odum *et al.*, 1988
Perturbation of cell proliferation and/or apoptosis	No data.	No data.	
Inhibition of GJIC	No data.	No data.	
Hepatocyte oxidative stress	No data.	No data.	
Selective clonal expansion	No data.	No data.	

Table 2
Trichloroacetic Acid and PPARα Mode of Action

Event	Evidence in Animals	Evidence in Humans	References
Activation of PPARα	Mouse PPARα activated in COS-1 cells and human hepatocyte transfection reporter assays.	Human PPARα activated in COS-1 cell transfection assay, but not in cultured human hepatocytes cells.	Zhou and Waxman, 1998; Maloney and Waxman, 1999; Walgren *et al.*, 2000b
PPARα-dependent regulation of proliferation/apoptosis	No data.	No data.	
PPARα-dependent regulation of fatty acid metabolism genes	Increased CYP4A and acyl CoA oxidase protein expression in liver from wild-type, but not PPARα-null mice.	No data.	Laughter *et al.*, 2004
Peroxisome proliferation	Mice: increased peroxisomal enzyme activity, and number and size of peroxisomes, but not in PPARα-null mice. Rats: increased peroxisome activity, and CYP4A activity.		Mice: Elcombe, 1985; Goldsworthy and Popp, 1987; DeAngelo *et al.*, 1989; Nelson *et al.*, 1989; Parrish *et al.*, 1996; Laughter *et al.*, 2004. Rats: Elcombe, 1985; Goldsworthy and Popp, 1987; Zanelli *et al.*, 1996
Perturbation of cell proliferation and/or apoptosis	Increased [^{3}H] thymidine incorporation into liver DNA and labeling index, and dose-dependent increase in cell proliferation. Liver hypertrophy occurred in PPARα wild-type, but not in PPARα-null mice.	No data.	Sanchez and Bull, 1990; Dees and Travis, 1994; Stauber and Bull, 1998; Laughter *et al.*, 2004; Ge *et al.*, 2001
Inhibition of GJIC	Inhibited GJIC in mouse, but not rat, hepatocytes.	No data.	Klaunig *et al.*, 1989
Hepatocyte oxidative stress	No change in 8-OHdG levels in nuclear DNA from mouse liver (up to 10 weeks exposure)		Parrish *et al.*, 1996
Selective clonal expansion	Hypomethylation seen in TCA-induced tumors in promoters of protooncogenes c-myc and c-jun. Transformation of mouse liver cells from anchorage-dependent to –	No data.	Tao *et al.*, 1999; Tao *et al.*, 2000; Stauber and Bull, 1997; Stauber *et al.*, 1998; Latendresse and Pereira, 1997

	independent with same immunoreactivity (lack of c-Jun and c-Fos expression) as TCA-induced tumors. Increased clonal expansion of tumors that resemble those seen by peroxisomal proliferators.		

Appendix 5

Comments on the US EPA TSCA Perchloroethylene Risk Evaluation: Inhalation Exposure from Brake Cleaning

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Table of Contents

1 Executive Summary

In the draft risk evaluation for perchloroethylene (PCE), the United States Environmental Protection Agency (EPA) assessed the potential human health risk of commercial and consumer exposure to PCE through the use of aerosol degreasing products and aerosol lubricants (PCE) (EPA, 2020, p. 154). Specifically, EPA identified and evaluated inhalation exposure monitoring data collected during the use of PCE-containing aerosol degreasers during brake servicing and supplemented the monitoring with modeling of PCE exposures using the Brake Servicing Near-Field/Far-Field Inhalation Exposure Model as a representative use of aerosol degreasing products containing PCE (EPA, 2020, p. 154-155). Overall, EPA concluded that inhalation exposure from the commercial and consumer use of PCE in aerosol degreasing products, including brake cleaners, present an unreasonable risk of non-cancer effects and cancer (EPA, 2020, p. 36). In some cases, unreasonable risks were found for central tendency estimates of exposure, with and without PPE.

Based on the inhalation exposure monitoring data, EPA calculated a central tendency exposure (CTE) (50th percentile) of 1.4 ppm and a high-end (95th percentile) of 7.8 ppm for 8-hour time weighted average (TWA) concentrations and a 50th percentile of 29 ppm and 95th percentile of 123 ppm for 15-minute TWA concentrations (EPA, 2020, p. 155). EPA stated that the monitoring data may "underestimate 'typical' exposures" because PCE concentrations in the products used in two of the available studies selected by EPA were below a median concentration of 78.4%. EPA indicated that aerosol brake degreasing products can contain anywhere between 20 and 99% PCE, but that the monitoring data EPA used included products with < 78.4% PCE (EPA, 2020, p. 156). (EPA, 2020, p. 155-156).

Regarding the modeled exposures, EPA reported 8-hour TWA concentrations of 5.5 ppm as a 50th percentile and 17 ppm as a 95th percentile, respectively, and maximum 1-hour TWA concentrations of 17 ppm and 50 ppm for the 50th and 95th percentiles, respectively (EPA, 2020, p. 156). EPA noted that the model-derived central tendency and high-end exposures were greater than those found in the monitoring data, which was "not unexpected" because the model was intended to "capture a wider range of shop conditions" and some brake cleaning products may have higher PCE concentrations.

To evaluate EPA's modeled PCE worker exposures during the use of PCE-containing aerosol brake cleaner, an alternative modeling approach was utilized. First, a well-accepted, peer-reviewed model (IH Mod 2.0) was parameterized based on empirical observations and subsequently validated against measurement data collected under reasonable worst-case conditions for a similar brake cleaning application, using a different solvent. A single-parameter optimization analysis was performed for those reasonable worst-case conditions to determine an appropriate selection for the near-field radius (a two-zone modeling parameter). Following the optimization, PCE-specific information was then substituted into the model to develop lower and upper bound estimates of short-term, near-field exposure concentrations for auto mechanics using PCE-containing brake cleaner while performing brake work under reasonable worst-case conditions. Lower and upper bound and mid-point 8-hour TWA concentrations were then

calculated for two different PCE product content and brake work scenarios using the short-term exposure concentrations.

The lower and upper bound 8-hour TWA concentrations, representing a range of potential exposures under reasonable worst-case conditions, encompassed the 50th and 95th percentiles modeled by the EPA, while the mid-point estimates were generally similar to or somewhat higher than the 50th percentile modeled by the EPA. This demonstrates that EPA's approach is appropriate for estimating reasonable worst-case exposures (i.e., high product use amount and minimal air exchange or local air movement). However, EPA's use of survey-derived brake cleaner usage data rather than measured data of brake cleaner use likely results in an approximately 2- to 4- fold overestimate of exposure concentrations from its model application. Note that the EPA model would not represent all usage scenarios (e.g., typical to low product use amount scenarios in well-ventilated garages), and thus, EPA's estimates are most consistent with high product use scenarios. The actual CTE value among users of such products is likely even more than 2- to 4-fold lower than the EPA model estimates.

2 Modeling Inhalation Exposure to PCE During Brake Cleaning

2.1 Scenario Description to Validate IH Mod for Brake Cleaning

Brake cleaner studies involving the simultaneous measurement of inhalation exposures and generation rate/mass loss in the canisters were available for petroleum-solvent-based (non-chlorinated) brake cleaners are available to inform the brake cleaning scenario. One of the most recent studies is Fries et al. (2018), a case study that evaluated typical exposures associated with use of an aerosol brake cleaner during automotive vehicle repair work.

A CRC® brand non-chlorinated brake cleaner was utilized during the study. The product contained the following: toluene (38.3%), methanol (35.5%), acetone (19.5%), carbon dioxide (6.5%), and xylene (0.2%) (Fries et al., 2018). Toluene is a reasonable surrogate for PCE for modeling vapor-liquid equilibrium behavior in spray applications because both chemicals have a similar vapor pressure (22 mmHg vs. 14 mmHg at 25°C) (NIST, 2018). However, the two chemicals would exhibit substantially different liquid-phase behavior due to the other ingredients in the toluene-based formulation. This limitation was assumed to have negligible effect on the example below.

During each application of brake cleaner during a single brake change, the mechanic sprayed between one to three bursts of brake cleaner, ranging in duration from five to 27 seconds (Fries et al., 2018). The amount of brake cleaner used per wheel ranged from 13.9 to 84.3 g (Fries et al. 2018). The mechanic was instructed to use the product generously to simulate reasonable worst-case use volumes for brake work.

Personal breathing zone samples were collected for a mechanic during use of the brake cleaner for short-term (15-minute) and task-length durations. The short-term samples captured the period of active use of brake cleaner during repair on a single wheel to determine the maximum 15-minute exposure for the use condition. The study was performed in a full-service automotive service garage located in Cincinnati, Ohio. High temperatures and stagnant conditions were recorded throughout the study, with ambient temperatures and relative humidity ranging from 82 to 96°F and 48 to 73%, respectively. The mechanic's work area was located in the southwest corner of the garage and was approximately 2.4 by 4.6 meters in size (Fries et al., 2018).

2.2 Model and Parameter Selection

A two-zone model with a constant emission rate was selected as the best representative model for the exposure scenario in IHMod 2.0.

The study conducted by Fries et al. (2018) was useful because all modeling variables were either a) measured or b) able to be reasonably bounded such that only one variable remained for a parameter-fitting sensitivity analysis: the near-field radius. The near-field was conceptualized as a half-sphere with a radius equivalent to the distance of the worker from the brake axle (approximately 0.3 m to 1.5 m) while the far-field was defined as the remainder of the general garage work area. The model input parameters selected for use and rationale for selection are provided in Table 1.

Table 1 Model Input Parameters

Parameter	Value or Selection	Rationale
Contaminant Mass Emission Rate (G)	31,916 mg/min	The brake cleaner container was weighed before and after each 15-min application event. For the model, assume that approximately 50 grams of the spray was used per 15-min application event based on the midpoint of the empirical data. The brake cleaner was 38.3% toluene by weight. • 50 g x 38.3%= 19.15 g toluene per application • 19.15 g / 0.6 min x (1000 mg/g) = 31,916 mg/min
Near-Field Radius (r_n)	0.3 - 1.5 m (subject of parameter-fitting optimization analysis)	The near-field was conceptualized as a half-sphere with a radius equivalent to the distance of the worker from the brake axle.
Room Volume (Vr)	50.8 m^3	The work area was 2.4 m by 4.6 m, with a ceiling height ranging from 4.6 m to 7.6 m in the full garage. A ceiling height of 4.6 m was assumed, such that the volume of the workspace is: • 2.4 m x 4.6 m x 4.6 m = 50.8 m^3
Room Supply/ Exhaust Air Rate (Q)	5.08 m^3/min	Burton (2002) indicated that typical automotive garage employment occupancies have an air change rate of 6-30 hr^{-1}. An air exchange rate of 6 hr^{-1} was assumed to reflect a lower-end air change rate. • 6 hr^{-1} x 50.8 m^3 x (1 hr/ 60 min) = 5.08 m^3/ min
Random Air Velocity (S)	3.6 m/min	The random airspeed was set at 3.6 m/min (12 ft/min) based on the geometric mean air speed observed in a survey of indoor workspaces (Baldwin and Maynard, 1998). This result is consistent with air speed measurements in the Fries et al study.
Simulation and Generation Time	ST= 15 min GT= 0.6 min	A simulation time of 15-minutes was assumed based on the short-term air sample length, which included aerosol brake cleaner use during a brake repair on a single wheel. An average of 18 seconds and two sprays per brake repair was used to estimate the amount of time during which spraying occurred. • 18 sec x 2 bursts x (1 min/ 60 sec) = 0.6 min

2.3 Model Results and Fitting of the NF Radius via Single-Parameter Optimization Analysis

The near-field and far-field 15-minute TWA concentrations of toluene were 1,443 mg/m^3 and 193 mg/m^3, respectively, when a near-field radius of 0.3 m (~1 foot) was used. The molecular weight of toluene is 92.14 g/mol and ideal gas conditions were assumed such that the concentration in parts per million (ppm) in the near-field was 383 ppm.

While actively servicing the brake, a mechanic may be as close as 0.3 meters away from the axle for a very short period of time. However, a mechanic performing brake work would move beyond 0.3 meters (~1 foot) from the brake after spraying, while continuing with the brake change. A distance of 0.6 meters can be used as an approximation of the distance between a mechanic and the sprayed brake component over the 15-minute period in which the person is actively working on the brake components. This reflects that the mechanic would likely spend time both closer and farther away than 0.6 meters. Using a radius of 0.6 meters (~2 feet) to define the near-field, yields a near-field 15-minute TWA concentration of 505 mg/m^3 (134 ppm).

Finally, a distance of 1.5 meters (~ 5 feet) can be used as an estimate of the average distance a mechanic would be away from the sprayed brake considering all elements of the task (e.g., moving away to retrieve replacement parts or a tool). Thus, the near-field encompasses the total area the mechanic would likely move around in (and experience exposure in) during the 15-minute period. Using a radius of 1.5 meters (~ 5 feet) to define the near-field, results in a near-field 15-minute TWA concentration of 240 mg/m^3 (64 ppm). This is considered the best estimate of the average modeled exposure for the 15-minute brake job period based on observation and concordance with the empirical data.

The estimated far-field 15-minute TWA concentrations are similar in all three scenarios (range: 191 – 193 mg/m^3).

Equation demonstrating conversion from mg/m^3 to ppm (model with near-field radius of 1.5 meters):

$$\frac{240\,\frac{mg}{m^3}}{\left(\frac{92.14\,\frac{g}{mol}}{24.45\,\frac{L}{mol}}\right)} \times \frac{1\,g}{1000\,mg} \times \frac{1\,m^3}{1000\,L} \times 10^6\,ppm\; = 64\,ppm$$

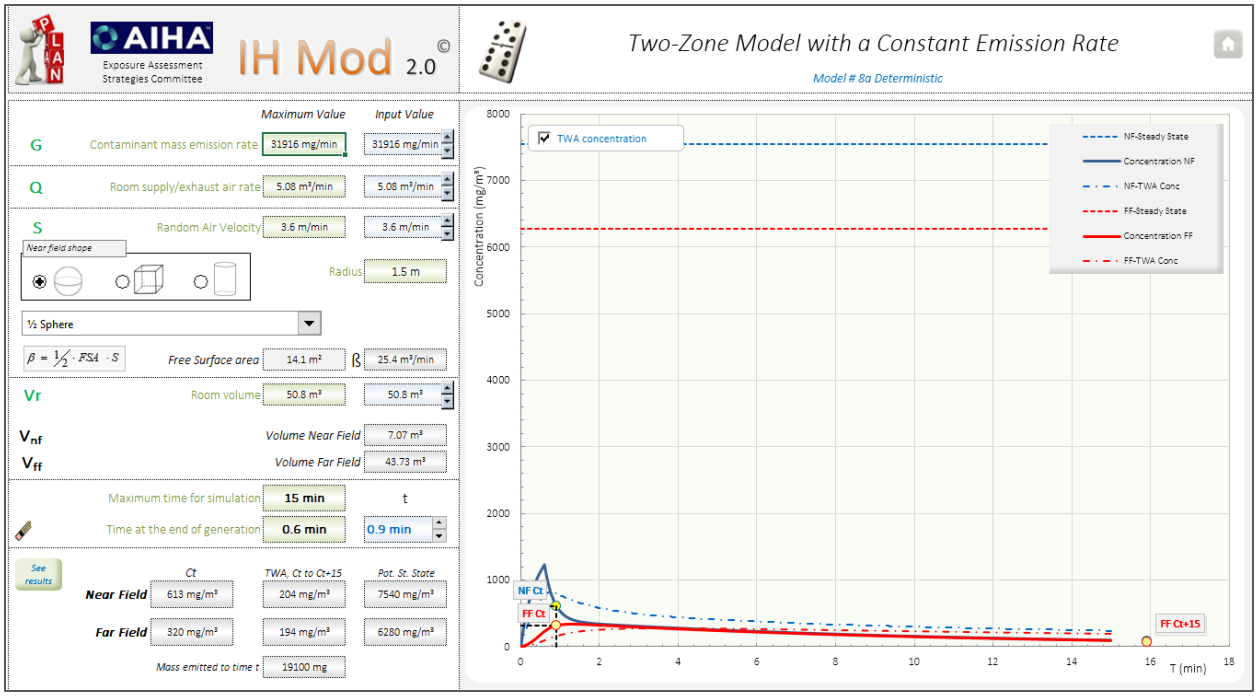

Figure 1 Output of Two-Zone model with near-field radius of 1.5 m from IHMOD 2.0 (toluene scenario)

In Fries et al. (2018), the mean toluene concentrations reported for personal short-term samples ranged from 2.2 ppm to 44 ppm (Figure 2) among scenarios. The most relevant scenarios to the modeling performed in our analysis are Scenarios 1, 5 and 6 (Figure 2, right panel), and using approximately 50 g of product yielded 15-minute exposure concentrations of approximately 18 to 35 ppm. The concentration estimated using the model with the near-field radius set at 0.3 meters was approximately 11-fold greater than the upper bound of the empirical measurements for the most relevant scenarios (35 ppm). The near-field concentration estimated using the model with a near-field radius of 0.6 meters was approximately 4-fold greater than the upper bound of the empirical measurements for the most relevant scenarios, while the concentration estimate using a radius of 1.5 meters was approximately 1.8-fold greater. This range of concentrations demonstrates the sensitivity of near-field concentrations to the characterization of the near-field characteristic dimension (the radius for the hemispherical geometry). Use of 1.5 meters as the near-field radius yields estimates within the range anticipated from a well-designed two-zone model, which has been reported to range from one-half to two fold that of measured values (Nicas, 2009) while use of the other radiuses are more conservative in that they overestimate the concentrations in comparison to the measured values.

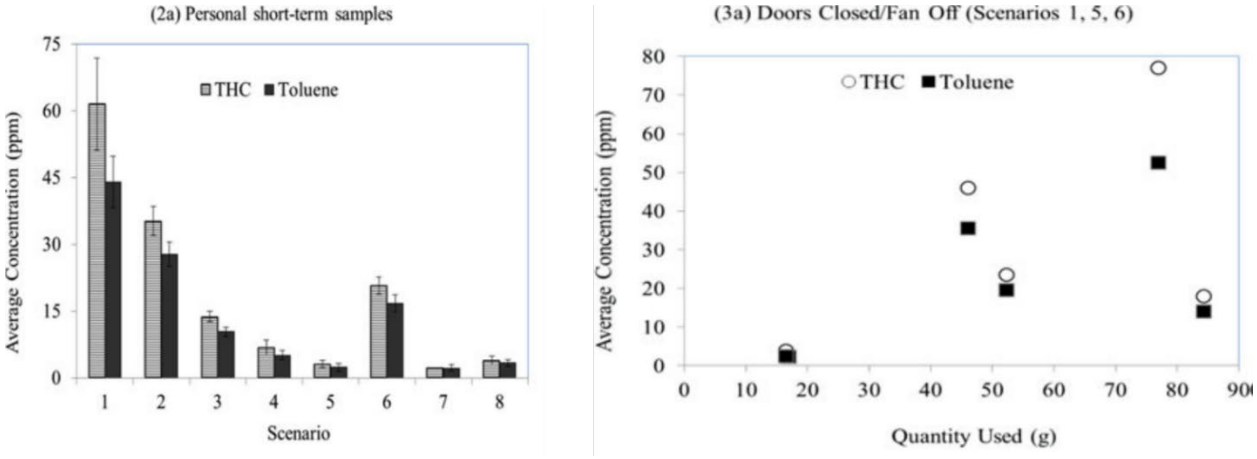

Figure 2 Figure 2a and 3a from Fries et al. (2018), depicting average (mean, standard error) concentrations for personal short-term samples and average concentrations by quantity used for low ventilation conditions (doors closed/ fan off).

Based on these validations of the model to the empirical data a near-field distance (radius) of 1.5 meters for the worker is the best estimate of the actual measured exposure concentrations. A near-field with a radius of 1.5 meters should be considered representative of the area in which a worker would move about in during a brake change task with some time within the 15-minute averaging period spent closer to the actual brake equipment. Use of this distance as the near-field radius still yields overestimates of the actual exposure by approximately 1.8-fold under reasonable worst-case conditions (high product use volume, little air movement).

2.4 Application of Toluene Model Results to Perchloroethylene

The most appropriate NF radius (1.5 meters) identified in Section 1.3 was used in a two-zone modeling analysis for PCE-containing products. In addition to assuming that toluene and perchloroethylene have similar volatilities when sprayed as described in Section 1.1, this approach also assumes that the non-chlorinated and chlorinated aerosol brake cleaner products are used in an equivalent manner under the same ventilation conditions. Similar brake cleaning products containing PCE were evaluated by EPA using its Brake Servicing Near-Field/Far-Field Inhalation Exposure Model. A weight fraction of 20 to 99 percent PCE was used by EPA based on survey results from CARB 2000 (EPA, 2020, p. 258, 261-262). Consistent with our finding that a 1.5-meter radius for the near-field is the best estimate for measured exposures when validating the model described above, EPA also selected a near-field radius of 1.5 meters (EPA, 2020, p. 261). The only input parameter in the previously validated reasonable worst-case model (utilizing 1.5 meters as the near-field radius) requiring substitution in order to estimate PCE exposure concentrations is the contaminant mass emission rate, G.

Assuming that 50 grams of product were used per application based on the data reported by Fries et al. (2018) and that the content of PCE was 20 percent as a lower bound and 99 percent as an upper bound, the amount of PCE applied during replacement of a single brake is 10 grams as a lower bound (50 g x 20 percent) and 49.5 grams as an upper bound (50 g x 99 percent). Using these estimates of mass applied and a generation time of 0.6 minutes as in the previously validated model, G is estimated as:

$$G\ (lower\ bound) = \frac{10\ grams}{0.6\ minutes}\ x\ \frac{1{,}000\ mg}{1\ g} = 16{,}667\ mg/min$$

$$G\ (upper\ bound) = \frac{49.5\ grams}{0.6\ minutes}\ x\ \frac{1{,}000\ mg}{1\ g} = 82{,}500\ mg/min$$

Using the lower bound contaminant mass emission rate in the model, the resulting near-field 15-minute time weighted average concentration was 125 mg/m^3. Using the upper bound contaminant mass emission rate, the resulting near-field 15-minute TWA concentration was 621 mg/m^3. Assuming ideal gas conditions and using the molecular weight of PCE of 165.83 g/mol, the lower bound and upper bound near-field concentrations in ppm can be estimated as:

$$\frac{125\ \frac{mg}{m^3}}{\left(\frac{165.83\ \frac{g}{mol}}{24.45\ \frac{L}{mol}}\right)} \times \frac{1\ g}{1000\ mg} \times \frac{1\ m^3}{1000\ L} \times 10^6\ ppm\ = 18\ ppm\ (lower\ bound\ for\ 20\%\ product)$$

$$\frac{621\ \frac{mg}{m^3}}{\left(\frac{165.83\ \frac{g}{mol}}{24.45\ \frac{L}{mol}}\right)} \times \frac{1\ g}{1000\ mg} \times \frac{1\ m^3}{1000\ L} \times 10^6\ ppm\ = 92\ ppm\ (upper\ bound\ for\ 99\%\ product)$$

These concentrations are the model-estimated lower and upper bound estimates of 15-minute TWA concentrations a mechanic would experience while using a PCE containing aerosol brake cleaner in a reasonable worst-case scenario (high use of a 50-g product and limited ventilation).

Utilization of Modeled 15-minute Near-Field TWA Concentrations to Estimate 8-hour TWA Concentrations

Eight-hour TWA concentrations can be estimated using the above modeled 15-minute near-field TWA concentrations of 18 ppm and 92 ppm (modeled assuming 20% and 99% PCE in the cleaner, respectively).

In its modeling of brake cleaner related exposures, EPA estimated that one to four brake jobs were performed per shift per site (EPA, 2020, p. 259, 263). Further, EPA assumed that a single worker performed these one to four brake jobs (EPA, 2020, p. 251). These values for low and high activity ranges appear reasonable based on observations in Fries et al. (2018) regarding length of time needed to complete a brake job. Norton (1993) calculated an estimated average of brake jobs performed per week based on survey data collected from automotive repair facilities of 7.8 and 8.1 for aerosol-using shops and all shops, respectively. Assuming a 5-day work week of 8-hour days (40 hours of operation), approximately 1.6 brake jobs are performed per day per shop. Norton (1993) reported that approximately half of the shops surveyed were open for a half day on Saturday. Additionally, EPA utilized a range of 40 to 122.5 hours of operation per week based on data reported by CARB 2000. Therefore, calculating an average number of brake jobs performed per day using a 5-day week is conservative (i.e., it yields an estimate that is likely higher than the true average). Rounding the value of 1.6 brake jobs to 2 whole brake jobs performed per day gives a conservative estimate of the average number of brake jobs performed at a shop per day.

Lower, mid-point (using either low- or high-PCE content product and one- or two-axle brake jobs), and upper bound 8-hour TWA exposure concentrations can be estimated using the following assumptions (also shown in Table 2):

- One, two, or four brake jobs per shift,
- Two to four brakes changed per brake job (e.g. brake changes performed on both wheels of either one or both axles),
- The previously modeled lower bound or upper bound short-term (15-minute) TWA concentration represented exposure during brake cleaner application to one wheel,
- Exposure lasted for 15 minutes per application, and
- Exposure outside of the 15 minutes associated with each application is minimal and therefore not incorporated due to movement of mechanics throughout the facilities, the relatively large volumes of the areas where brake work is typically performed, and air exchange.

Table 2. Parameters used in estimating lower and upper bound 8-hour TWA exposure

	Brake Jobs per Shift	Brakes Changed per Brake Job	Exposure Duration per Brake Change	15-Min TWA Exposure Concentration	Total Shift Duration
Lower Bound 8-hour TWA Estimate	1	2	15 min (0.25 hours)	18 ppm (modeled assuming 20% PCE in cleaner)	8 hours
Mid-Point 8-hour TWA Estimate (low % PCE product)	2	4	15 min (0.25 hours)	18 ppm (modeled assuming 20% PCE in cleaner)	8 hours
Mid-Point 8-hour TWA Estimate (high % PCE product)	2	2	15 min (0.25 hours)	92 ppm (modeled assuming 99% PCE in cleaner)	8 hours
Upper Bound 8-hour TWA Estimate	4	4	15 min (0.25 hour)	92 ppm (modeled assuming 99% PCE in cleaner)	8 hours

Notes: PCE = perchloroethylene; ppm = parts per million; TWA = time-weighted average

Using these parameters in the following equations, lower and upper bound 8-hour TWA concentration estimates can be calculated:

$$8-hr\ TWA\ (lower\ bound) = \frac{1\ brake\ job\ x\ 2\frac{brakes}{job} x\ 0.25\frac{hr}{brake} x\ 18\ ppm}{8\ hrs} = 1\ ppm$$

$$8-hr\ TWA\ (mid-point, 20\%\ PCE\ product) = \frac{2\ brake\ job\ x\ 4\frac{brakes}{job} x\ 0.25\frac{hr}{brake} x\ 18\ ppm}{8\ hrs} = 5\ ppm$$

$$8-hr\ TWA\ (mid-point, 99\%\ PCE\ product) = \frac{2\ brake\ job\ x\ 2\frac{brakes}{job} x\ 0.25\frac{hr}{brake} x\ 92\ ppm}{8\ hrs} = 12\ ppm$$

$$8-hr\ TWA\ (upper\ bound) = \frac{4\ brake\ jobs\ x\ 4\frac{brakes}{job} x\ 0.25\frac{hr}{brake} x\ 92\ ppm}{8\ hrs} = 46\ ppm$$

These estimated 8-hour TWA exposures can be used to evaluate the 8-hour TWA exposure concentrations of 5.5 ppm (50th percentile) and 17 ppm (95th percentile) modeled by the EPA (EPA, 2020, p. 156). The estimated lower bound and upper bound concentrations (e.g., using lower and upper bound assumptions, respectively, for number of brake jobs per day, number of brakes repaired per job, and PCE content) encompass the EPA's modeled 8-hour TWA exposure concentrations of 5.5 ppm as a 50th percentile and 17 ppm as a 95th percentile. Additionally, the estimated mid-point concentrations (assuming 20% PCE content and four brakes repaired per job or 99% PCE content and two brakes repaired per job) are similar to EPA's modeled 50th percentile or between the 50th and 95th percentile. It is important to note that these estimated mid-point 8-hour TWAs are modeled using a reasonable worst-case approach and are not actual estimates of the average 8-hour TWA across all usage scenarios. These estimated 8-hour TWAs (lower and upper bound and mid-points) are representative of a reasonable worst-case for the following reasons:

- While the selected model approximated the measured data in the model validation, it was still an overestimate by about 1.8-fold.
- The estimate of 50 g as the amount of brake cleaner used is representative of generous use of the product intended to represent a reasonable worst-case use.
- The low-end value for reported air exchange rates in automotive garages is used.
- The model was validated against measurements collected with no local ventilation (e.g., such as a fan blowing in the mechanic's work area).
- Fries et al. (2018) found that concentrations were reduced when air flow was increased (especially in regards to operation of a floor fan).

Overall, the results of modeling 15-minute TWA near-field concentrations using a reasonable worst-case model parameterized based on empirical data (Fries et al. 2018) and then utilizing these concentrations to estimate 8-hour TWA exposures indicate that EPA's modeling approach is consistent with other industrial hygiene modeling approaches validated against empirical data. Further, comparison of these estimated 8-hour TWA exposures, modeled using reasonable worst-case conditions, with EPA's modeled 50th and 95th percentiles indicates that EPA's model is also representative of reasonable worst-case conditions, but not all usage scenarios (e.g., typical or low-use scenarios).

Analysis of Sensitivity of Assumptions Regarding Amount of Products Used

The importance of the assumptions made regarding the amount of product used is illustrated by the sensitivity of the modeled 15-minute near-field TWA concentration estimates to the contaminant mass emission rate used. This generation rate sensitivity can be observed by substituting lower and upper bound contaminant mass emission rates estimated utilizing EPA's assumptions regarding brake cleaner usage rather than 50 g of brake cleaner used based on the

data reported by Fries et al. (2018). Based on data from CARB (2000), EPA estimated that 14.4 oz of brake cleaner was used in a single brake job (involving either two or four wheels) and that the weight fraction of PCE ranged from 20 to 99% (EPA, 2020, p. 258, 262). These estimates equate to lower and upper bound estimates of 20 g to 202 g of PCE used per brake as shown in the following equations.

$$PCE\ Used\ per\ Brake\ (g)\ (lower\ bound) = \frac{14.4\ oz\ x\ 28.3495\ \frac{g}{oz}\ x\ 0.20}{4\ brakes} = 20\ g$$

$$PCE\ Used\ per\ Brake\ (g)\ (upper\ bound) = \frac{14.4\ oz\ x\ 28.3495\ \frac{g}{oz}\ x\ 0.99}{2\ brakes} = 202\ g$$

Assuming the brake cleaner was applied to the brake for a total of 0.6 minutes as above from the Fries et al. (2018) observations, contaminant mass emission rates using estimates of PCE use based on EPA's assumptions can be calculated:

$$G\ (EPA\ based -\ lower\ bound) = \frac{20\ grams}{0.6\ minutes}\ x\ \frac{1{,}000\ mg}{1\ g} = 33{,}333\ mg/min$$

$$G\ (EPA\ based -\ upper\ bound) = \frac{202\ grams}{0.6\ minutes}\ x\ \frac{1{,}000\ mg}{1\ g} = 336{,}667 mg/min$$

These contaminant mass emission rates based on EPA's assumptions including the amount of brake cleaner used per brake job exceed the lower and upper bound contaminant mass emission rates estimated based on empirical data regarding the amount of brake cleaner used per brake when a mechanic was instructed to use the product generously while performing a brake job from Fries et al. (2018). Substituting these EPA based G values into the two-zone model utilizing 1.5 meters for the near field-radius, results in a 15-minute TWA near-field concentration approximately 2-fold higher than the lower bound estimate of 18 ppm and 4-fold higher than the upper bound estimate of 92 ppm using the contaminant mass emission rates based on Fries et al. (2018) measured brake cleaner use. This suggests that reducing the amount of product used in the EPA model to a reasonable worst-case value based on empirical data would decrease EPA's estimates by approximately two- to four-fold.

Conclusions Regarding Modeling of PCE Exposures from Aerosol Brake Cleaner Use

Overall, the estimated 8-hour TWA exposures based on 15-minute TWA concentrations modeled using a reasonable worst-case approach developed using empirical data (Fries et al. 2018), indicate that EPA's modeling approach is representative of reasonable worst-case conditions, but not all usage scenarios (e.g., typical or low use scenarios). Further, use of a contaminant mass emission rate based on EPA's estimate of 14.4 oz of brake cleaner used per brake job resulted in estimated 15-minute TWA near-field concentrations which exceeded those derived from the Fries et al. 2018 based model by 2 to 4 fold. EPA's modeling efforts would benefit from use of empirically derived data regarding brake cleaner use rather than CARB 2000's estimate of brake cleaner use, which appeared to be based on survey data. Further, the CARB 2000 data is over 20 years old as CARB 2000 reported data from a survey conducted by the California Air Resources Board in 1998 and site visits presumably conducted sometime in the 1990s (CARB,

2000, p. V-2, V-8 - V-9). Additionally, the data reported by CARB (2000) is restricted to California and is not a nationwide sample (CARB, 2000, p. V-2, V-8). Direct observation and measurement of mass used from Fries et al. (2018) indicate that the upper bound estimate of product use amount per brake estimated by EPA is excessive for reasonable worst-case use conditions. Further, EPA should consider using a range of product use amounts in its analysis in order to represent reasonable worst-case use conditions as well as typical and low use conditions.

2.5 Discussion of Norton 1993

Norton (1993) reported the results of a survey of automotive repair facilities on chemical brake cleaner usage conducted by the Halogenated Solvents Industry Alliance, Inc. in 1993. This study provides information regarding the use of brake cleaners and the context of that use relevant to the inputs in the previously used model and 8-hour TWA concentration estimates. Specifically, information regarding facility size, brake cleaner use, and number of brake jobs performed per week were reported by Norton (1993), all of which are relevant either to the model inputs or 8-hour TWA concentration estimate inputs. However, a limitation of much of the information reported by Norton (1993) is that it was collected on a categorical basis, which makes it difficult to estimate averages and maximum and minimum values. Further, similar to the CARB (2000) data, the data reported by Norton (1993) are over 20 years old.

The survey was sent to a total of 5,000 facilities across the United States (Norton, 1993, p. 3). A response rate of 12 percent (n=594) was achieved by the date after which returned questionnaires were no longer processed (Norton, 1993, p. 3). Respondents indicated that automotive brake repairs were performed at 569 of the shops, with 436 reporting use of aerosol chemical brake cleaners (Norton, 1993, p. 3). Norton (1993) stated that postmarks on return envelopes “indicated that surveys were received in numbers roughly proportional to the populations of the 45 states from which they were returned” (Norton, 1993, p. 3). Further, it was stated that nonresponse bias was not “likely to be a problem” though it was not quantified (Norton, 1993, p. 16).

According to the survey results, service areas of the shops averaged approximately 70 feet by approximately 53 feet with a ceiling height of 15.6 feet (Norton, 1993, p. 4). Total volume averaged 73,288 ft^3 (2,075 m^3) for all shops and 66,172 ft^3 (1,874 m^3) for aerosol users (Norton, 1993, Table 2). Norton (1993) noted that the Building Officials and Code Administrators standard for air flow in an automotive repair facility was 1.5 cubic feet per minute per square foot of floor area, which was reported to equate to 4.5 air changes per hour for an “average-sized shop” with a 20-foot ceiling (Norton, 1993, p. 4). Norton (1993) reported average shop sizes much greater than the area of 50.8 m^3 used to define the room volume in the models described in previous sections. However, modeling of near-field concentrations, which are those of primary interest in estimating exposures of workers directly using a product, are generally not sensitive to the room volume, except in unusual circumstances of small room volume or very high airflow.

Norton (1993) estimated that an average of 7.8 and 8.1 brake jobs in aerosol-using shops and all shops, respectively, were performed per week based on categorical data (Norton, 1993, Table 6). The response category of 1 to 5 brake jobs per week had the highest percent response (48% for all shops and 47% for aerosol users) while the category of $\geq$ 31 had the lowest response (~1-2%). According to results from a follow-up telephone survey of respondents, a brake job was reported to be brake repairs on a single car with approximately half involving only the front or rear brakes and the other involving all four brakes (Norton, 1993, p. 5-6). Seventy-seven percent of shops

reported that they had one to three workers performing brake work (Norton, 1993, Table 4). Cross-tabulation of the data indicated that only approximately 11% of shops reported 11 or more brake jobs per week with only 1 to 3 employees performing brake work whereas 66% of shops reported performing 1 to 10 brake jobs per week with 1 to 3 employees performing brake work (Norton, 1993, Table 10). Norton (1993) reported brake jobs performed per week (categorical data). While this information does not directly inform estimating the number of brake jobs performed per day by a single mechanic (an input into estimating the 8-hour TWA exposure concentration), the cross-tabulation of the brake jobs performed per week and number of employees performing brake work at a shop is supportive of the use of 1 to 4 brake jobs performed per day as lower and upper bound estimates.

Norton (1993) estimated that 0.85 aerosol cans were used per brake job based on categorical data (Norton, 1993, Table 6). Of the aerosol users, 75% indicated they used less than one can per job (amount used not further specified) (Norton, 1993, Table 6). Based on responses to a separate question, 50% of aerosol users indicated they used 1 to 3 cans at their facility per week (Norton, 1993, Table 7). Norton (1993) estimated that 5.6 cans were used per facility per week on average (Norton, 1993, Table 7). Norton (1993) noted that approximately half of respondents reported using aerosol brake cleaners for applications other than cleaning brakes.

The findings of Norton (1993) that most respondents' use of less than one can of aerosol brake cleaner per brake is consistent with the estimate of 50 g of brake cleaner applied per brake. The 50 g estimate is considered a reasonable worst-case use mass, based on the empirical data in Fries et al. (2018), in which a mechanic was instructed to use the product generously. Use of 50 g of brake cleaner per brake equates to 100 g to 200 g used per brake job (on two to four brakes, respectively), or 3.5 to 7 ounces. This is lower than the EPA's assumption of one 14.4 oz can per brake job, indicating that EPA's scenario may represent "beyond" reasonable worst-case.

3 Conclusions

EPA included aerosol degreasing and aerosol lubricants in the draft PCE risk evaluation (EPA, 2020, p. 154). Specifically, EPA identified and evaluated inhalation exposure monitoring data collected during the use of PCE-containing aerosol degreasers during brake servicing and supplemented the monitoring with modeling of PCE exposures using the Brake Servicing Near-Field/Far-Field Inhalation Exposure Model as a representative use of aerosol degreasing products containing PCE (EPA, 2020, p. 154-155). Based on the inhalation exposure monitoring data, EPA calculated a central tendency exposure (CTE) (50^{th} percentile) of 1.4 ppm and a high-end (95^{th} percentile) of 7.8 ppm for 8-hour time weighted average (TWA) concentrations and a 50^{th} percentile of 29 ppm and 95^{th} percentile of 123 ppm for 15-min TWA concentrations (EPA, 2020, p. 155). Overall, EPA found inhalation exposure from the commercial and consumer use of PCE in aerosol degreasing products, including brake cleaners, present an unreasonable risk of non-cancer effects and cancer (EPA, 2020, p. 36). In some cases, unreasonable risks were found for central tendency estimates of exposure, with and without PPE.

An alternative modeling approach was conducted to estimate worker exposures to PCE from the use of aerosol degreaser during brake cleaning using a commonly used model (IH Mod 2.0), which was parameterized based on empirical observations and subsequently validated against measurement data collected under reasonable, worst-case conditions for a similar aerosol brake cleaner with different chemical ingredients. PCE-specific assumptions (e.g., percent PCE in the product) were then substituted into the model to develop lower and upper bound estimates of short-term, near-field exposure concentrations for auto mechanics using brake cleaner while performing brake work under reasonable, worst-case conditions. Lower and upper bound 8-hour TWA concentrations were then calculated using the short-term exposure concentrations as well as lower and upper bound estimates of the number of brake jobs and corresponding brake changes performed per day. The lower and upper bound 8-hour TWA concentrations, representing a range of potential exposures under reasonable, worst-case conditions encompassed the 50^{th} and 95^{th} percentiles modeled by the EPA. This indicates that EPA's approach is consistent with other industrial hygiene models for estimating reasonable, worst-case exposures. However, EPA's use of survey-derived brake cleaner usage data rather than measured data of brake cleaner use likely results in an approximately 2- to 4-fold overestimate of PCE exposure concentrations for reasonable worst-case conditions. Actual central tendency estimates for the range of common users would be even lower after accounting for typical use amounts below 50 g, presence of local ventilation, and a higher mid-point estimate for air exchange rates than applied in the modeling done here.

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Appendix 7

Comments on the US EPA TSCA Perchloroethylene Risk Evaluation: Occupational Dry Cleaning Exposure

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1 Introduction

In the draft risk evaluation for perchloroethylene (PCE), the United States Environmental Protection Agency (EPA) concluded that occupational exposures to PCE from dry cleaning and spot cleaning posed an unreasonable risk of injury to workers for specific scenarios (particularly for high-end estimates, but also some central tendency exposures) (EPA, 2020). EPA based these conclusions on exposure estimates derived using two sets of monitoring data: “post 2006” data from the Occupational Safety and Health Administration (OSHA) (machine types unidentified) and data for fourth and fifth generation machines only. As described further below, based on limitations in the data used in the draft risk evaluation and additional datasets that are available, EPA should consider:

- Using a weight-of-evidence approach to test the reasonableness of the central tendency and upper bound estimates of exposure based on maximum drum concentrations of PCE, and considering current emission controls and work activity patterns.
- Obtaining updated data collected by the New York Department of Environmental Conservation (NYSDEC) (and any other similar previously unidentified sources), and include these data in the exposure estimates.
- For ONUs in the dry cleaning industry, relying on a weighted average of the NYSDEC data and work activity patterns that include combinations of time spent in the production and non-production areas.

2 Dry Cleaning Technology and EPA Assumptions

One of the COUs evaluated in the draft risk evaluation is the use of PCE for dry cleaning. The magnitude of potential worker exposures in the dry cleaning industry has reduced dramatically over the last several decades.

Until the mid-1990s, many PCE dry cleaning facilities used what is known as first generation technology, which consisted of separate washing and drying machines (Nealis, 2020). Damp clothes were moved manually between the washer and dryer allowing for off-gassing into the work area; some residual solvent vapor was also released when the dryer was opened. Second generation machines became available around the 1970s; these machines were a combined washer/dryer, avoiding transfer of solvent-laden clothes. The solvent consumption (g/kg of textiles) was also lower in second generation machines (and all produced thereafter) (von Grote et al., 2006). Third generation machines, introduced in the late 1970s to 1980s, used additional solvent recovery controls (NIOSH, 1997; Nealis, 2020). While each generation reduced exposures to some degree, NIOSH reported that peak exposures could be as high as 1,000-4,000 ppm PCE for eahc of the first three generations of machines (NIOSH, 1997).

In 1993, EPA passed the National Emission Standards for Hazardous Air Pollutants (NESHAP) for dry cleaning facilities, which banned the purchase of new first generation and second generation dry cleaning machines. The emission requirements led to development and routine use of fourth generation dry cleaning machines, which were developed in the mid-1990s. Compared to earlier designs, fourth generation machines added an improved coil system that substantially reduced peak residual PCE concentrations (NIOSH, 1997). In addition, a carbon sparging cycle was added to scrub PCE from the air in the machine, leaving 300 ppm or less residual solvent inside the drum of the machine after a cycle. Fifth generation machines are not common in the United States, but essentially are a fourth generation machine with a solvent monitor that locks the machine door until residual PCE levels in the drum are ≤ 300 ppm (NIOSH, 1997).

For occupational scenarios, EPA assumed that workers were primarily exposed to PCE when 1) loading and unloading garments from machines, 2) cleaning stains (spot cleaning), or 3) transferring solvent from a storage container into the dry cleaning machine. EPA used 8-hour time weighted average (TWA) personal breathing zone (PBZ) monitoring data for workers and ONUs at dry cleaning facilities from several sources, including OSHA facility inspections, 2) NIOSH studies, and 3) data submitted by the Department of Defense. EPA separated the dry cleaning exposure data by machine type in an attempt to control for the changes in regulations and technology over the years. Because the typical life span of dry cleaning machines is reportedly 15 years, EPA used 2006 as a starting point for data intended to include only shops using third, fourth, and fifth generation machines. EPA then divided exposure and risk estimates into two bins for: 1) “post 2006” which included third through fifth generation machines, and 2) data for fourth and fifth generation dry cleaning machines only.

EPA's efforts to assess exposure to dry cleaners based on data using only newer machines is appropriate since this is most representative of current exposures. However, EPA could improve upon their assessment of this COU. Two key improvements include: 1) more thoroughly evaluating the datasets that they used in the draft risk evaluation, and 2) incorporating additional occupational datasets to enhance the empirical basis for the risk determination.

3 Datasets Used by EPA

As noted above, EPA used an OSHA dataset for the analysis for “post 2006” dry cleaning machines. The OSHA data were collected during compliance inspections at nine different facilities between 2012-2016; these inspections may have been complaint-triggered and thus would tend to be in the high-end of the true distribution of exposures in such ndustrial ssettings. EPA notes this uncertainty in the draft risk evaluation, stating, “Since the OSHA data are from compliance inspections often as a result of worker complaints, they may not necessarily be representative of PCE concentrations encountered in the typical commercial dry cleaning establishment.” OSHA data also did not specify the dry cleaner types (machine generation). EPA assumed that they were representative, but one does not know the impact that any misclassification of machine type could have had on the estimates.

In addition, the datasets relied upon by EPA have relatively small sample sizes. Notably, there were only 9 and 6 data points for 15-minute TWA “Post-2006 NESHAP” worker exposures and “Fourth and Fifth Generation” data, respectively. For ONUs, there was only 1 data point for post-2006 and 4 data points for fourth and fifth generation machines; no data were available for 15-minute concentrations.

Specifically, with regard to ONUs, EPA presented an equivalent central tendency and 95th percentile based off the single data point collected for an “inspector” at the worksite. It is unclear, but presumed that EPA is referring to an inspector who visits the facility on behalf of a regulatory body, and who performs an exhaustive review of machinery, ventilation, record keeping, and operation of the plant. In New York, for example, inspectors must be present for at least two full-load cycles, and they must collect PCE exposure badges (Tatch, 2002). Thus, while they do not operate machinery, they are in the area and likely have a higher acute exposure to PCE than an ONU in the same time period of machine operation. They would also ehave a higher exposure than would be expected over the course of a full shift for a representative ONU that moves between areas of the facility. Even if EPA is referring to an “inspector” in the sense of the worker in a dry cleaning facility that is responsible for ensuring the stains have been removed, that creases in the clothing are sufficient, and who bags and assembles the order, this also may not be an appropriate surrogate. Exposure likely varies across ONUs, particularly for those that spend time “in the back,” including the inspector, relative to those who spend most of their time “in the front” (e.g., counter clerk).

Perhaps more importantly, not only are there few data points, but the averages calculated by EPA (Table 2-41) indicate the possible influence of outlier data points. This is apparent in the spread between the central tendency estimate (CTE) and 95th percentiles for the 15-minute TWA for fourth and fifth generation machines, which is very large (CTE of 48 ppm and 95TH percentile of 899 ppm). These values are from a dataset that includes only newer machines, and yet the upper-end 15-minute TWA estimate is nearly 10-fold higher than the 15-minute TWA (94 ppm) for the post-2006 dataset, which may include third generation machines. It is likely this high-end represents an equipment failure or instance of misuse, which would not represent a routine exposure in a dry cleaning facility. This conclusion is supported by equipment design

specifications that only allow for 300 ppm residual vapor in the drum of the machine post drying. Unless there was an unusual event or lack of appropriate equipment operation the EPA's high end estimate of 899 ppm is not a reasonable representation of the upper bound routine exposure scenario.

Rather than relying solely on a limited dataset that appears impacted by complaint-oriented and probably non-routine scenarios, EPA should consider utilizing alternative datasets to estimate exposure to workers in the dry cleaning industry. Most notably, the New York Department of Environmental Conservation (NYSDEC) has been collecting data under 6 NYCRR Part 232, which regulates dry cleaning. Under this regulation, New York requires yearly compliance inspections with trained inspectors registered with the state (e.g., an engineer or Certified Industrial Hygienist) (6 NYCRR 232-2.11). The inspector must collect badge monitoring data, which they provide to NYSDEC.

It is our understanding that the NYSDEC monitoring data are available to EPA for use in the risk evaluation and that the dataset is very robust, covering a large number of facilities and collected under normal operating conditions. Inspection data obtained for the years 2013 to 2016, which includes thousands of data points, revealed that many PCE area concentrations were less than the limit of detection (0.18 ppm), and most were < 1 ppm (NYSDEC, 2016). While personal breathing zone samples are typically preferred as a source of worker exposure data, area samples from this dataset can also provide reliable estimates of TWA exposures appropriate for assessing 8-hour and longer-term daily dose estimates. This reflects that workers in the industry move around in the facility in the cleaning and pressing departments. Such data might not adequately account for worst-case peak exposures associated with the short amount of time a worker spends unloading a recently completed run cycle. However, accounting for brief peaks of exposure to a maximum of 300 ppm PCE over the course of a work day should not generate a large difference between representative personal samples and areas samples. A work time analysis could be completed to verify this conclusion based on input from industry sector experts.

4 Conclusions

In the draft PCE risk evaluation, EPA relied upon empirical data to estimate inhalation exposures for dry cleaning workers. When data are sufficient, empirical data are preferred over exposure modeling. However, based on the data described and additional data sets that are available to EPA, the following suggestions are provided to improve the accuracy of the risk evaluation. EPA should:

- Use a weight-of-evidence approach to test the reasonableness of the CTE and upper bound estimates based on maximum drum concentrations of PCE and considering current emission controls and work activity patterns,
- Obtain and include the updated data collected via the NYSDEC program in revised exposure assessments, and
- For ONUs, rely on a weighted average of the NYSDEC data and work activity patterns that would include combinations of time spent in the production and non-production areas.

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Appendix 10

Comments on the US EPA TSCA Perchloroethylene Risk Evaluation: Dermal Exposure Assessment

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1 Executive Summary

The draft risk evaluation for perchloroethylene (PCE) incorporates a hierarchical approach when ranking the quality of data sources used in exposure characterizations. This report provides specific comments related to the dermal exposure characterizations and dermal scenario risk evaluations in the EPA TSCA draft risk evaluation for PCE. Specifically, the report focuses on PCE use in closed industrial systems, such as manufacturing, repackaging, and processing as a reactant, to highlight the impact of exposure assumptions on modeled estimates. A number of dermal occupational scenarios in the draft risk evaluation assuming worst-case exposure scenarios yielded estimates of "unreasonable risk" as described in the EPA's risk characterization. However, revised scenarios with more appropriate exposure assumptions result in substantially lower exposure estimates by as much as 10-fold that may affect the risk characterizations. EPA should consider whether a more refined exposure assessment approach is warranted for some scenarios in the revised risk evaluation using additional information on realistic workplace scenarios coupled with appropriate modeling. Further, the methods in the PCE exposure assessment suffer from some of the same limitations as those used by EPA for similar chemicals (for example, trichloroethylene). Therefore, EPA should refine its overarching approach for dermal exposure estimation and apply it to all forthcoming TSCA chemical risk evaluations.

2 Overarching Approach for Dermal Exposure Assessment

In the draft risk evaluation for perchloroethylene (PCE) (CAS number 127-18-4), occupational exposures were categorized into various conditions of use, with 20 specific occupational exposure scenarios (OES). Potential worker dermal exposures were assessed for six exposure scenario categories, which were subcategorized into six bins. A description of activities within each bin are summarized in Table 1.

Table 1. Description of Exposure Scenarios Categorized in each Bin (adapted from EPA 2020a Table 2-61)

Bin Category	Occupational Exposure Scenarios
Bin 1	Manufacture; Import/Repackaging; Processing as a Reactant; Incorporation into Formulation, Mixture, or Reaction Product; Industrial Processing Aid; Other Industrial Uses; Waste Handling, Disposal, Treatment, and Recycling
Bin 2	Batch Open-Top Vapor Degreasing; Batch Closed-Loop Vapor Degreasing; Conveyorized Vapor Degreasing; Web Degreasing; Cold Cleaning; Maskant for Chemical Milling;
Bin 3	Aerosol Degreasing and Aerosol Lubricants
Bin 4	Dry Cleaning and Spot Cleaning; Wipe Cleaning and Metal/Stone Polishes; Other Spot Cleaning/Spot Remover; Other Commercial Uses
Bin 5	Metalworking Fluids
Bin 6	Adhesives, Sealants, Paints, and Coatings (Industrial); Adhesives, Sealants, Paints, and Coatings (Commercial)

The following comments focus on the dermal exposure assessment component of the draft risk evaluation, which yielded findings of unreasonable risk for many OES. The inputs and models that were utilized resulted in estimates of exposure, and consequently, estimates of risk, that do not reflect actual industry working conditions for chemical manufacturing and similar use scenarios. Specifically, in the draft risk evaluation, because EPA did not identify information on how many dermal contact events occur each day; EPA assumed that for all dermal scenarios that there was one exposure event (applied dose) per work-day with a steady-state fractional absorption rate achieved. These dermal uptake estimates are not likely representative of routine Bin 1 (chemical manufacturing) work scenarios.

2.1 Assumptions Regarding Glove Protection

With regard to personal protective equipment, EPA assessed dermal exposure assuming several different scenarios, including:

1) Dermal exposure to PCE with no personal protective equipment (gloves).

2) Using gloves, assuming overall glove protection factors of 1, 5, 10, or 20. These scenarios assume there are no occluded exposures (*i.e.*, chemical is not trapped inside the glove). The protection factors, as presented in the draft risk evaluation, are detailed in Table 1.

3) EPA discussed occluded scenarios, which assume a worker is wearing gloves, some PCE penetrates through or splashes under the cuff of gloves and remains trapped, enhancing dermal penetration. Occluded exposures were considered for some OESs, discussed below in Section 2.3.

Table 1. Summary of Dermal Protection Factors

Dermal Protection Characteristics	Affected User Group	Indicated Efficiency (%)	Protection Factor, PF
a. Any glove / gauntlet without permeation data and without employee training	Both industrial and professional users	0	1
b. Gloves with available permeation data indicating that the material of construction offers good protection for the substance		80	5
c. Chemically resistant gloves (i.e., as *b* above) with "basic" employee training		90	10
d. Chemically resistant gloves in combination with specific activity training (e.g., procedure for glove removal and disposal) for tasks where dermal exposure can be expected to occur	Industrial users only	95	20

Source: US EPA (2020a), pg. 298

In the draft risk evaluation, for the scenarios without gloves, EPA assumes that a worker comes into contact with undiluted PCE one time per work shift, after which they do not wash their hands at any point during the day. For scenarios with gloves, EPA assumes that a worker wears the same pair of gloves for the entire work shift (8 hours) without stopping to wash their hands and/or change their gloves.

The amount of PCE that is able to penetrate a glove depends on the assumed protection factor (PF) based on the glove material and worker training. For a glove PF of 5, it is assumed that the glove material is "good" and there is no worker training; in this scenario, 20% of the total PCE in contact with the gloved hand will penetrate the glove and come into contact with skin. For the PF of 20, which assumes a chemically-resistant glove type and good worker training, EPA assumes 5% of PCE will still permeate the glove.

The PFs utilized by EPA in the dermal exposure assessment were developed for the ECETOC targeted risk assessment (TRA) model. There is very little information on how these protection factors were derived. Appendix D-3 of the ECETOC TR Report 107 (2009) describes the chosen protection factors as follows (ECETOC, 2009, p. 78):

> *Protection offered by gloves is much less well researched than that offered by respiratory protection. However some studies that have been undertaken on the effectiveness of different dermal protection ensembles and practices suggest that the following levels of actual protection are afforded in practice.*

This statement is the only explanation of the derived PFs, and none of the studies used to support the PFs are cited.

In the draft risk evaluation for PCE, EPA cited the Marquart et al. (2017) study in support of the use of the ECETOC PFs. Marquart et al. (2017) was the first study to attempt to validate the dermal ECETOC model. The authors used data from more than 35 data sources to compile 106 exposure cases, which were compared to ECETOC model estimates. The studies included a range of chemicals, including pesticides. The authors noted that "the model was shown to have clear bias towards (severe) overestimation of dermal exposure at low measured exposure values." Any instances of underestimation occurred at high exposure values. Across the dataset, the effect of gloves yielded an average protective factor of 34, relative to PFs of 5 to 10 in the model estimations. In other words, the empirical data demonstrated that measurements taken from underneath protective gloves resulted in an average of 97% lower values than measurements taken without gloves or on the outside of gloves. More specifically, Marquart et al. (2017) stated that six of the eleven studies of glove efficacy had an average exposure reduction of > 95% for gloves, which would yield a PF > 20. Marquart et al. (2017) concluded, "the effect of gloves is underestimated if the reasonable worst case defaults used in regulatory risk assessment practice are used."

While the underlying case studies in Marquart et al. (2017) predominantly included uses other than chemical manufacturing, they noted the following:

> *Several other highly relevant PROCs* [processing category] *that are typically found in the manufacturing of chemicals and chemical products in closed systems (PROCs 1 to 4) are not or hardly covered in this study. This is probably due to the fact that these situations are expected to lead to (very) low exposures and therefore are less likely to be the subject of measurements compared to situations where higher exposures are expected, such as in product transfer or application.*

The conclusion of Marquart et al. (2017) is consistent with the low exposure potential for closed systems utilized in PCE manufacturing.

Based on the findings of Marquart et al. (2017) and typical hygiene practices, it is apparent the PF value of 20 would be a significant underestimate of glove protection for many industrial chemicals. More specifically, in the chemical industry, a glove is selected to ensure suitability for the specific chemical being used based on empirical breakthrough test data supplied by the manufacturer. The allowable use time and replacement schedule are selected to ensure no chemical breakthrough for the duration of specific tasks. General industrial hygiene practice in place at facilities incorporate PPE change out schedules designed to limit breakthrough time. Further, any detectable breakthrough or glove degradation would indicate the need for new gloves. It also noted that situations in chemical manufacturing with full glove coverage of liquid material would be rare, and if considered probable would involve specific job hazard analyses

that would include specific controls (e.g., use of an inner glove or taped sleeves) to limit dermal contact.

Given that the PFs used in the dermal evaluation go beyond "worst case" glove performance, EPA should reevaluate and consider revising the PFs for the final risk evaluation. EPA should incorporate empirically-derived protection factors using literature on chemical permeation through gloves, considering critical factors such as the extent and length of contact with the chemical, the amount of hand/glove flexion, and worker behavior (Chao et al. 2004; Cherrie et al. 2004). This is important as direct observation by experienced industrial hygienists in the field indicate little in any dermal contact with solvent liquids through gloves during routine chemical manufacturing tasks. While "in-use" empirical studies of permeation through gloves under a company's specific working conditions would be ideal, there are also methods to calculate/model glove protection using chemical-specific inputs. For example, Cherrie et al. (2004) presented a technique for estimating chemical-specific glove protection factors using toluene as a case study.

2.2 Assumptions for Open Surface Contact (Non-Occluded)

For non-occluded scenarios, it is assumed that approximately 13% of the applied dose is absorbed through the skin for industrial scenarios and 19% is absorbed in commercial scenarios. Surface area of contact is assumed to be one full hand for central tendency estimates, and two full hands for high-end estimates (i.e., equivalent to dipping both hands into neat PCE). The quantity remaining on the skin was input as 1.4 mg/cm^2-event and 2.1 mg/cm^2-event for the central tendency and high-end scenarios, respectively, and the scenarios assume that the hands remain unwashed for 8 hours.

2.3 Assumptions for Occluded Scenarios

EPA assessed the possibility of occluded exposure conditions for consumers and some OESs. Conceptually, occlusion is similar to the "infinite dose" study design used in *in vitro* and *ex vivo* dermal penetration studies, which does not account for evaporative loss out of the gloves or cuffs, the low likelihood that liquid permeating all the way through the glove would coat the entire hand, or that liquid spilled over the cuff would typically result in removal of the glove.

For consumers, EPA estimated dermal exposure assuming occlusive conditions for the following uses: immersive parts cleaning, aerosol degreasers, liquid stone and marble polishes, liquid sealants, liquid paint primers and the wearing of recently dry cleaned articles. Specifically, EPA used the permeability module from the Consumer Exposure Model (CEM) to incorporate impeded evaporation. EPA stated that there was uncertainty surrounding whether consumer exposures would be associated with impeded evaporation, and if occuring, whether evaporation would have been fully (as assumed) or only partially impeded (EPA, 2020a, p. 402).

With regard to occupational scenarios, EPA indicated that it "expects occlusion" at sites where workers may come in contact with bulk liquid chemical and handle the chemical in open systems, which includes vapor degreasing, cold cleaning, and dry cleaning (EPA, 2020b, p. 297). In the occupational exposure appendix to the risk evaluation, EPA provided methods whereby the dermal models could be modified to account for liquid that is trapped in the glove. However,

ultimately EPA did not quantitatively consider occlusion in the dermal exposure estimates for occupational scenarios. Rather, EPA stated:

> *Given the significant variability in inner glove exposure and lack of information on the specific mechanism in which the inner glove contamination occurs, EPA addresses the occlusion scenario in combination with other glove contamination and permeation factors through the use of a protection factor, as described in the next section.*

2.4 Conclusions

Overall, the exposure assessment for the dermal route includes various default, scenario-centric parameters that are applied with minimal justification. In the sections that follow, an analysis of the occupational dermal exposure modeling approach is presented, and alternative modeling exercises are presented for assumptions that better approximate real-world dermal exposure scenarios. Considering the typical exposure scenarios that are likely under normal operational scenarios (particularly in chemical manufacturing facilities) following typical industrial hygiene practices with satisfactory employee training, the dermal PCE exposures are likely to be overestimated.

3 IH SkinPerm_V2.3 and Flux-Based Modeling Analyses and Critique

In the EPA draft risk evaluation for PCE, dermal exposure was estimated using the Dermal Exposure to Volatile Liquids (DEVL) model (non-occluded scenarios), or estimated using a simple mass-balance calculation (occluded scenarios, consumers only) due to a lack of empirical data. In its estimations of exposure, EPA did not account for the exposure duration nor the saturation of the skin by PCE, and applied scenario-centric parameters with little justification. When the exposure duration and skin saturation factors are appropriately accounted for, the EPA may have overestimated:

- The absorption fraction of PCE by 40 to 80-fold for exposure to an ungloved hand.
- The total dermal dose of PCE by approximately 2.5 to 10-fold for exposure to an ungloved hand assuming eight one-hour exposure events per day.

Assuming the EPA's approach for modeling the reduction in dermal exposure due to use of gloves as personal protective equipment using protection factors is appropriate; it is likely that the dermal exposure estimates presented in the draft risk assessment were also overestimated by approximately 2.5 to 10-fold because the protection factors were applied directly to the bare skin estimates. Note that for a volatile substance like PCE, these factors are not realistic because they do not adequately account for the evaporation of the solvent off of the glove. Thus, with proper glove use, the actual dose available for penetration through the skin is likely much lower than accounted for using the PF values.

Additionally, the EPA's use of scenario binning for PCE was inappropriate. Many of the scenarios grouped in bins have drastically different potentials for dermal contact with PCE and should have been documented and assessed separately. In fact, the EPA's simplistic approach resulted in the same results for separate bins with completely distinct exposure profiles, such as:

- Bin 1 (closed systems such as manufacturing, import, processing as a reactant… etc.) = Bin 2 (vapor degreasing, web degreasing, cold cleaning, use as a maskant for chemical milling), and
- Bin 3 (aerosol uses) = Bin 4 (dry cleaning, spot cleaning, wipe cleaning, polishes, etc.).

With respect to Bin 1 and Bin 2, it is noted in the EPA assessment that Bin 1 "covers industrial uses that generally occur in closed systems" for which dermal exposure is limited, whereas Bin 2 covers uses that "are not closed systems" and therefore have "greater opportunity for dermal exposure" (EPA, 2020a, p. 192). Therefore, to consider Bin 1 and 2 comparable would result in an overestimation of dermal exposures to workers performing Bin 1 tasks. These problems of mixing dissimilar exposures into a presumed similar exposure group is not appropriate occupational risk assessment practice. It is exactly for this reason industrial hygienists take a task-by-task job hazard analysis (JHA) profile method in conducting task risk assessments and designing customized exposure control programs that are tailored to the hazards and exposures that are present. JHAs are typically developed in concert with industrial hygienists, line management, and workers who are most familiar the nature of the work to be done. Such JHAs ensure that health risks are mitigated for the specific use case under examination. This

simplification may cause over- or under-estimates of the PCE exposure for these exposure scenarios.

The sections that follow provide alternative estimates of exposure that better estimate dermal absorption considering working conditions more representative of the industry. Analyses were performed using IHSkinPerm, an Excel application for estimating dermal absorption, which was developed by the American Industrial Hygiene Association (AIHA). DEVL uses an absorption estimate derived under steady state conditions. However, IHSkinPerm was used to estimate the impacts of dermal flux and conditions other than steady state on absorption.

IHSkinPerm is a peer-reviewed exposure assessment tool published by the AIHA's Exposure Assessment Strategies Committee. It is a common tool to produce reliable estimates of dermal exposure by practitioners of industrial hygiene and exposure assessment. The model is designed to predict the dermal absorption of volatile chemicals using known, measured physicochemical properties of the chemical, including molecular weight, octanol-water partition coefficient, pH on the skin surface, vapor pressure, and water solubility (Tibaldi et al., 2017). The model also contains critical, simplifying assumptions, such as a maximum absorption volume for the stratum corneum and the thickness of the stratum corneum. The model is designed to report a reasonable estimate for the dermal dose of chemical and the fraction of applied chemical absorbed by the skin based on a number of input parameters (Tibaldi et al., 2017). The IHSkinPerm model was selected for the present assessment because it accounts for exposure duration, skin loading, all possible mass transport routes (including absorption, evaporation and bulk loss via exceedance of maximum skin adherence), and the potential for skin saturation.

3.1 Contact with Ungloved Hands

This section contains examples of the overestimates in the PCE absorption fraction and dermal dose resulting from the EPA's use of a dermal model that did not account for exposure duration for industrial scenarios and the saturation of the skin by PCE.

Bin 1 included manufacture, import/repackaging, processing as a reactant, incorporation into formulation, mixture, or reaction product, industrial processing aid, "other industrial uses" and waste handling, disposal, treatment, and recycling (EPA 2020b Table 2-61 p. 193). Dermal exposure to workers may occur during Bin 1 tasks, connecting and disconnecting hoses and transfer lines to containers, packaging, and storage vessels to be loaded with PCE product (e.g., railcars, tank trucks, totes, drums, bottles, storage tanks, pressure vessels), and when unloading PCE into mixing vessels, taking QC samples, and packaging formulated products into containers and tank trucks, and with PCE-containing waste (EPA 2020b p. 39, 58-59). In addition, for such environments, preparing equipment for maintenance is another common task with potential dermal exposure.

Example 1: Bin 1 OES group – Instantaneous PCE Dose at the Beginning of the Task Time (unloading and loading process)

- Bin 1 OES Central Tendency PCE dose value was 1.2 mg/kg/day (USEPA 2020a Table 2-61 p. 193).
- The USEPA estimated the CT dose of 1.2 mg/kg/day using the following equation (Equation 1) and assumptions:

$$D_{exp} = S \times \frac{Q_u \times f_{abs}}{PF \times BW} \times Y_{derm} \times FT$$

Equation 1

- D_{exp} = dermal exposure dose = 1.2 mg/kg/day
- S = surface area = 535 cm^2 (one whole hand)
- Q_u = quantity remaining on skin = 1.4 mg/cm^2/event
- F_{abs} = fraction of PCE absorbed = 0.13
- PF = protection factor from gloves = 1
- Y_{derm} = weight fraction = 1 (100% PCE solvent)
- FT = Exposure event frequency = 1 event/day
- BW = Body weight = 80 kg was used

Notably, Equation 1 is a steady-state, event frequency-based dermal dosage model. One weakness of this type of model is that it does not consider task exposure duration, one of the key determinants of human exposure. Based on the parameters for modeling exposure during loading and unloading, EPA assumed one tank truck per shift for the central tendency scenario, or one railcar for the high end scenario, each averaged over an eight-hour work day (EPA 2020b: p. 225). The duration of each loading/unloading event was assumed to be 0.5 hour (tank truck) or 1 hour (railcar) (30 to 60 minutes per task) (EPA 2020b: p. 225-226).

When the EPA's parameters are used in IH SkinPerm, modifications are required because IH SkinPerm accounts for absorption over time. For Example 1, it was assumed that all of the PCE was deposited at the beginning of each event (to simulate a wetting or soaking of hands during unloading/loading procedure). The variables entered into IH SkinPerm for Example 1 were as follows (Figure 1a and Figure 1b):

- Instantaneous deposition dose = 749 mg/event = 1.4 mg/cm^2/event x 535 cm^2 (calculated using the EPA's assumed Q_u and S values)
- Affected skin area = 535 cm^2
- Maximum skin adherence = 0.648 mg/cm^2
  - The maximum volume for absorption is equal to 0.0004 (cm) x density (mg/cm^3) based on assumptions of 20 µm stratum corneum thickness and 20% stratum corneum saturation volume (Tibaldi et al. 2014)
  - The density of pure PCE is 1.62 g/cm^3 (1620 mg/cm^3) (EPA 2020a Table 2-64, p. 213)
- Thickness of stagnant air = 1 cm
- 1 cm is recommended for bare skin (Tibaldi et al. 2014).
- Weight fraction PCE = 1.0
- Start deposition = 0 h
- End time = 0.5 hr (Example 1a) OR 1 h (Example 1b)

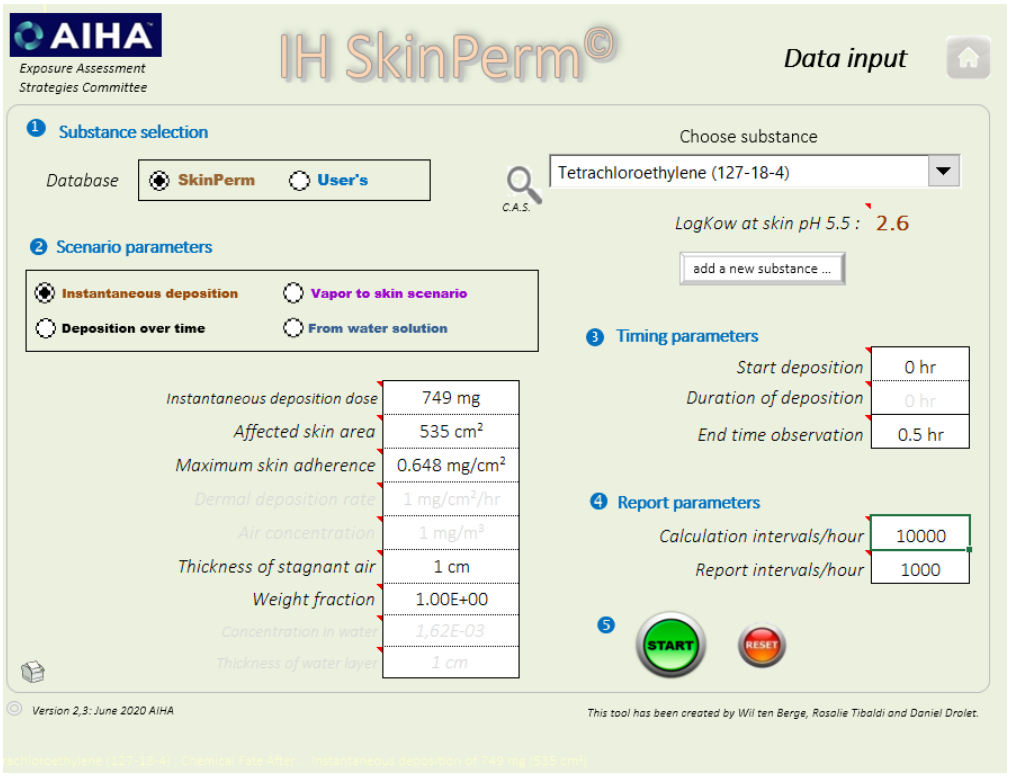

Figure 1a: IHSkinPerm Input Screen for Example 1 (0.5 hr task time)

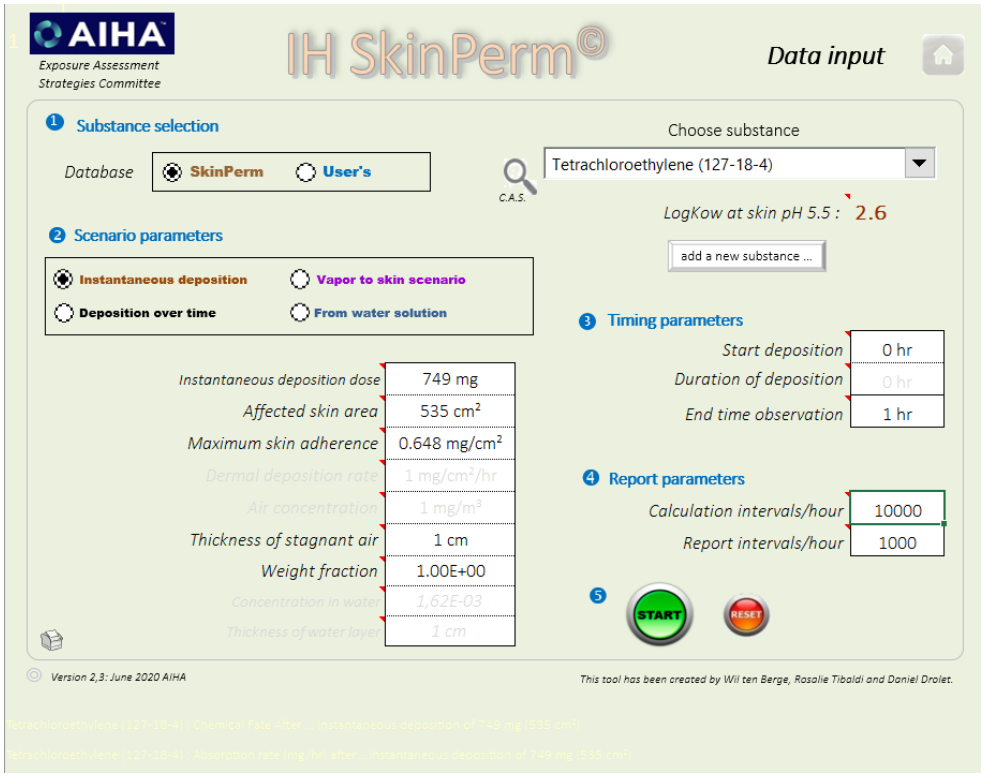

Figure 1b: IHSkinPerm Input Screen for Example 1 (one hour task time)

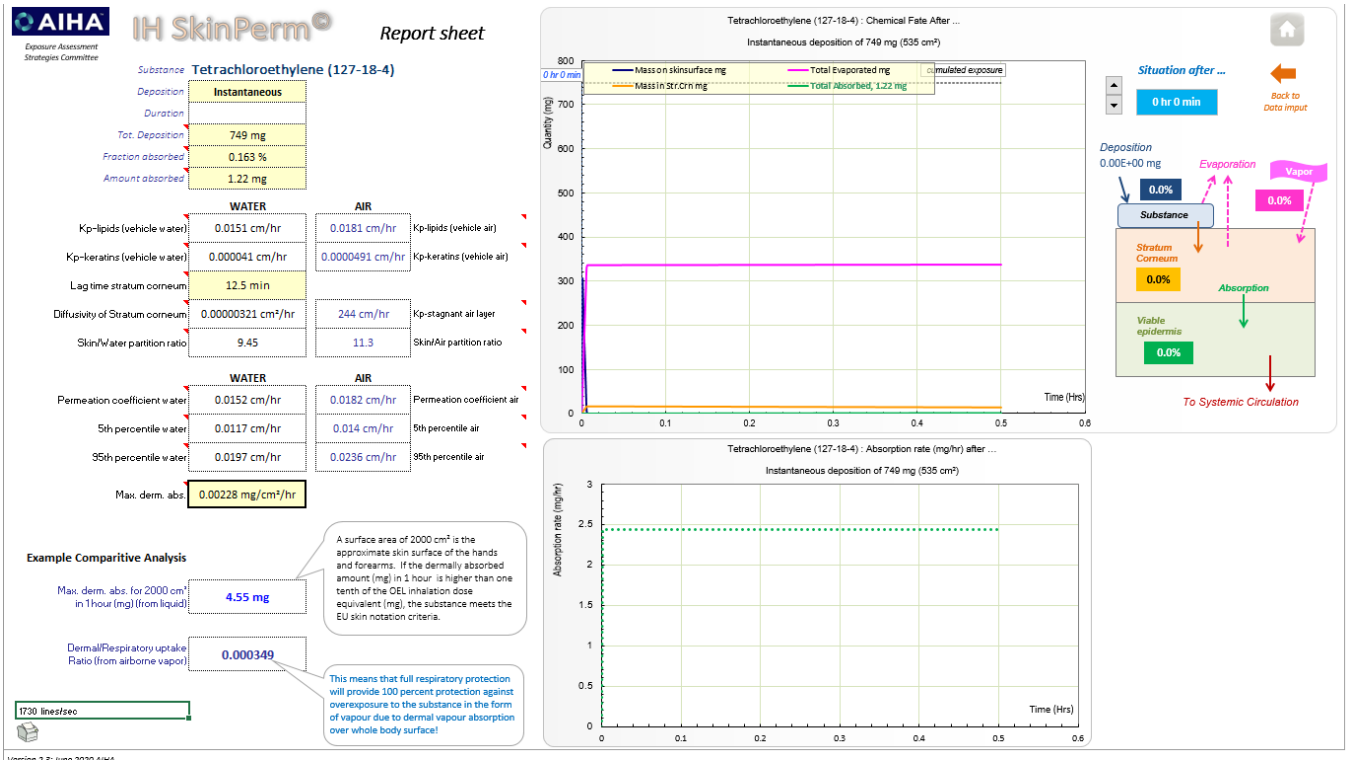

Figure 2a: IHSkinPerm Output Screen for Example 1 (0.5 hour scenario)

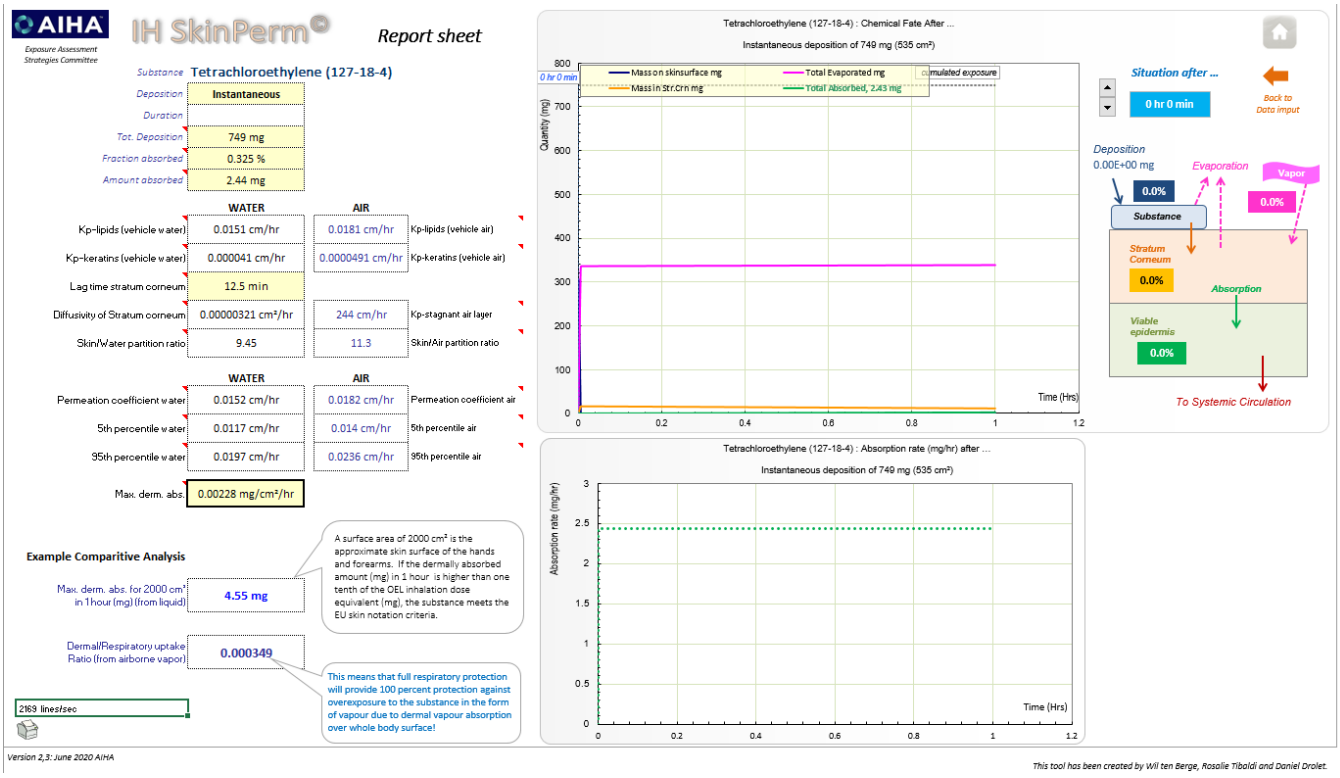

Figure 2b: IHSkinPerm Output Screen for Example 1 (1 hour scenario)

The results for the Example 1 scenarios (Figures 2a and 2b) demonstrate that only about 0.163-0.325% (fabs = 0.00163 to 0.00325) of the PCE applied to skin would be the estimated amount absorbed – the rest evaporates or falls off of the skin due to saturation of the stratum corneum. This absorption fraction is 40 to 80-fold lower than the 13% fraction assumed by the EPA. The total dose per event is estimated to be 1.22 to 2.44 mg. When applied eight or 16 times per day, the total dose per day is 9.76 to 19.52 mg/day (8 events per day) or 19.52 to 39.04 mg/day (16 events per day). When applied to a person with an 80 kg body weight, the range of estimated doses for 8 to 16 contact loadings is 0.122 or 0.488 mg/kg/day and is approximately 2.5 to 10-fold lower than the USEPA's central tendency estimate of 1.2 mg/day. For Bin 1 tasks common to the chemical manufacturing, such periodic skin loadings that yield lower absorbed doses are much more likely than a continuous loading dose scenario.

In addition, for this scenario, a weight fraction of PCE was assumed to be 100% similar to the EPA parameters. However, it was noted that a formulated PCE product may contain less PCE by weight (between 30 and 80%) (EPA 2020b: p. 233). Moreover, in many aspects of the manufacturing process that involve dermal exposure (e.g., QC sample collection of intermediate process streams) the liquid material may not be neat PCE. Bin 1 tasks include handling formulated products, including unloading PCE into mixing vessels, taking QC samples, packaging formulated products into containers and tank trucks, and with PCE-containing waste, and therefore the estimated dermal exposures in Example 1a & 1b may be an overestimate of exposure due to the maximum weight fraction assumption.

Example 2: Bin 1 OES Constant Dose over Task Time

In Example 2, the exact same scenario was performed as in Example 1, but the mass loading of PCE was uniformly spread over the 0.5 hour or 1 hour exposure event rather than being instantaneously loaded at the start of the event. This scenario more accurately represents splashing over the course of a task, dripping or minimal contact loading through incidental exposure.

The variables entered into IH SkinPerm for Example 2a were as follows (Figure 3a):

- Affected skin area = 535 cm^2
- Maximum skin adherence = 0.648 mg/cm^2
- Dermal deposition rate = 2.8 $mg/cm^2/h$ (assuming a 30 min event)
- Thickness of stagnant air = 1 cm
- Weight fraction PCE = 1
- Start deposition = 0 h
- Duration of deposition = 0.5
- End time = 0.5 h

The variables entered into IH SkinPerm for Example 2b were as follows (Figure 3b):

- Affected skin area = 535 cm^2
- Maximum skin adherence = 0.648 mg/cm^2
- Dermal deposition rate = 1.4 $mg/cm^2/h$ (assuming a 1 h event)

- Thickness of stagnant air = 1 cm
- Weight fraction PCE = 1
- Start deposition = 0 h
- Duration of deposition = 1 h
- End time = 1 h

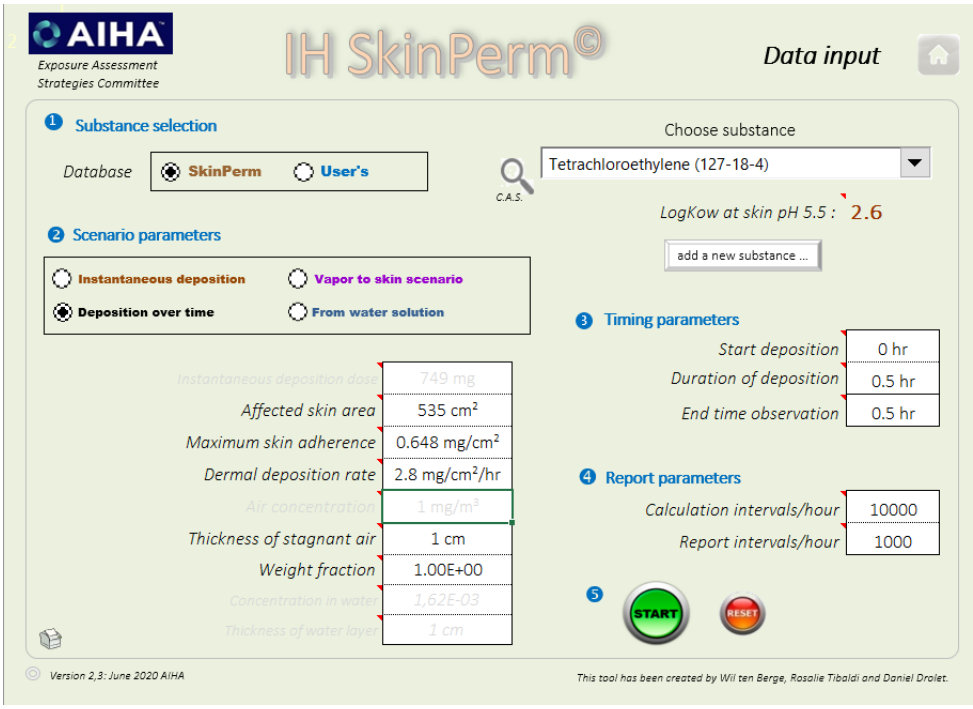

Figure 3a: IHSkinPerm Input Screen for Example 2 (30 min constant dose, assuming a 30 min event)

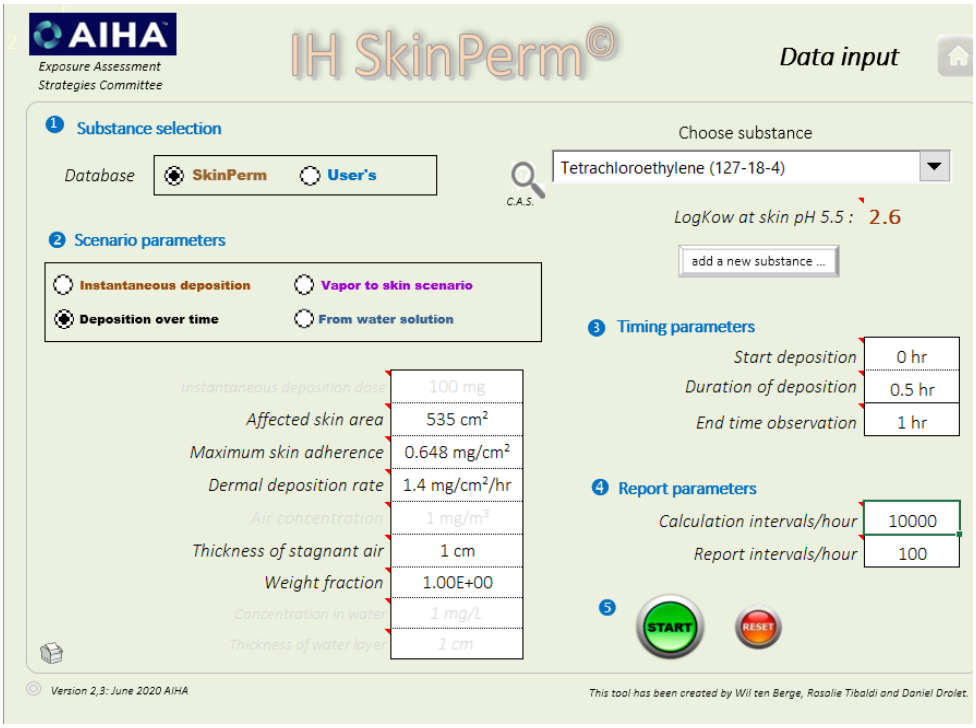

Figure 3b: IHSkinPerm Input Screen for Example 2 (30 min constant dose, assuming a 1hr exposure event)

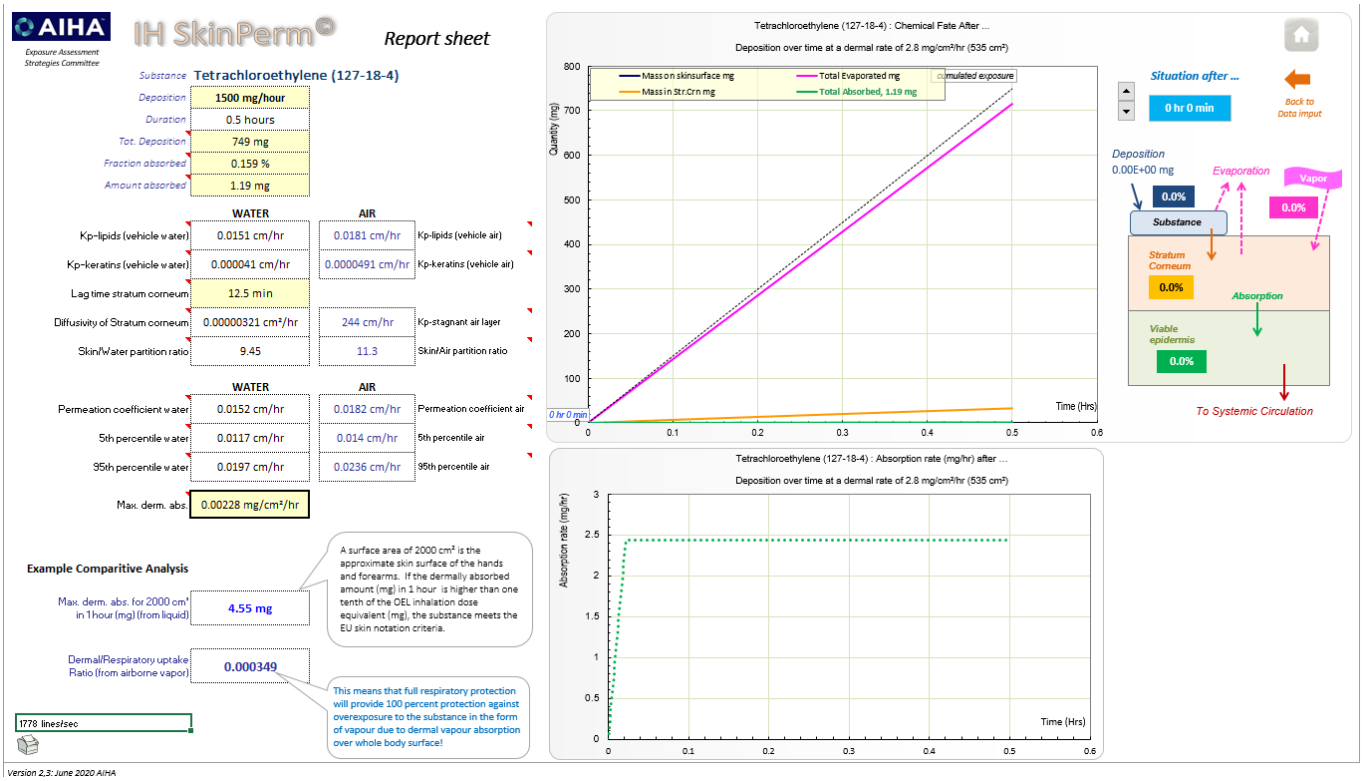

Figure 4a: IHSkinPerm Output Screen for Example 2a (30 min constant dose)

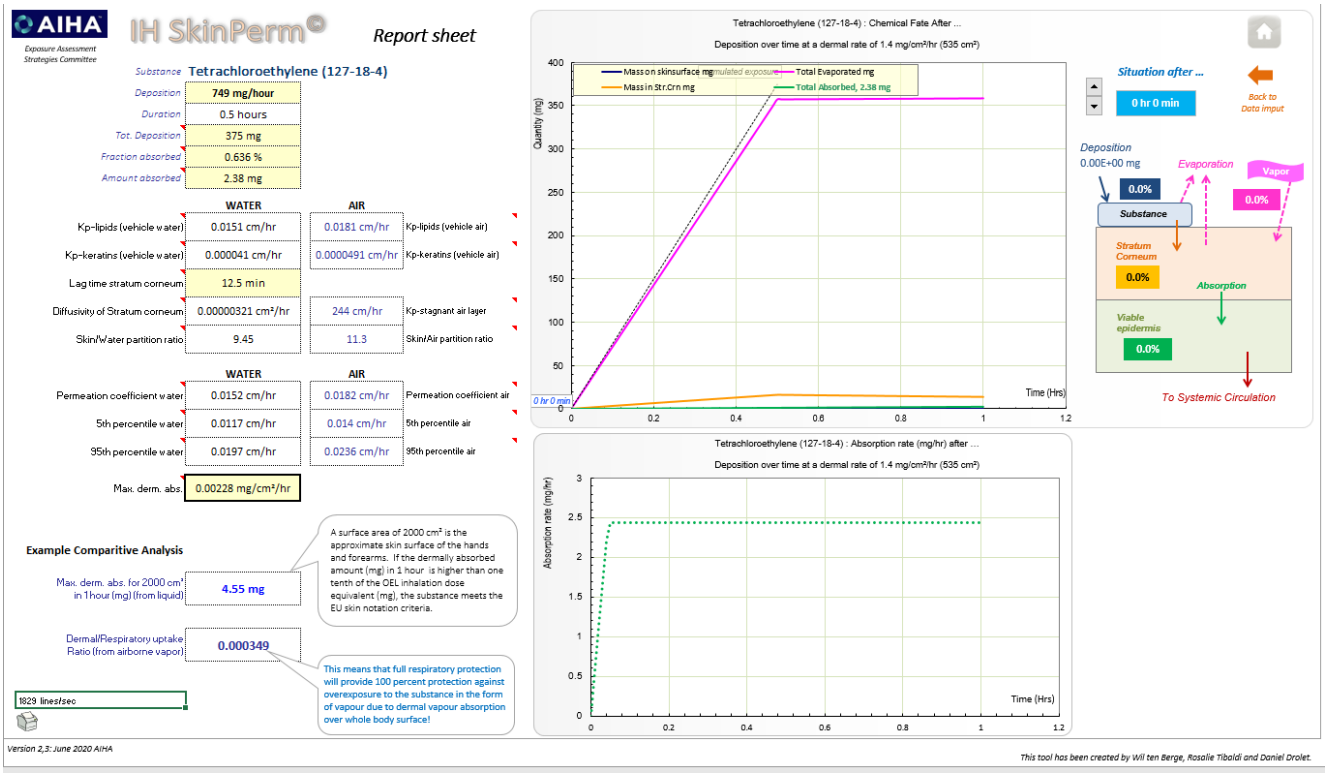

Figure 4b: IH SkinPerm Output Screen for Example 2b (1hr constant dose)

The results for Example 2a, a 30 minute constant dose (Figure 4a) demonstrate that only about 0.159% (f_{abs} = 0.00159) of the PCE applied to skin would be the estimated amount absorbed – the rest evaporates or falls off of the skin due to saturation of the stratum corneum. This absorption fraction is 80-fold lower than the 13% fraction assumed by the EPA. The total dose per event is estimated to be 1.19 to 2.38 mg. When applied 16 times per day, the total dose per day is 19.04 mg/day, which, when applied to a person with an 80 kg body weight, is equal to 0.24 mg/kg/day and is approximately 5-fold lower than the EPA's central tendency estimate of 1.2 mg/day.

The results for Example 2b, a 1 hour constant dose (Figure 4b) demonstrate that only about 0.636% (f_{abs} = 0.00636) of the PCE applied to skin would be the estimated amount absorbed – the rest evaporates or falls off of the skin due to saturation of the stratum corneum. This absorption fraction is 20-fold lower than the 13% fraction assumed by the EPA. The total dose per event is estimated to be 2.38 mg. When applied 8 times per day, the total dose per day is 38.08 mg/day, which, when applied to a person with an 80 kg body weight, is equal to 0.48 mg/kg/day and is 2.5-fold lower than the EPA's central tendency estimate of 1.2 mg/day. Note that these illustrative scenarios of frequent constant dose loading would be very rare in the chemical manufacturing environment as they represents nearly continuous contact with liquid PCE over the course of an 8-hour work day.

3.2 Contact with Gloved Hands

The EPA's approach of applying a protection factor is appropriate, but simplistic, for accounting for solvent contact with a gloved hand. Notably, the volatile chemical will evaporate off the gloved

hand just as it does when contacting the hand itself. If such factors are used; however, the protection factors should be applied to the ungloved estimates listed above, not the original estimates presented in the risk assessment (which were likely 2.5 to 10-fold too large).

4 Conclusions

Overall, both occluded and non-occluded dermal PCE exposure estimates were likely substantially overestimated based on numerous factors, including (but not limited to):

- The absorption factor used (13-19%), which is higher than expected for PCE under realistic scenarios assuming evaporation and saturation kinetics,
- The assumption that the skin surface area that comes in contact with PCE is one to two full hands, rather than the more likely interior hand surfaces,
- The assumption that PCE exposure occurs continuously for 8 hours rather than intermittently; and
- The assumption that the worker does not change gloves or wash hands at all during the time needed for the PCE to be absorbed.

In the case of the occluded scenarios, additional overestimation likely occurred based on the assumption that the whole hand (or hands) were coated with PCE in-glove and the lack of consideration for possible permeation back out of the glove and evaporative losses off of the glove.

The PCE risk evaluation would be strengthened by refinements to the methodology of the exposure characterization. EPA should first consider whether grouping OES into six categories of general exposure are truly representative, or whether EPA should consider more specific groupings. EPA should then consider the incorporation of additional exposure modeling in the revised risk evaluation that reflects well characterized industrial handling practices. Moreover, at a minimum, the risk evaluation should include discussion of the impacts of these assumptions on the level of confidence in the overall estimates, and the degree to which the assumptions are more than adequately protective. Given the many uncertainties inherent in the PCE dermal assessment, EPA should also investigate whether an empirical study of dermal exposure to PCE can be conducted, and the findings incorporated into the revised draft. Another data gathering approach could include conducting or soliciting surveys that characterize the current tasks at facilities manufacturing and utilizing PCE, including information on task duration, contact volumes and frequencies, and PPE practices. Moving forward in future risk evaluations, EPA should more thoroughly consider data gaps and methods to fill them in the scoping and problem formulation phases of the risk evaluation.

5 References

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Appendix 11

Distribution Analysis of Perchloroethylene Manufacturing Data

Cardno ChemRisk

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Table of Contents

1 Introduction

In August 2018, the Halogenated Solvents Industry Alliance, Inc. (HSIA) submitted commentary to the United States Environmental Protection Agency (EPA) in response to the EPA's problem formulation phase of the perchloroethylene (PCE) Toxic Substances Control Act (TSCA) risk evaluation. Within these comments, HSIA provided an occupational exposure dataset for various exposure scenarios in PCE manufacturing facilities, including 8- and 12-hour full-shift samples and 15- and 30-minute task-length samples.

EPA utilized the dataset provided by HSIA in its 2020 draft PCE risk evaluation to characterize exposures to workers and occupational non-users (ONUs) for manufacturing use scenarios (EPA, 2020). The 50th percentile central tendency exposure (CTE) and the 95th percentile values for 15-minute, 30-minute, 8-hour, and 12-hour time-weighted average (TWA) exposures calculated from the HSIA data were selected as representative of typical worker exposures, while the 50th CTE was selected as representative of ONU exposures.

The exposure data submitted by HSIA were highly censored, with 65%, 73%, 24%, and 55% of the 8-hour, 12-hour, 15-minute, and 30-minute TWA exposure data below the limit of detection (LOD), respectively. Therefore, the calculated exposure estimates are highly influenced by the high-end outliers in this dataset. Because of the task-oriented nature of chemical manufacturing, as discussed further below, these EPA estimates are likely an inappropriate lumping of routine and non-routine tasks.

To address values reported as below the LOD, EPA relied upon guidance provided in the EPA Guidelines for Statistical Analysis of Occupational Exposure Data (EPA, 1994). For the 8-hour, 12-hour, and 15-min samples, the LOD divided by 2 (LOD/2) was used as a substitute for values reported as lower than the LOD, while the LOD divided by the square root of 2 was substituted for 30-min samples below the LOD. The EPA recognized the potential introduction of bias through the use of LOD substitution methods on highly censored data sets (>50% samples below the LOD), stating that the "[e]stimation of exposure values for results below the LOD may over or under-estimate actual exposure thus skewing the calculated statistics higher or lower, respectively" (EPA, 2020, p. 134).

Below are alternative approaches for the assessment of the PCE manufacturing dataset, conducted according to best practices and with resources utilized by occupational health and safety professionals.

2 Background on IH Data Sets

When assessing exposure monitoring data to make risk management decisions, it is important to consider that workers may have different exposures based on the nature of their tasks, including the frequency and duration of each task, specific materials used, and the manner in which the tasks are performed (AIHA, 2015, p. 38). The American Industrial Hygiene Association (AIHA) recommends that occupational data be categorized by similar exposure groups (SEGs) in order to accurately represent the exposure profiles for workers conducting similar tasks (AIHA, 2015, p. 40). Indeed, according to AIHA, considering differences in exposures among groups is critical for risk assessment and risk management, because "good risk management is almost always predicated on good risk assessment, which in turn is driven by the quality of the industrial hygienist's exposure assessments" (AIHA, 2015, p. 5). As such, it is critical that risk managers have confidence that their exposure data are grouped in a manner that accurately represents the exposures experienced by workers with different exposure profiles (AIHA, 2015, p. 305).

The degree of granular information obtained using SEGs based on tasks allows for a greater understanding of the potential exposures presented during those tasks. This is particularly true when considering non-routine operations that may be infrequent, but may have higher exposures (e.g., sample collection) (AIHA, 2015, p. 18, 41). Failure to distinguish between SEGs in exposure data by combining data for workers or tasks with different exposure profiles may lead to misrepresentation of exposures and misguided risk management decisions.

AIHA emphasizes the use of descriptive statistics to understand the distribution of exposures within an exposure monitoring dataset (AIHA, 2015, p. 409). AIHA recommends that the following statistics be calculated for all monitoring data: number of samples (n), maximum exposure, minimum exposure, range, percent of exposures greater than the applicable occupational exposure limit (OEL), mean exposure, standard deviation, mean of log-transformed exposures, standard deviation of log-transformed exposures, geometric mean, and geometric standard deviation (AIHA, 2015, p. 409-410). To avoid misclassifying worker exposures, AIHA further recommends that when analyzing occupational exposure data, "SEGs with large geometric standard deviations (>3) should be reviewed, and if appropriate, subdivided into two or more SEGs" (AIHA, 2015, p. 48). Applying descriptive statistics to monitoring data thereby allows industrial hygienists and risk managers to gain a deeper understanding of what their data represent, as well as distinguish and properly characterize different exposure groups.

3 Case Study Using HSIA Data Set

As noted above, HSIA provided occupational exposure data for various exposure scenarios, including full-shift and task-length samples from PCE manufacturing facilities. Where applicable for each sample, the worker exposure group, task name, approximate frequency and duration of the task, task description, sample date, sample duration, and PCE concentration in parts per million (ppm) were provided.

Overall, the data set consisted of 375 individual entries. Twenty-three samples (18 full-shift and 5 unspecified samples) were reported as below the detection limit (BDL) with no LOD reported, so these samples were not included in subsequent analyses. A standard substitution method of LOD divided by the square root of 2 was utilized for samples that were reported as below an identified LOD.

Following the AIHA recommendations for exposure monitoring data sets, summary statistics were calculated for the full, task-length, and unspecified samples, provided in Table 1.

Table 1: Summary Statistics of Full-shift, Task-length, and Unspecified Sample Types from 2018 HSIA Manufacturing Monitoring Data

	Full-Shift	Task Length	Unspecified Sample Type
Sample Count [a]	171	195	9
Average Duration (min)	586	16.9	23.2
Average Concentration (ppm)	0.29	5.19	5.89
Standard Deviation (ppm)	0.98	16.2	4.82
Minimum	0.01	0.03	1.52
Maximum	8.74	200	11.2
Average of Ln Concentration	-2.92	0.52	1.44
St. Dev. of Ln Concentration	1.40	1.46	1.00
Geometric Mean	0.05	1.68	4.21
Geometric SD	4.06	4.30	2.72

[a] Includes 18 (full-shift) and 5 (unspecified) samples indicated as BDL with no LOD reported. SD = standard deviation.

When all full-shift and task-length samples are grouped together, the geometric standard deviation, an indication of the spread of the data, is high. When utilizing the central tendency of this data set as a representative exposure profile for the average manufacturing worker, it is likely that there is a mischaracterization of various SEGs, each of which has a unique exposure profile dependent upon the types of tasks.

Task-length samples included in the dataset were reportedly used to characterize specific tasks that occurred at various frequencies within the manufacturing facility, ranging from daily to infrequent. In Table 2, the descriptive statistics for three frequency categories – daily, weekly, and infrequent – are displayed.

Table 2: Summary Statistics for Task-Length Samples from 2018 HSIA Manufacturing Monitoring Data

	Daily	Weekly	Infrequent
Sample Count	44	42	11
Average Duration (min)	18.0	16.5	16.3
Average Concentration (ppm)	2.59	7.92	20.7
Standard Deviation (ppm)	5.01	15.1	59.5
Minimum	0.03	0.15	1.20
Maximum	28	80	200
Average of Ln Concentration	-0.05	0.85	1.25
St. Dev. of Ln Concentration	1.34	1.70	1.46
Geometric Mean	0.95	2.34	3.47
Geometric SD	3.84	5.48	4.29

The average concentration for routine, daily tasks differed 8-fold from that of the infrequent tasks and 3-fold from the weekly tasks. Similarly, there was an approximately 7-fold increase in the maximum concentration from daily to infrequent tasks. The GSDs of these groups of task-length samples are high, indicating that there may be room for further refinement of the exposure profiles to classify individual SEGs. This brief analysis of the task-length samples by frequency indicates the importance of understanding the representativeness of a data set before utilizing it for risk management decisions. Were a practitioner to include infrequent, non-routine samples in an exposure profile describing typical exposures, the resulting central tendency and 95th percentile would be greater than if the profile correctly included just routine work and classified infrequent tasks separately.

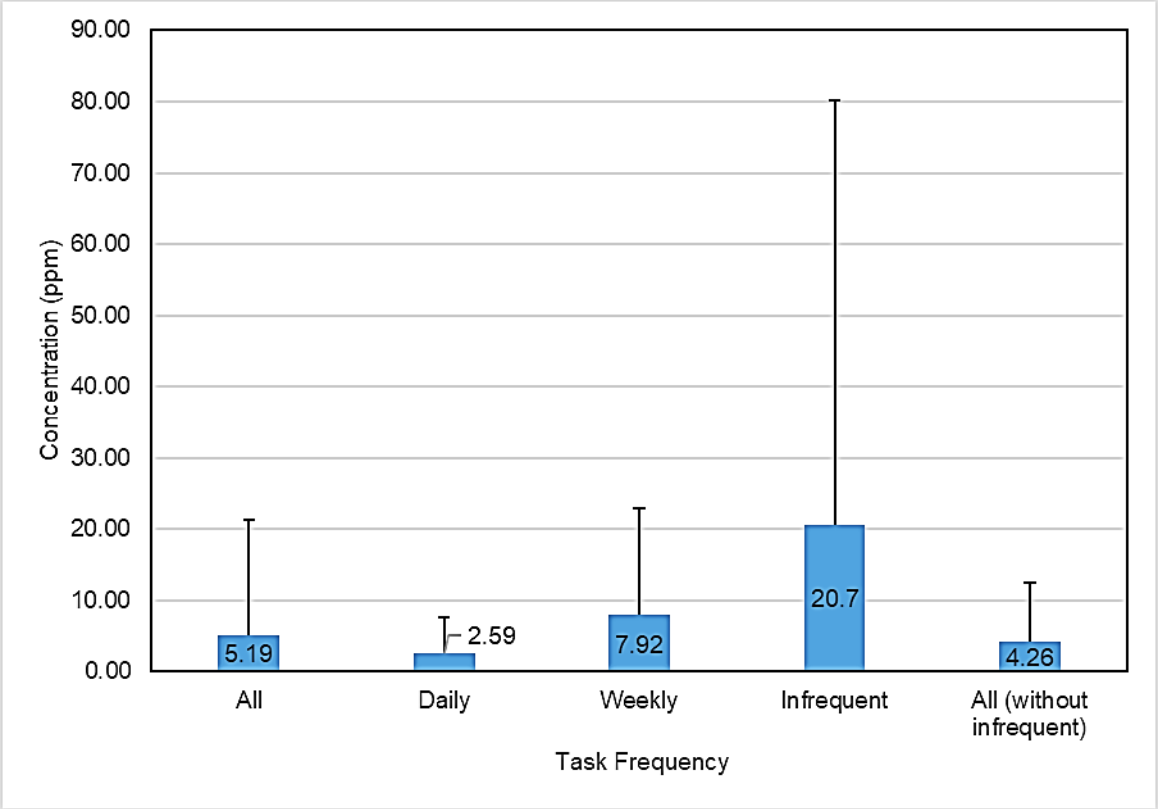

Figure 1: Average PCE concentrations (ppm) by task frequency for all frequencies combined, daily tasks, weekly tasks, infrequent tasks, and all frequencies (except infrequent) combined. Error bars indicate standard deviation.

Figure 1 displays the average PCE concentrations by task frequency for all frequencies combined, daily, weekly, and infrequent tasks separately, and all frequencies combined with infrequent tasks removed. The substantial variability in the infrequent tasks led to a 2-fold increase in the standard deviation of all task frequencies combined. Classification of these tasks separately is an appropriate solution to ensure that the data set is representative of the true central tendency of exposures on a routine basis.

Furthermore, it is worth also nothing that, for non-routine tasks, facilities have specific processes in place to minimize exposure for tasks with potential for high-level air concentrations. As stated in previous comments submitted to the PCE docket:

> *The samples with high concentrations may reflect scenarios that have job hazard analyses conducted at the facility. These job hazard analyses would take into account special precautions for non-routine exposures. Such exposures should not be included as part of the long-term daily average calculation.*

Based on the job hazard analysis, safety professionals would identify controls to reduce or eliminate exposures during these tasks (e.g., through behavioral, work environment conditions, and PPE).

4 Occupational Non-Users

While the above analysis focused on workers, EPA should also reassess its approach to exposure assessment for ONUs; specifically, EPA should not rely on extremely limited empirical data. As noted in previous comments on carbon tetrachloride (HSIA, 2020), in the absence of adequate ONU monitoring data, a more appropriate approach to estimate the ONU exposures would be to use ONU-specific near-field/far-field exposure models.

An initial near-field modeling scenario for carbon tetrachloride (presented in HSIA, 2020) demonstrated that the method is practical. The analysis also indicated that EPA's methods (in that case, using the CTE for workers as a surrogate for ONUs) was a substantial overestimation of ONU exposure to carbon tetrachloride.

5 Conclusions

As demonstrated above, alternative analyses of occupational exposure data for PCE manufacturing by task length and task frequency reveal important differences in exposure potential based on the nature of specific tasks. Comparing these results to the occupational exposure estimates for PCE manufacturing presented in the draft risk evaluation, which group all HSIA data points together, indicate that EPA's exposure estimates do not represent average routine exposures in the industry.

Specifically, infrequent, non-routine tasks may present a substantially greater potential for worker exposure, a distinction that is not made in EPA's current approach to its PCE risk evaluation. Grouping data for infrequent tasks with high exposure potential with data for routine tasks based solely on task length overestimates both the central tendency and 95th percentile PCE exposures. As such, it would be prudent for EPA to adopt a more refined approach in the revised risk evaluation for PCE. EPA should re-analyze the HSIA data to not only consider task length, but also task frequency, in estimating exposures. Estimates for non-routine, infrequent exposures should be compared with acute health benchmarks, and estimates of routine exposures should be compared with chronic benchmarks. Such an approach will allow EPA to distinguish the SEGs present within the HSIA dataset and develop a more robust characterization of potential risks to PCE manufacturing workers. Finally, EPA should consider conducting near-field/far-field modeling of ONU exposures rather than relying on a single empirical data point.

6 References

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